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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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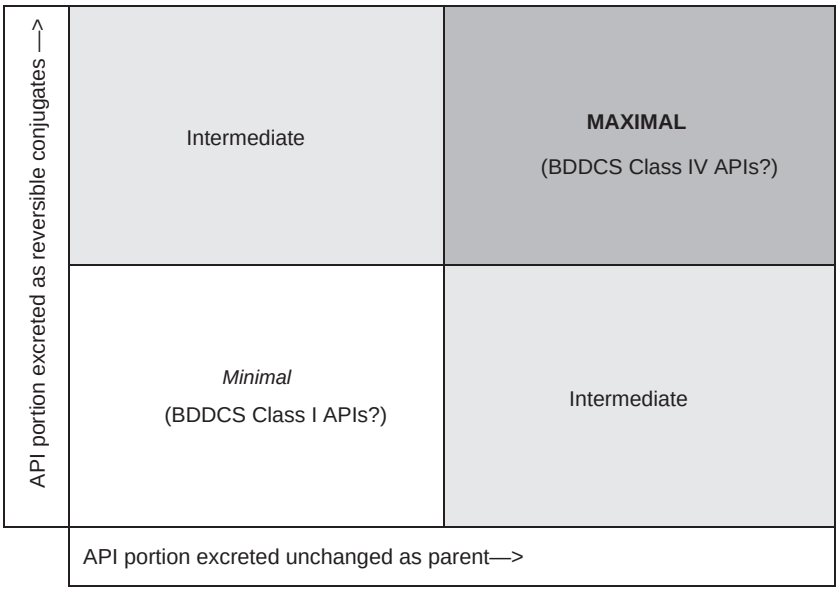

Fig. 1. Environmental loadings of APIs as a function of excretion and reversible conjugation. See Supplemental Table S-3 for a list of example APIs (and supporting references) that have shown "negative removals" during sewage treatment — often, perhaps, as a result of deconjugation. The possible predictive 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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Table S-1. Published environmental occurrence data for 322 APIs in BDDCS Class I [1]

API (alternate name)	Reported occurrence data [2]	Notes (including data of absence)	Selected references [2]
Abundant occurrence data [3]			
Acebutolol hydrochloride	Up to 2,683 ng/L* in STP influents. Up to 168 ng/L in rivers.	Up to 80% removal in STPs.	(Benner et al., 2008; Gabet-Giraud et al., 2010; Gabet-Giraud et al., 2013; Lee et al., 2007; Lin et al., 2010; Petrović et al., 2005; Saussereau et al., 2013; Vieno et al., 2007; Vieno et al., 2006)
Alprazolam	Several studies reporting sporadic samples of 2.58-4.7 µg/L* in STP influent. Single study reporting range 0.05-3.69 µg/kg in sediment from lake receiving treated wastewater. Sporadic detection in groundwater at levels up to 6.38 ng/L. Sporadic levels up to 27 and 17 ng/L in STP influent and effluent.	Some studies report non-detection for STP influent and effluent and surface waters (e.g., Gracia-Lor et al., 2012; Gros et al., 2012; Huerta-Fontela et al., 2010; Valcárcel et al., 2012; Yuan et al., 2013b)	(Esteban et al., 2012; Grabic et al., 2012; Jurado et al., 2012; Ottmar et al., 2013; Salgado et al., 2011; Sundelin, 2013)
Aminophenazone (dimethyl-aminophenazone, aminopyrine among others)	River bank filtrate: 15 ng/L. Single report of 430 ng/L in 1 of 7 STP effluents. Sporadic levels up to 3.7 and 4.3 µg/L* in STP influent and effluent.	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b). Not quantifiable in surface waters (de Jongh et al., 2012). Not detected in 6 of 7 STP effluents (Andreozzi et al., 2003).	(Andreozzi et al., 2003; de Jongh et al., 2012; Hollender et al., 2009; Salgado et al., 2010)
Amitriptyline	Single studies reporting mean levels of 110 ng/g in sewage sludge and 768 ng/g in biosolids. Sporadic occurrence and maximum value of 9 ng/L in river water. Frequent or sporadic occurrence in STP influent and effluent, with ranges of 341-11,100* and 53–357 ng/L.		(Baker and Kasprzyk-Hordern, 2013; Grabic et al., 2012; Kasprzyk-Hordern et al., 2009; Komori et al., 2013; Lajeunesse et al., 2012; Martínez Bueno et al., 2012; Mwenesongole et al., 2013; Peysson and Vulliet, 2013)
Amlodipine	Mean levels in STP influent and effluent of 48.5 and 41.4 ng/L. Mean levels of 1.44 ng/L in bay water, 0.53 ng/g ww in mussel tissue, and not detected in bay sediment. Level in biosolids (120 ng/g dw) and sewage sludge (260 µg/kg dw).	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b). Not detected in surface waters or STPs (Gros et al., 2012), or landfill leachates, ground waters, and STPs (Rodríguez-Navas et al., 2013), or lakes (Ferrey, 2013).	(Al-Odaini et al., 2013a; Chari and Halden, 2012; Klosterhaus et al., 2013; Nordic Council of Ministers, 2012; Sabourin et al., 2012; Santos et al., 2013)
Antipyrine (phenazone, phenazon)	Levels in receiving waters ranged from 10-62 ng/L. Maximum STP influent levels of 60 ng/L. Maximum groundwater level of 39.7 ng/L. Reported at 52 ng/g in 1 of 7 sewage sludge samples. Levels up to 2.5 ng/L in raw drinking water. Levels reported for rivers (37.5 ng/L) and surface waters (120 ng/L).		(Hübner et al., 2012; Kosma et al., 2014; López-Serna et al., 2013; López-Serna et al., 2012; Peysson and Vulliet, 2013; Stamatis and Konstantinou, 2013; Valcárcel et al., 2013; Zuhlke et al., 2004)

Betaxolol	Up to 9 ng/L in STP influent, 18 ng/L in effluent, and 0.6 ng/L in surface water. Raw drinking water: maximum of 13 and mean of 5 ng/L.	Not detected in: ground waters (López-Serna et al., 2013), rivers or STPs (Dahane et al., 2013; Gros et al., 2009; López-Serna et al., 2011), or STP effluents (Andreozzi et al., 2003; Vázquez et al., 2010). Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b).	(Gabet-Giraud et al., 2013; Huerta-Fontela et al., 2011; Wick et al., 2009)
Bromazepam	Mean and maximum levels in raw drinking water of 14 and 7 ng/L. Infrequently detected in STP influent at mean level of 5 ng/L. Single study reporting ranges of 797-3,662 ng/L* and 104-15,542 ng/L* for STP influent and effluent.	Not detected in STP influent (Repice et al., 2013). Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b). Identified but not quantified in a river (Vystavna et al., 2012). Infrequently detected but not quantified in coastal waters (Munaron et al., 2012). Below MQL in STPs (Sousa et al., 2011). Not detected in surface waters (Hummel et al., 2006).	(Huerta-Fontela et al., 2010, 2011; Salgado et al., 2011)
Buprenorphine	Single study reporting influent levels of 42-195 ng/L in 3 of 25 STPs and effluent level of 40 ng/L in 1 of 25 STPs. Single study reporting infrequent mean influent and effluent levels of 46.6 and 15.2 ng/L. Maximum levels entering and exiting 4 wetlands: 28 and 19 ng/L. Detected at: 15 ng/L in 1 of 13 surface waters, 31-1,000* and 10-47 ng/L in all influents and effluents from 12 STPs, and 21-140 µg/kg in sewage sludge from 4 of 4 STPs.	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b). Not detected in a 7-day sampling study of a single STP (Baker et al., 2012). Not detected at 6 river locations (Baker and Kasprzyk-Hordern, 2011a).	(Baker and Kasprzyk-Hordern, 2011a, 2013; Breitholtz et al., 2012; Fick et al., 2011; Karolak et al., 2010; Nefau et al., 2013)
Bupropion	Mean levels in 15 activated sludge STPs (570 ng/L) and in 6 trickling filter STPs (950 ng/L). Biofilm level downstream from STP: 4.2 µg/kg. Levels in creek samples up to 227 ng/L. Levels of 0.8-5.2 ng/L in effluents from 6 STPs. Maximum levels entering and exiting 4 wetlands: 9 and 16 ng/L. Detected at: 0.46-19 ng/L in all of 13 surface waters, 12-82 and 9.1-41 ng/L in all influents and effluents from 12 STPs, and not detected in sewage sludge from any of 4 STPs.		(Breitholtz et al., 2012; Fick et al., 2011; Grabic et al., 2012; Metcalfe et al., 2010; Schultz et al., 2010; Writer et al., 2013a; Writer et al., 2013b)
Butalbital	Raw sewage sludge: 16.6 ng/g. Single study reporting data for various matrices including STP effluent (up to 42 ng/L) and groundwater (up to 6.6 ng/L). Single study reporting frequent detections with mean level of 1.6 µg/L* in STP influent, maximum level of 69 ng/L in 8 of 27 stream samples. Single study reporting 2 of 18 river	Not detected in ground water at 3 locations (López-Serna et al., 2013), in rivers (Boleda et al., 2013; Gros et al., 2009; López-Serna et al., 2010; López-Serna et al., 2011, 2012), or wastewaters (Gros et al., 2009; Gros et al., 2010).	(Ekberg and Pletsch, 2011; Peschka et al., 2006; Phillips et al., 2010; Rodríguez-Rodríguez et al., 2012)

	samples with 0.88 and 5.3 µg/L*, with others less than 0.29 µg/L.		
Chloramphenicol	Large number of studies, especially in Asia. Wide range of levels in STP influent and effluent, ranging from non-detection to 40 µg/L* and higher; also present in sewage sludge.	Banned in many countries for use in food-producing animals but still widely used illicitly. Also enters the environment from natural sources (Berendsen et al., 2013).	(Chen et al., 2013a; Leung et al., 2012; Liu et al., 2009; Zhou et al., 2013a; Zhou et al., 2013b)
Clindamycin	Large number of studies. Mass fluxes determined in STP influents. Levels in STP influent and effluent ranged from 6.8-13.3 ng/L and 14.9-32.5 ng/L and in biosolids from 3.7-15.4 µg/kg. Various sewage samples up to 120 ng/L. Levels in biosolids: 23.2 µg/kg. Surface waters (21 samples) from a single lake: 31-48 ng/L.	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b).	(Chenxi et al., 2008; Coutu et al., 2013a; Coutu et al., 2013b; Heberer et al., 2008; Siemens et al., 2008; Spongberg and Witter, 2008)
Clofibric	Ubiquitous occurrence - very large number of studies. Levels in: raw drinking water (11.5-20.0 ng/L), tap water (1.2-3.3 ng/L), 3 of 4 sewage sludge samples (24.1-155 ng/g), 4 STP effluents (up to 59.7 ng/L), surface waters (0.4-20 ng/L).	Active metabolite (and API) from multiple prodrug fibrates.	(Boleda et al., 2011a, 2013; Gros et al., 2009; Leung et al., 2013; Yu and Wu, 2012; Zhao et al., 2010)
Codeine monohydrate	Large number of studies. Mean dissolved and particulate-suspended 1-week ranges in STP influents: 164.8-216.9 ng/L and 8.2-14.4 ng/g. Median levels in 11 of 11 STP influents, 10 of 12 STP effluents, and 10 of 11 surface waters: 220, 85, and 38 ng/L. Daily levels over 15 days for STP influents and effluents: 275-335 and 110-124 ng/L.		(Baker et al., 2012; Hummel et al., 2006; Repice et al., 2013; Wick et al., 2009)
Cortisone	Large number of studies. STP influents levels for 2 of 4 monthly samples: 122 and 135 ng/L; none detected in STP effluent. STP influent and effluent: 174 and 229 ng/L. STP influent (45.8 ng/L) but not detected in effluent or sludge.	Cortisone (inactive) interconverted from active form (cortisol). Below LOQ in sewage sludge (Herrero et al., 2013). Product of endogenous biosynthesis. Major topical usage.	(Herrero et al., 2012; Liu et al., 2011; Piram et al., 2008)
Cyclophosphamide	Substantial numbers of studies. Level in 1 of 7 STP sludge samples: 12.5 µg/kg dw. Level in: 1 of 3 STP influents (25.5 ng/L), 1 of 3 STP influents (13.1 µg/L*) and none in the effluents. Other studies report STP levels usually below 200 ng/L.	Median level in 65 hospital effluents: 100 ng/L (Yin et al., 2010a). Not detected in STP effluents after upgrades to three STPs (Moldovan et al., 2009). Not detected in drinking waters or surface waters (Garcia-Ac et al., 2009a; Garcia-Ac et al., 2009b).	(Buerge et al., 2006; Ferrando-Climent et al., 2013; Garcia-Ac et al., 2009a; Gómez-Canela et al., 2012; Llewellyn et al., 2011; Seira et al., 2013; Steger-Hartmann et al., 1996; Ternes et al., 2004)
Dexamethasone	Mean levels of 0.81 ng/L in STP influent and 0.06 ng/g in sludge. Mean levels of 3.8-22.6 ng/L in STP influent and not detectable in sludge. Low levels in STP waters. Levels (combined with betamethasone) 9.0 and 9.4	Epimer of betamethasone (see separate entry) - often determined together. Not detected in STP sludge (Herrero et al., 2013). Levels reported in swine feeding operation (Liu et al., 2012a; Liu et al., 2012c). Levels below 0.07 ng/L in rivers	(Anumol et al., 2013; Fan et al., 2011; Kitaichi et al., 2010; Liu et al., 2011; Piram et al., 2008)

	ng/L in 2 of 4 STPs. Levels in STP influent and effluent: 15 and 7 ng/L.	(Tölgyesi et al., 2010). Major topical usage.	
Diazepam	Review article reporting an upper range of 1.18 µg/L* in STP influent. Reports vary regarding presence in influents and effluents, but generally in the low ng/L range if present. Lake sediments: 0.92 to 4.24 µg/kg. Up to 35 ng/L in ground water. Finished drinking water: 0.33 ng/L.	Not detected in STP influent (Du et al., 2014; Mwenesongole et al., 2013; Repice et al., 2013), groundwater or surface water (Reh et al., 2013), or sewage sludge (Peysson and Vulliet, 2013).	(Benotti et al., 2009; Calisto and Esteves, 2009; López-Serna et al., 2013; Rodríguez-Navas et al., 2013; Sundelin, 2013; Valcárcel et al., 2013; van der Aa et al., 2013; Wilson and Jones-Lepp, 2013)
Diclofenac	Numerous studies reporting near-ubiquitous presence across most matrices, with levels in STPs sometimes exceeding 1 µg/L*.		(Dahane et al., 2013; Du et al., 2014; Kosma et al., 2014; López-Serna et al., 2013; Narumiya et al., 2013; Petrović et al., 2014; Rodríguez-Navas et al., 2013; Stamatis and Konstantinou, 2013; Valcárcel et al., 2013)
Diltiazem	Numerous studies reporting near-ubiquitous presence across most matrices, with levels in STPs sometimes exceeding 1 µg/L*.		(Batt et al., 2008; Du et al., 2014; Grabic et al., 2012; Gros et al., 2012; Rodríguez-Navas et al., 2013)
Diphenhydramine	Numerous studies reporting near-ubiquitous presence across most matrices, with levels in STPs and sludge sometimes exceeding 1 µg/L*.		(Du et al., 2014; Li et al., 2013; Long et al., 2013; Loos et al., 2013; McClellan and Halden, 2010; Wu et al., 2010)
Enalapril	Median levels in STP influent (140-150 ng/L) and effluent (not detected). Levels in 21 STP influents range from 4-28 ng/L. Mean levels in rivers: 3 ng/L. Sub-ng/L levels in ground waters. STP influent levels sometimes exceed 1-10 µg/L*.	Prodrug ester of enalaprilat. Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b).	(Castiglioni et al., 2006; Gracia-Lor et al., 2012; Huerta-Fontela et al., 2010; López-Serna et al., 2013; López-Serna et al., 2011, 2012; Salgado et al., 2012; Salgado et al., 2011; Salgado et al., 2010; Varga et al., 2011)
Ethinylestradiol (ethynylestradiol; EE2)	Numerous studies and abundant data. Because of low-mass usage (high potency), levels trend toward low ng/L range, but can vary widely as a function of national birth control policies. Numerous studies reporting presence especially in STP influents. While levels are generally reported in the ng/L range, some studies have reported STP influent and effluent levels up to 1.6* and 0.48 µg/L, and river levels up to 57 ng/L.		(Huang et al., 2013; Janex-Habibi et al., 2009; Kolpin et al., 2002; Vallejo et al., 2013; Zhou et al., 2012)
Fentanyl	Sporadic levels in STP influents and effluents up to 8.4 ng/L. Levels in surface waters up to 4 ng/L and sewage sludge up to 0.79 µg/kg.	In one study, very low levels reported but not quantified in river sediments (Chen et al., 2013b). Not detected in receiving waters (Baker and Kasprzyk-Hordern, 2013). Some studies report non-detection in STPs (e.g., Baker et al.,	(Baker and Kasprzyk-Hordern, 2011a, 2013; Fick et al., 2011; Grabic et al., 2012; Loos et al., 2013; van der Aa et al., 2013)

		2012; Boleda et al., 2007; Huerta-Fontela et al., 2008a; Huerta-Fontela et al., 2008b; Postigo et al., 2012) and tap water (Boleda et al., 2011b).	
Fluoxetine	Numerous studies reporting near-ubiquitous presence across most matrices. One study reports levels in STP influent and effluent up to 22 ng/L and 21 ng/L. Another study reports levels up to 119 ng/L in receiving waters, in sediment up to 17.4 ng/g ww, and mussel tissue up to 79.1 ng/g ww. Levels in fish tissue up to 1 µg/kg ww.	Additional data is referenced in Barclay et al. (2012 and Oakes et al. (2010.	(Barclay et al., 2012; Bringolf et al., 2010; Chu and Metcalfe, 2007)
Fluvoxamine	Levels in STP influents and effluents up to 3.9 and 0.8 ng/L. Sporadic mean levels of 5.2 and 3.4 ng/L in STP influents and effluents and 23 ng/g in biosolids. Sporadic levels up to 4.6 ng/L in water but not sediment from two creeks.	Not detected in any of 19 STP influents or 16 effluents (Yuan et al., 2013a; Yuan et al., 2013b). Not detected in STP effluents or sludge (Lajeunesse et al., 2013).	(Lajeunesse et al., 2012; Schultz et al., 2010; Vasskog et al., 2008; Vasskog et al., 2006)
Hydrocodone	Levels in 7 STP effluents (28-190 ng/L) and one surface water (10 ng/L); 2 of 11 STP influents (maximum: 95 ng/L), 3 of 12 effluents (47 ng/L), and 8 of 11 surface waters (28 ng/L). STP influents: 59 ng/L and 14-210 ng/L.	Methods may encounter significant cross-interference from hydrocodone and codeine. Not detected in sewage sludge (Peysson and Vulliet, 2013). Not detected in bay water (with one exception at 7.2 ng/L), sediment, or mussels (Klosterhaus et al., 2013).	(Batt et al., 2008; Bisceglia et al., 2010a; Chiaia et al., 2008; Chiu and Westerhoff, 2010; Emery et al., 2010; Hummel et al., 2006; Trenholm et al., 2006; Vanderford et al., 2003)
Hydroxyzine	Mean levels in STP influents: 216-470 ng/L, with a maximum of 1,168 ng/L*. Levels in STP effluents range from 0.5-51 ng/L. Levels in all of 13 surface waters ranged up to 4.8 ng/L and in 4 of 4 sewage sludge samples from 22-39 µg/kg. Low ng/L levels in wetlands.	Metabolism yields cetirizine (an API itself). Recreational use serves as another source. Levels in STP influents are episodic or sporadic, depending often on time of day (e.g., Salgado et al., 2011). Sorption to sewage sludge can be extensive* (Salgado et al., 2012).	(Breitholtz et al., 2012; Fick et al., 2011; Grabic et al., 2012; Hai et al., 2011; Loos et al., 2013; Salgado et al., 2011; Tadkaew et al., 2011)
Ifosfamide	Numerous studies show occurrence primarily in STPs at low ng/L levels. Levels in STP influent and effluents ranging from 9-16.4 ng/L. Single study reporting level in one STP influent of 130 ng/L. Sole report of 41 ng/L in a single receiving water.	Not detected in STPs (Llewellyn et al., 2011; Plósz et al., 2010). Levels highly influenced by hospital contributions (e.g., Yin et al., 2010a).	(Buerge et al., 2006; Ferrando-Climent et al., 2013; Valcárcel et al., 2011; Verlicchi et al., 2012; Yin et al., 2010b)
Ketamine	In 6 of 8 STP effluents (2-28 ng/L) but not influents. Single report of STP influent mean level of 97.2 ng/L. Levels in STP influents roughly between 0.7 and 1 µg/L*. Levels in STP influents and effluents up to 447 and 278 ng/L and in receiving waters up to 53.7 ng/L. Reported in wetlands at mean and maximum levels of 21 and 415 ng/L.	Mass loadings reported for STPs (Lai et al., 2013). Detected in only a few STP samples at very low ng/L levels (Baker et al., 2012; Bijlsma et al., 2013). Other data summarized (Vazquez-Roig et al., 2012).	(Baker and Kasprzyk-Hordern, 2013; Bijlsma et al., 2012; Lai et al., 2013; Mwenesongole et al., 2013; van der Aa et al., 2013; Vazquez-Roig et al., 2012)
Lidocaine (xylocaine; lignocaine)	Daily median levels in STP influent and effluent: 0.14 and 0.16 µg/L. Median	Indirect photolysis is the dominant removal mechanism in surface waters (Rúa-Gómez and	(Majewsky et al., 2013; Peysson and Vulliet, 2013; Rúa-Gómez and

	composite levels in STP influent and effluent: 60 and 51 ng/L. Mean levels in STP effluent (107 ng/L) and maximum range and mean levels in surface waters: 176 ng/ and 131 ng/L. Levels in STP influent and effluent ranged from 70-257 and 55-183 ng/L. Detected in only 1 of 7 sewage sludge samples (147 ng/g).	Püttmann, 2013). Significant topical usage.	Püttmann, 2012; Rúa-Gómez et al., 2012; Rua-Gomez and Puttmann, 2012; Saussereau et al., 2013)
Lorazepam	Below MQL in 12 of 19 and in 8 of 16 STP influents and effluents. Often not detected in STP influent or effluent. Range and mean levels (ng/L) in STP influent and effluent: 221-446 (299) and 175-346 (294). Reclaimed water used for irrigation: 117 ng/L. Levels in river: 87-705 ng/L. Infrequent occurrence in groundwater up to 54 ng/L.		(Gonçalves et al., 2013; López-Serna et al., 2013; Proia et al., 2013; Repice et al., 2013; Santos et al., 2013; Wang and Gardinali, 2013; Yuan et al., 2013a; Yuan et al., 2013b)
Mepivacaine	STP influent and effluent: 15-32 ng/L. Tertiary treated wastewater (30-152 ng/L) and ground waters (4.5-8.4 ng/L). Levels in surface waters downstream of STPs: 3-7 ng/L. Levels in rivers: 9-346 (median 25 ng/L).		(Cabeza et al., 2012; Martínez Bueno et al., 2010; Prieto-Rodriguez et al., 2012; Prieto-Rodríguez et al., 2013; Teijon et al., 2010; Valcárcel et al., 2013; Valcárcel et al., 2011)
Meprobamate	Numerous studies in a wide spectrum of matrices. STP effluent range: 390-2,000 ng/L*. Surface waters up to 13 ng/L. Levels in 4 of 20 public wells: 5.4 ng/L. Routine detection in bay water: 6-36 ng/L. Maximum levels in raw and finished drinking water: 73 and 42 ng/L.	Metabolite of prodrug carisoprodol.	(Benner et al., 2013; Klosterhaus et al., 2013; Saussereau et al., 2013; Schaider et al., 2014; Vidal-Dorsch et al., 2013; Wilson and Jones-Lepp, 2013)
Methadone	Numerous studies in a wide spectrum of matrices. Levels in STP influent and effluent: 16-64 and 6-56 ng/L.	Possibly substantial contributions from illicit usage. Various monitoring studies for sewage, surface waters, ground water, and drinking water are compiled in Pal et al. (2013.	(van der Aa et al., 2013)
Metoprolol	Numerous studies reporting near-ubiquitous presence across many matrices. Levels in STP influents ranging over 1 µg/L*.		(Hernando et al., 2007; Kostich et al., 2014; Narumiya et al., 2013; Petrović et al., 2014; Ratola et al., 2012; Verlicchi et al., 2012)
Metronidazole	Numerous studies. Range (and mean) levels (ng/L) in STP influent and effluent: 44-165 (90) and <LOQ-127 (55). Mean levels in STP influent and effluent: 1,168* and 567 ng/L. Levels in surface waters downstream of STPs: 5-19 ng/L. Levels in river: 0.1-4.5 ng/L. Reclaimed water used for irrigation: 117 ng/L. Routinely detected in Chinese tap	Not detected in ground waters (López-Serna et al., 2013).	(Leung et al., 2013; Margot et al., 2013; Prieto-Rodríguez et al., 2013; Proia et al., 2013; Rosal et al., 2010; Valcárcel et al., 2013; Wang and Gardinali, 2013)

	water: 1.8-19.3 ng/L.		
Minocycline	Studies focus on partitioning to solids because of strong sorption. Maximum and mean levels in sewage biosolids: 2,630 and 1,884 µg/kg* dw. Another study reports a dry-weight range in biosolids of: 351-8,650 µg/kg*. Levels up to 5,622 µg/kg* in sediments.		(Hu et al., 2012; McClellan and Halden, 2010; Stevens, 2010)
Norethindrone (norethisterone)	Numerous studies and abundant data. Because of low-mass usage (high potency), levels trend toward low ng/L range but can vary widely as a function of national birth control policies. Not detected in STP effluent. Drinking water treatment plant: 66% of samples had median and maximum level of 2 and 6.8 ng/L; another study found maximum level of 7.5 ng/L. Biosolids: <7.89 ng/g dw. Mean levels (ng/g) in two samples of sediments, soils, and biosolids: 90&ND, 93&91, and 106&105. Half of surface and ground waters: mean levels of 3.6 and 4.0 ng/L. More than half of surface and ground waters: mean levels of 2.0 and 1.9 ng/L.	Norethindrone acetate is a prodrug form. Not detected in rivers (Al-Odaini et al., 2013b).	(Anumol et al., 2013; Gottschall et al., 2013; Liu et al., 2011; Viglino et al., 2011; Vulliet and Cren-Olivé, 2011; Vulliet et al., 2011)
Norgestrel	Numerous studies and abundant data. Because of low-mass usage (high potency), levels trend toward low ng/L range, but can vary widely as a function of national birth control policies. STP influent: up to 620 ng/L; frequently not detected in STP effluent. Influent and effluent for drinking water treatment: 2.0-10.0 ng/L; another study reports maximum level of 11.1 ng/L. Biosolids: <9.06 ng/g dw. Mean levels (ng/g) in two samples of sediments, soils, and biosolids: 19&ND, 24&52, and 33& 53. Half of surface and ground waters: mean levels of 3.6 and 4.0 ng/L. River up to 22.2 ng/L.	Only the levonorgestrel enantiomer of racemic norgestrel is biologically active, so levonorgestrel is often the targeted analyte.	(Al-Odaini et al., 2013b; Anumol et al., 2013; Fick et al., 2011; Gottschall et al., 2013; Grabic et al., 2012; Guedes-Alonso et al., 2013; Liu et al., 2011; Liu et al., 2012b; Viglino et al., 2011; Vulliet and Cren-Olivé, 2011; Vulliet et al., 2011)
Omeprazole	Despite numerous studies, only a few report positive occurrence data (e.g., Martínez Bueno et al., 2012; Rodríguez-Navas et al., 2013). STP influent and effluent ranges (and means) in ng/L: 57-2,134* (365) and <LOQ-922 (334).	Although omeprazole has been extensively studied, occurrence data are mixed. Many studies report STP levels below the LOD (e.g., Castiglioni et al., 2005; Castiglioni et al., 2006; Gracia-Lor et al., 2010; Jones-Lepp et al., 2004; Pedrouzo et al., 2011). Omeprazole is extensively metabolized to numerous products (Boix et al., 2014).	(Martínez Bueno et al., 2007; Martínez Bueno et al., 2012; Rosal et al., 2010)

Oseltamivir phosphate	Levels during seasonal influenza ranged up to 293 ng/L (STP effluent) and 190 ng/L (receiving rivers).	Oseltamivir (ethyl ester) is an inactive prodrug that is extensively metabolized to the active form (oseltamivir carboxylate) but is stable in STPs (Fick et al., 2007). Monitoring data tends to focus on the more prevalent carboxylate. Oseltamivir also exhibits strong episodic usage (correlated with seasonal influenza).	(Azuma et al., 2012, 2013; Ghosh et al., 2010; Jain et al., 2013; Prasse et al., 2010; Takanami et al., 2010, 2012)
Oxycodone	Reported in effluents from 30 of 50 STPs: 310 ng/L (maximum) and 53 ng/L (mean). Ranges (and median level) in STP influent and effluent (ng/L): 5.1-49.4 (8.6) and 2.0-34.7 (7.0); rivers up to 6.5 ng/L. Two other studies report ranges of 53-150 ng/L and 15-220 in all of 7 STP effluents. Inconsistent presence but maximum levels in biosolids: 157 µg/kg.	Other studies report individual or median levels below LOD in STPs, rivers, sea water, and drinking water (e.g., Baker et al., 2012; Gros et al., 2012; Hummel et al., 2006; Santos et al., 2013).	(Baker and Kasprzyk-Hordern, 2013; Batt et al., 2008; Chari and Halden, 2012; Chiaia et al., 2008; Kostich et al., 2014)
Paroxetine	Numerous studies in many matrices. STP influent: 13 ng/L. Sporadic seasonal presence in drinking water reservoir: 5 ng/L. Mean levels for STP influents up to 16 ng/L. Surface waters up to 90 ng/L. Sewage sludge levels up to 89 ng/g. Biosolids up to 87 µg/kg. Creeks up to 2.2 ng/L.	Not detected in STPs (Kostich et al., 2014; Santos et al., 2013; Yuan et al., 2013a; Yuan et al., 2013b).	(Chari and Halden, 2012; Lajeunesse et al., 2008; Lajeunesse et al., 2012; Metcalfe et al., 2010; Niemi et al., 2013; Peysson and Vulliet, 2013; Radjenović et al., 2009; Schultz and Furlong, 2008; Valcárcel et al., 2013; Verlicchi et al., 2012; Wu et al., 2009)
Pentoxifylline (pentoxifyllin)	Median and maximum levels in freshwaters: 197 and 299 ng/L (compiled from six studies). Maximum (95th percentile level) in rivers: 24.1 ng/L. Infrequent presence in STP effluent at mean level of 0.5 µg/L. Ranges for STP influent and effluent: 98-191 and 56-147 ng/L; and 30-360 ng/L in another study.	Some studies reported levels below LOD for STPs (Moldovan et al., 2009; Moldovan et al., 2007; Snyder, 2008) and rivers (Sacher et al., 2008).	(Chiu and Westerhoff, 2010; Hughes et al., 2013; Kim et al., 2007; Klečka et al., 2010; Lin et al., 2009; Lin et al., 2008; Miège et al., 2009; Moldovan et al., 2007; Slobodnik et al., 2012)
Phenobarbital	Reported in a wide spectrum of matrices. STP effluent levels for 6 STPs: 0.09-0.21 µg/L; sporadic influent levels of 0.04 µg/L. Another study reported STP effluent levels up to 0.36 µg/L and mean of 0.12 µg/L. Reclaimed water used for irrigation: 55.7 ng/L. Municipal groundwater levels up to 47.2 ng/L; another study reported maximum and average groundwater levels of 1.35* and 0.38 µg/L.	Also the major active metabolite from the prodrug primidone (Hass et al., 2012). Not detected in river samples (López-Serna et al., 2010; López-Serna et al., 2011) or STPs (Gros et al., 2010).	(Hass et al., 2012; Hass et al., 2011; López-Serna et al., 2013; van der Aa et al., 2011; Wang and Gardinali, 2013)
Prednisolone	Levels in STP influent: 25-33 ng/L; not detected in effluent. Another study reports ranges (and means) in influent and effluent:	Active metabolite of prednisone. Not detected in effluents from 50 STPs (Kostich et al., 2014). Not detected in STPs, surface waters, sediments,	(Chang et al., 2007; Fan et al., 2011; Herrero et al., 2013; Herrero et al., 2012; Liu et al., 2012b;

	1.5-7.5 (3.0) and 0.47-0.72 (0.56) ng/L. Levels in dewatered sewage sludge: 0.4-48.9 µg/kg.	or sewage sludge (Baranowska and Kowalski, 2012; Huerta-Fontela et al., 2010; Liu et al., 2011; Pérez-Carrera et al., 2010). Many studies focus on hospital wastewater (e.g., Kovalova et al., 2012; Schriks et al., 2010) and animal (e.g., swine) farms (e.g., Liu et al., 2012c).	Tölgyesi et al., 2010)
Propranolol	Numerous studies reporting near-ubiquitous presence across most matrices, including STPs (generally at levels of tens of ng/L), sewage sludge and biosolids, surface water, ground water, coastal water, drinking water, and aquatic biota.	Often the most frequently detected and most abundant beta-blocker. Sorption may play a major role in determining fate (Maskaoui and Zhou, 2010).	(Claessens et al., 2013; Gabet-Giraud et al., 2013; Gottschall et al., 2012; Kostich et al., 2014; López-Serna et al., 2013; Maskaoui and Zhou, 2010; Petrović et al., 2014; Salem et al., 2012)
Risperidone	STP effluents: 85.8 ng/L (maximum) and 6.9 ng/L (mean). Levels in 6 of 6 STP effluents: 3.1-22 ng/L. STP influent and effluent approximate maximum levels: 1,900* and 10 ng/L. Sea water (30% occurrence): 1.4 ng/L (maximum). Finished drinking water: 2.9 ng/L (maximum).	Detected in hospital effluents but not municipal STPs (Gracia-Lor et al., 2010, 2011; Gracia-Lor et al., 2012; Vanderford and Snyder, 2006; Yuan et al., 2013b). Sorption may play a major role in determining fate (Stevens-Garmon et al., 2011).	(Benotti et al., 2009; Loos et al., 2013; Tadkaew et al., 2011; Vidal-Dorsch et al., 2012)
Sertraline	Numerous studies reporting widespread occurrence across many matrices. Effluents from 50 STPs (ng/L): 21 (mean) and 71 (maximum). STP effluents: up to 2,190* ng/L. Mean levels in biosolids (ng/kg ww): 230 and 63,000. Creek water and sediments (maximum): 37.5 ng/L and 17.7 ng/g.	Not detected in STPs (Yuan et al., 2013a; Yuan et al., 2013b). Many studies focus on levels in aquatic biota (e.g., Gelsleichter and Szabo, 2013; Subedi et al., 2012).	(Kostich et al., 2014; Metcalfe et al., 2010; Niemi et al., 2013; Sagristà et al., 2012; Schultz et al., 2010; Togunde et al., 2012)
Sildenafil	Levels (and medians) in STP influent and effluent (ng/L): 4.7-349.5 (15.0) and 5.1-28.6 (9.7). Rivers up to 2.9 ng/L. Maximum levels (and means) in influent and effluent (ng/L) from 7 STPs: 49.8 (24.9) and 10.2 (7.0). Levels in sewage sludge up to about 17 ng/g.	Up to 20% sorbs to STP suspended particulates (Baker and Kasprzyk-Hordern, 2011b; Baker et al., 2012). Not detectable in rivers (Baker and Kasprzyk-Hordern, 2011a).	(Baker and Kasprzyk-Hordern, 2011a, 2013; MacLeod and Wong, 2010; Nieto et al., 2010; Schröder et al., 2010)
Tamoxifen	Levels in 4 of 8 STP influents: 3.5-17.2 ng/L. Levels in 3 STP influents: 30-58.3 ng/L. River: 12.4-20.1 ng/L. Groundwater: 6-16.5 ng/L. Coastal tidal sediments: 212-431 ng/g dw.	Also see references cited in Besse et al. (2012 and López-Serna et al. (2012.	(Ferrando-Climent et al., 2013; López-Serna et al., 2012; Negreira et al., 2013; Reh et al., 2013; Yang et al., 2011)
Temazepam	Frequently detected in STPs. Levels (and means) in 8 of 8 STP influents and effluents: 255-813 (427) and 389-1,016* (568) ng/L; 12 of 14 surface waters: 3-32 (12) ng/L; and 7 of 17 drinking waters: 1-10 (4) ng/L. Levels (and medians) in 100 of 109 STP	Active metabolite of diazepam (see separate entry) and also yields the active metabolite oxazepam.	(Baker and Kasprzyk-Hordern, 2011a, b, 2013; Bijlsma et al., 2012; Houtman et al., 2013; MacLeod and Wong, 2010; van der Aa et al., 2013)

	influents and effluents: 16.8-254.7 (84.9) and 16.9-249.5 (78.6) ng/L; maximum level in receiving waters: 77.8 ng/L. Range of means for STP influents and effluents from 5 cities: 164-297 and 233-406 ng/L.		
Timolol	Frequently detected in STPs. Levels (and median) from 3 STP effluents: 1.5-9.5 (3.6) ng/L. Levels for influents and effluents from 3 STPs: 7.4-11 and 4.2-6.8 ng/L; another study reports 32 and 58 ng/L. Levels (and means) for 18 samples from 3 locations in a river: 1.2-153.5 (14.7), 1.9-2.9 (1.8), and 2.2-10.3 (6.8) ng/L. Infrequently detected in groundwater, with a maximum of 3.88 ng/L. Infrequently detected in suspended solids: up to 1.84 ng/g.	Not detected in sewage sludge (Ginebreda et al., 2012) or rivers (López-Serna et al., 2010; Silva et al., 2011).	(Gabet-Giraud et al., 2010; Gabet-Giraud et al., 2013; Ginebreda et al., 2012; López-Serna et al., 2013; López-Serna et al., 2012; Piram et al., 2008; Proia et al., 2013; Silva et al., 2011)
Tramadol	Frequently detected in STPs. STP effluents: 1,166 ng/L* (maximum) and 256 ng/L (mean). Levels (and medians) in 100 of 109 STP influents and effluents: 204.7-4,631* (1,123) and 86.2-1,603* (739) ng/L; maximum level in receiving waters: 539 ng/L. Unusually high level (and mean) in STP influents and effluent: 86 (32) µg/L* and 57 (20) µg/L*. Levels in 3 of 7 sewage sludge samples: 33-43 ng/g.		(Baker and Kasprzyk-Hordern, 2013; Grabic et al., 2012; Loos et al., 2013; Peysson and Vulliet, 2013; Rúa-Gómez and Püttmann, 2012; Rua-Gomez and Puttmann, 2012; Verlicchi et al., 2012)
Venlafaxine	Numerous studies. Frequently detected in a wide range of matrices, especially STPs at levels exceeding 1 µg/L*. STP effluent and influent: mean levels up to 2,190 ng/L*; surface waters: up to 1,310 ng/L*. Creeks: up to 690 ng/L. STP sludge: 0.97-24.2 ng/g dw.	Environmental levels sufficient to possibly be toxic to certain plants (Feito et al., 2013).	(Gracia-Lor et al., 2011; Rua-Gomez and Puttmann, 2012; Santos et al., 2013; Saussereau et al., 2013; Schultz et al., 2010; Subedi et al., 2013; Writer et al., 2013b)
Limited occurrence data [4]			
Alfuzosin	Comparatively low levels in wide range of matrices.		(Breitholtz et al., 2012; Fick et al., 2011; Näslund, 2010; Nordic Council of Ministers, 2012; Verlicchi and Zambello, 2014)
Betamethasone	Mean levels of 3.45 ng/L in bay water, 1.24 ng/g ww in mussel tissue, and not detected in bay sediment. Sporadic levels up to 27 and 17 ng/L in STP influent and effluent. Sporadic mean levels up to 145 ng/L in STP influent.	C-16 epimer of dexamethasone (see separate entry) - often determined together. Not detected in six STP influents, effluents, or biosolids (Guerra et al., 2014). Targeted in surface waters but not reported (Iglesias et al., 2014). Targeted in large-scale monitoring campaign of effluents from 50 STPs but data not reported because of	(Kitaichi et al., 2010; Klosterhaus et al., 2013; Piram et al., 2008; Salgado et al., 2011)

		quality assurance problems (Kostich et al., 2014). Major topical usage.	
Biperiden	Low levels in a spectrum of matrices. STP effluents: maximum of 2.4 ng/L (mean 0.1 ng/L). Levels in 6 of 6 STP effluents: 0.2-11 ng/L.		(Chen et al., 2013b; Fick et al., 2011; Grabic et al., 2012; Loos et al., 2013; Rutgersson et al., 2013)
Budesonide	In a single study, mean levels in STP influents and effluents ranging from 26-70 ng/L and <LOD-289 ng/L, and highest levels of 270 ng/L and 455 ng/L; levels higher in STP effluents than influents. In another study, levels in 3 of 6 STP effluents: 28-96 ng/L.	In other studies, all levels ranged from non-detectable to low ng/L (e.g., Verlicchi and Zambello, 2014).	(Grabic et al., 2012; Kosma et al., 2014; Møskeland, 2006; Piram et al., 2008; Salgado et al., 2011)
Chlorpromazine	Maximum of 10 ng/L in raw drinking water. Detected at: 5.1-68 ng/L in 6 of 12 STP influents and 9.6-20 ng/L in 4 of 12 STP effluents, and 8.1 µg/kg in 1 of 4 STP sewage sludges. Detected in 45% of river samples in range 0.9-2.6 ng/L (median 2.2 ng/L). STP effluent levels up to 11 ng/L.	Below MQL or not detected in STP influent and effluent (Borova et al., 2014; Yuan et al., 2013b). In one study, very low levels reported but not quantified in river sediments (Chen et al., 2013b). Not detected in all of 13 surface waters (Fick et al., 2011) or river samples (Nakada et al., 2007). Not detected in Nairobi River basin (Kenya) (K'oreje et al., 2012). Rarely reported in STP effluents (1% frequency at 10.4 ng/L) (Loos et al., 2013).	(Fernández et al., 2010; Fick et al., 2011; Huerta-Fontela et al., 2011; Roberts and Bersuder, 2006)
Cilazapril	Levels in one study generally below 10 ng/L in sewage influent and effluent. Another study reports infrequent STP effluent levels of 2.2 ng/L (maximum) and 0.1 ng/L (mean). Levels in 2 of 6 STP effluents: 2.2 and 7.1 ng/L.	Prodrug ester of cilazaprilat. Sub-mg/L levels in fish plasma. Rarely reported in STP effluents (4% frequency at maximum of 2.2 ng/L) (Loos et al., 2013).	(Fick et al., 2011; Fick et al., 2010; Grabic et al., 2012; Loos et al., 2013)
Clomipramine	Levels of 0.8-8.6 ng/L in 4 of 6 STP effluents, mean of 4 ng/L in 7 of 15 STP effluents, 27 ng/L in 1 of 75 drinking water samples, 3-6 ng/L in influent to wetlands. Detected at: 0.52-1 ng/L in 4 of 13 surface waters, 0.83-8.1 µg/kg in 3 of 7 biota samples, 0.81-72 ng/L in all influents and effluents from 12 STPs, and 36-46 µg/kg in sewage sludge from 4 of 4 STPs. Levels in effluent from three STPs: 77.5-101.7 ng/L.	Below MQL in STPs (Urtiaga et al., 2013; Yuan et al., 2013b). Infrequently detected in STP effluent (20% frequency at maximum of 3 ng/L) (Loos et al., 2013). Detected in STP effluent (67% frequency) and rivers (27% frequency) (Gómez et al., 2012). Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b). Below MQL in rivers (Valcárcel et al., 2011). Not detected in wetlands (Näslund, 2010) or residential canal (Ge and Lee, 2013).	(Breitholtz et al., 2012; Esteban et al., 2012; Fick et al., 2011; Grabic et al., 2012; Sheng et al., 2014)
Clonazepam	Levels of 12-30 ng/L in 5 of 6 STP effluents. Levels of 8.5-30 µg/kg in 4 of 4 sewage sludge samples but absent from STP influent and effluents.	Infrequently reported in STP effluents (9% frequency at mean of 1.6 ng/L and maximum of 43.7 ng/L) (Loos et al., 2013). Mean levels in emergency and general hospital effluent: 57 and 134 ng/L (de Almeida et al., 2013). Not detected in hospital effluent or in STP influents or	(Fick et al., 2011; Grabic et al., 2012)

		effluents (Yuan et al., 2013a; Yuan et al., 2013b). Not detected in wetlands (Näslund, 2010). Not detected in 21 surface water sites (Fedorova et al., 2014b).	
Cyproheptadine	One study reports up to 49 ng/L in 3 of 12 STP influent samples, 17 ng/L in 4 of 12 effluent samples, and 5.3 µg/kg in 1 of 4 sludge samples. Second study reports STP effluents: 325 ng/L (max) and 3.9 (mean). Third study reports 5.3 ng/L in 1 of 6 STP effluents.	Rarely reported in STP effluents (2% frequency at mean of 3.9 ng/L and maximum of 325 ng/L) (Loos et al., 2013).	(Fick et al., 2011; Grabic et al., 2012; Loos et al., 2013)
Dilevalol (reported as racemic labetalol)	No data for dilevalol as the single enantiomer. Data reported for the racemic labetalol. Levels in 4 of 6 STP influents (271-480 ng/L) and 3 of 6 effluents (155-309 ng/L). STP influent: 220 ng/L. STP effluent: 64-279 ng/L. Raw drinking water: 16 ng/L (maximum) and 6 ng/L (mean). Maximum level in 14% of raw drinking waters: 16 ng/L.	One of 4 stereoisomers of labetalol, for which levels in STPs have been reported (Lee et al., 2007); withdrawn from UK in 1990. Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b). Not detected in finished drinking water (Benner et al., 2013).	(Benner et al., 2013; Huerta-Fontela et al., 2010, 2011; Lee et al., 2007; Saussereau et al., 2013)
Dosulepin (dothiepin)	Single study reports levels in STP influents and effluents of 17-673 ng/L and 3-125 ng/L, and in receiving waters of 5-32 ng/L. Two studies reported sorption to STP suspended particulates up to 299 ng/g. STP loadings over 7 days of sampling range from 32.5-49.0 g/day (84.6-126 mg/day/1,000 people).		(Baker et al., 2013; Baker and Kasprzyk-Hordern, 2011a, b, 2013; Baker et al., 2012)
Doxepin	Levels in 2 of 7 sewage sludge samples: 17 and 60 ng/g. Maximum median levels in STP influent and effluent (150 and 170 ng/L) and surface water (54 ng/L); levels in some effluents above 500 ng/L.	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b). Not detected in rivers (Vystavna et al., 2012). Not detected in STP effluent, surface water, or drinking water (Rabiet et al., 2006; Togola and Budzinski, 2008).	(Borova et al., 2014; Hummel et al., 2006; Peysson and Vulliet, 2013; Wick et al., 2009)
Duloxetine	Levels in 4 of 12 STP influents range from 1-11 ng/L and in 7 of 12 STP effluents from 1.5-14 ng/L. Infrequent occurrence in STP effluent (maximum: 6.3 ng/L). Levels in wet sewage biosolids up to 40 ng/kg ww and in dry biosolids 2.3 µg/kg.	Not detected in water and sediment near fish nesting (Kolpin et al., 2013) or in any of 13 surface waters (Fick et al., 2011). Not detected in effluent-dominated creeks (and sediments) or fish brains (Schultz et al., 2010). Not detected in rivers (Alvarez et al., 2008).	(Grabic et al., 2012; Kinney et al., 2012; Loos et al., 2013; Niemi et al., 2013; Schultz and Furlong, 2008)
Escitalopram	Erratic detection in STP influent, with sporadic levels ranging up to 1.1-32.2 µg/L*. Range for 3 of 7 sewage sludge samples: 144-313 ng/g. Detected in passive sampling of river.	Active enantiomer (eutomer) of citalopram, for which extensive occurrence data exist – generally with levels less than 1 µg/L (e.g., Boleda et al., 2014; Borova et al., 2014; Collado et al., 2014; Writer et al., 2013b; Yuan et al., 2013b).	(Liscio et al., 2014; Peysson and Vulliet, 2013; Salgado et al., 2011)

Finasteride	Levels in 2 of 6 STP influents: 11-23 ng/L. Levels in 2 of 13 surface waters (12-42 ng/L), 5 of 12 STP influents and effluents (12-28 and 12-20 ng/L). Low ng/L levels in wetlands.	Not detected in sewage sludge (Fick et al., 2011) or wastewaters (Näslund, 2010).	(Breitholtz et al., 2012; Fick et al., 2011; Grabic et al., 2012; Hey et al., 2012; Liu et al., 2010)
Flunitrazepam (rohypnol, rohipnol)	Lake sediment: 0.19 to 0.71 µg/kg; up to 17 ng/L in STP influent but not other matrices; other studies report non-detection.	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b). The metabolite 7-aminoflunitrazepam is sometimes reported. Illegal abuse may contribute significantly to environmental levels.	(Fick et al., 2011; Helmfrid and Eriksson, 2010; Östman et al., 2014; Sundelin, 2013; van der Aa et al., 2011)
Fluorouracil (5-FU)	Review article (Straub, 2010). Single study with levels in STP influent up to 14 ng/L. Single study: range in 20 samples from rivers (5-160 ng/L) and STP influent (280 ng/L) and effluent (80 ng/L).	Active metabolite and API from its prodrug capecitabine (see separate entry). Non-detection in STPs (e.g., Martín et al., 2014; Martín et al., 2011b; Tauxe-Wuersch et al., 2006; Yu et al., 2012) may result from insufficient LODs (Johnson et al., 2013). Most monitoring done on hospital waste streams (e.g., see: Kosjek and Heath, 2011; Lin et al., 2014; Mahnik et al., 2007; Mahnik et al., 2004; Mullot et al., 2009).	(Kosjek et al., 2013; Lin et al., 2014)
Fluvastatin	Levels in influents and effluents from 1 of 2 STPs: 43 and 12 ng/L.	Not detected in STPs (Martín et al., 2011a; Santos et al., 2013), rivers (Gros et al., 2012), or raw drinking water (Helmfrid and Eriksson, 2010). Targeted in STPs but not reported (Petrović et al., 2014).	(Gros et al., 2012; Paxéus, 2011)
Labetalol	Levels in STP effluents ranged from 64-279 ng/L; another study reported influent levels of 271-480 ng/L and maximum effluent of 309 ng/L. Mean level in raw drinking water: 6 ng/L. Detected in 14% of raw drinking waters: 16 ng/L (maximum) and 6 ng/L (mean).	In one study, low levels reported but not quantified in river sediments (Chen et al., 2013b).	(Huerta-Fontela et al., 2010, 2011; Lee et al., 2007; Salem et al., 2012; Saussereau et al., 2013)
Levamisole	Ranges in STP influents and effluents: 7-48 and 8.7-80 ng/L. STP effluent maximum and mean levels of 340 and 40.6 ng/L. Levels up to 54 ng/L in rivers. Sporadically detected in surface water: 1.5 ng/L.	Veterinary use. Also may be used as a cutting agent for illicit cocaine.	(Collado et al., 2014; Gros et al., 2012; Loos et al., 2013; Petrović et al., 2014; Santos et al., 2013; Zrnčić et al., 2014)
Maprotiline	Four studies reported levels: below LOD in STP effluents; 16.5 ng/L (maximum), and 0.4 ng/L (mean); up to 52 ng/L in 9 of 12 STP influents, up to 27 ng/L in 6 of 12 STP effluents, and 5.2 µg/kg in 1 of 4 dewatered sewage sludges; and up to 2 ng/L in wetlands.		(Breitholtz et al., 2012; Fick et al., 2011; Grabic et al., 2012; Loos et al., 2013)
Methylphenidate	STP influent mean levels up to 9.4 ng/L. Loadings in 94% of STPs in range 1-25 mg/day/1,000 people.	Possibly substantial contributions from illicit recreational usage (e.g., see: Burgard et al., 2013). Not detected in STPs, presumably	(Du et al., 2014; Östman et al., 2014; van der Aa et al., 2013)

		because of extensive metabolism to ritalinic acid (Letzel et al., 2010). Not detected in 21 surface water sites (Fedorova et al., 2014b).	
Mianserin	Levels up to 65 ng/L and 61 ng/L in STP influents and effluents; up to 94 µg/kg in sewage sludge; 2.2 ng/L in 1 of 6 drinking water samples; up to 110 ng/L in wetlands. STP effluent (ng/L): 62.3 (max) and 1.5 (mean).	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b). Not detected in 21 surface water sites (Fedorova et al., 2014b). Not detected in raw drinking water (Helmfrid and Eriksson, 2010). Not approved for use in the US.	(Breitholtz et al., 2012; Fick et al., 2011; Fick et al., 2010; Grabic et al., 2012; Ho et al., 2007; Loos et al., 2013; Näslund, 2010)
Mirtazapine	STP influent and effluent levels up to 870 and 410 ng/L; up to 210 ng/L in surface waters; up to 120 µg/kg in sewage sludge. Levels from three STPs ranging from 62.8-84.2 ng/L.	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b).	(Borova et al., 2014; Fick et al., 2011; Gómez et al., 2012; Grabic et al., 2012; Lajeunesse et al., 2013; Lajeunesse et al., 2012; Sheng et al., 2014)
Norgestimate	No positive occurrence data. Limited studies report non-detection in a variety of matrices.	Acts as prodrug for levonorgestrel-3-oxime (norelgestromin) and other progestins. Not detected in STPs, biosolids [except for a solitary report: (Chari and Halden, 2012)], or surface waters. Reported in 2 of 10 samples of feather meal: 21-29 ng/g (Love et al., 2012).	(Emery et al., 2010; Lubliner et al., 2010; Stevens, 2010; USEPA, 2009; Walters et al., 2010)
Nortriptyline	STP influent and effluent: 4.7-27 and 2.9-25 ng/L; biosolids: 90 ng/g. STP influent and effluent ranges (and medians) in ng/L: 6.9-185.8 (22.6) and 0.9-53.8 (7.6). Levels from three STPs ranging from 35.1-47.8 ng/L. Ranges in 6 rivers downstream of STPs: 0.1-19 ng/L. STP loadings over 7 days of sampling range from 7.4-12.3 g/day (76.6-127 mg/day/1,000 people).	Active metabolite (N-desmethyl amitriptyline) of amitriptyline. Sorbs to wastewater-suspended particulates – up to 37.6 ng/g (Baker and Kasprzyk-Hordern, 2011b; Baker et al., 2012).	(Baker et al., 2013; Baker and Kasprzyk-Hordern, 2011b, 2013; Ho et al., 2007; Lajeunesse et al., 2013; Lajeunesse et al., 2008; Lajeunesse et al., 2012; Sheng et al., 2014)
Orphenadrine	Levels up to 180 and 81 ng/L in STP influent and effluent, 28 ng/L in surface waters, 2.2 µg/kg in biota, and 22 µg/kg in sewage sludge. STP effluents (ng/L): 46.7 (max) and 3.9 (mean). Levels up to 0.9 ng/mL in fish plasma. Levels up to 13 ng/L in wetlands.	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b).	(Breitholtz et al., 2012; Fick et al., 2011; Fick et al., 2010; Loos et al., 2013)
Oxprenolol	Multiple studies consistently report mean levels of 10-27 ng/L in STP effluent and 0.3 ng/L in receiving waters. STP effluent: 20 ng/L (mean) and 32 ng/L (maximum); surface waters: 1.3 ng/L (mean) and 3.4 ng/L (maximum). Several report absence in STP effluent and receiving waters.	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b).	(Andreozzi et al., 2003; Gabet-Giraud et al., 2010; Gabet-Giraud et al., 2013; Jacquet et al., 2012; Miege et al., 2006; Petrović et al., 2005; Verlicchi et al., 2012)
Pantoprazole	STP effluent (50-180 ng/L, median 130 ng/L) but not detected in STP influent. Rivers (4-7 ng/L) and surface waters	Not detected in STP influent (van Nuijs et al., 2010) or groundwater below rivers (Reh et al., 2013).	(Gracia-Lor et al., 2010, 2011; Gracia-Lor et al., 2012; Nödler et al., 2010; Varga et al., 2011)

	(maximum: 117 ng/L).		
Pefloxacin	Maximum levels for 4 of 18 surface waters (64 ng/L) and 1 of 19 STP effluents (112 ng/L). Coastal waters of Yellow Sea: 0.43-14.6 ng/L. Levels in Chinese STPs: influents (8-93 ng/L) and effluents (<LOD-10 ng/L).	Not detected in STPs (Gracia-Lor et al., 2012; Lin et al., 2008). Not detected in manured soils (Hu et al., 2010). Possibly significant sorption to sludge (Zhou et al., 2013a; Zhou et al., 2013b; Zhou et al., 2013c).	(Gracia-Lor et al., 2011; Na et al., 2011; Shi et al., 2009)
Phenylbutazone	STP influent and effluent: 6 and 3 ng/L. Maximum and mean levels in a river: 50.9 and 11 ng/L. Mean levels (ng/L) in: rivers (40), ground water (36), STP influent and effluent (106 and 100). Three raw drinking water samples: 87 ng/L (mean) and range 67–98 ng/L. Values from one study (ng/L): STP influent (106) and effluent (52), river (41 in 1 of 3 samples), groundwater (11-52 in 4 of 6 samples), and STP lagoon (28).	In the US and UK, veterinary use only. Not detected in pond sediments, sewage sludge, or river (Azzouz and Ballesteros, 2012; López-Serna et al., 2010; López-Serna et al., 2011), or STP effluents (Gros et al., 2009; Gros et al., 2010). Targeted in STPs but not reported (Lara-Martín et al., 2014).	(Azzouz and Ballesteros, 2013; Galletti, 2010; López-Serna et al., 2012; Verlicchi et al., 2012)
Promethazine	STP influent and effluent up to 190 ng/L (in 8 of 12 samples) and 86 ng/L (in 5 of 12 samples). Sewage biosolids: 22 µg/kg. Maximum levels entering and exiting 4 wetlands: 6 ng/L.	Not detected in effluents from 50 STPs (Kostich et al., 2014) or surface waters (Emery et al., 2010; Fick et al., 2011; Nakada et al., 2007).	(Batt et al., 2008; Breitholtz et al., 2012; Chari and Halden, 2012; Fick et al., 2011)
Ramipril	Infrequently detected in STPs (but 3 of 48 STP samples ranged up to 2,265 ng/L*; 1 of 10 influents: 5,445 ng/L*; 1 of 9 sludge samples: 488 ng/g). River samples: 2-5 ng/L.	Prodrug ester of ramiprilat. Not detected in STPs (González, 2012), surface waters (Rodríguez-Navas et al., 2013), or raw drinking water (ANSES, 2011; Helmfrid and Eriksson, 2010). Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b).	(Paxéus, 2011; Salgado et al., 2011; Salgado et al., 2010; Varga et al., 2011)
Secobarbital (quinalbarbitone)	Single study reporting levels in surface water up to 100 ng/L. Isolated report of 30 µg/L* in STP effluent.	Not detected in surface or drinking waters, or STPs (Boleda et al., 2014; Boleda et al., 2011a, 2013). Single study: non-detection in 17 STP samples (Terzic et al., 2008).	(Hug et al., 2014; Peschka et al., 2006; Schwarzbauer and Ricking, 2010; Yu et al., 2012; Yu et al., 2006)
Thioridazine	Multiple studies reporting very low ng/L levels in STPs and surface waters, as well as non-detection. STP influent and effluent levels (ng/L): 35-43 and 22-33; river levels: 53-265 ng/L.	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b). Usage has dropped because of severe adverse reactions.	(Długołęcka, 2007; Grover, 2012; Helmfrid and Eriksson, 2010; Paxéus, 2011; Woldegiorgis et al., 2007; Zhang et al., 2008; Zhang and Zhou, 2007; Zhou and Broodbank, 2014; Zhou et al., 2009)
Triamcinolone	Below LOD in STPs. Single study reported STP influent and effluent levels of 31 and 20 ng/L.	Glucocorticogenic activity of surface waters reported by Schriks et al. (2013). Major topical usage. Not detected in rivers receiving STP discharge (Sengupta et al., 2014).	(Anumol et al., 2013; Piram et al., 2008; Tölgyesi et al., 2010)
Triamcinolone acetonide	Below LOD in STPs. Single study reported	Detected in hospital wastewaters below 40 ng/L	(Herrero et al., 2012; Kitaichi et

	STP influent and effluent levels of 40 and 3 ng/L.	(Schriks et al., 2010). Major topical usage.	al., 2010; Piram et al., 2008; Tölgyesi et al., 2010)
Vardenafil	Single studies reporting levels in: STP influent and effluent up to 16 and 9 ng/L, STP influent and effluent up to 20 and 5 ng/L, and sporadically in sludge.	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b).	(MacLeod and Wong, 2010; Nieto et al., 2010; Schröder et al., 2010)
Verapamil	Mean levels in STP influent and effluent: 4.1 and 2.2 ng/L. Infrequently detected in STP effluent: maximum of 16.5 ng/L. In all of 12 STP influents: 14-110 ng/L. In 9 of 12 STP effluents: 11-29 ng/L. In 1 of 4 STP digested sludges: 18 µg/kg; in 15 of 16 STP sludges up to 16.8 ng/g dw. In 2 of 13 surface waters: 19-20 ng/L.	Not detected in a range of matrices, including STPs (Grabic et al., 2012; Gros et al., 2012). Targeted in STPs but not reported (Petrović et al., 2014). Routinely detected in STPs and significant variability in removal over year (Golovko et al., 2014).	(Fick et al., 2010; Loos et al., 2013; Santos et al., 2013; Subedi et al., 2013)
Zolpidem	Multiple studies reporting: non-detection in sewage sludge except for one sample (38 ng/g); levels of 4.2-44 ng/L in 12 STP influents and 2.9-41 ng/L in effluents; 7-17 ng/L in 3 of 6 STP effluents; less than 3 ng/L in STPs; 5 µg/g* in aquatic sediments; up to 6 ng/L in raw drinking water; up to 6 ng/L in surface waters. Detected in 29 of 33 STPs with highest daily load of 5.6 mg/1,000 people. Levels in estuaries from non-detects to about 5 ng/L.	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b). One study did not detect in influents or effluents from 6 STPs (Huerta-Fontela et al., 2010). Detected in 29 of 33 STP effluents at loading of 5.6 mg/1000 inhabitants/day (Östman et al., 2014). Detected in 18 of 21 surface water sites using passive sampling (Fedorova et al., 2014b).	(Długołęcka, 2007; Fick et al., 2011; Grabic et al., 2012; Huerta-Fontela et al., 2011; Jakobsen, 2009; Loos et al., 2013; Östman et al., 2014; Paxéus, 2011; Peysson and Vulliet, 2013; Sousa et al., 2011; Terzic and Ahel, 2011; Togola et al., 2008; Woldegiorgis et al., 2007)
Zopiclone (zoplikon)	Single studies reporting: 13 ng/L in leachate from a landfill but non-detection in 2 STPs and groundwater; levels up to 1 mg/kg* in sludge from 6 STPs.	In US available only as the stereoisomer eszopiclone (see separate entry), for which published occurrence data is lacking. Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b). Not detected in STPs (Woldegiorgis et al., 2007) or raw drinking water (Helmfrid and Eriksson, 2010).	(Długołęcka, 2007; González, 2012; Møskeland, 2006; Paxéus, 2011; Sundstøl Eriksen et al., 2009)
Paucity of occurrence data - possible MEOCs [5]			
Abacavir sulfate	Reported in one study. Levels up to 225 ng/L in STP influent. Not detectable in STP effluent.		(Prasse, 2012; Prasse et al., 2010)
Acarbose	*none available*		*none available*
Acetohexamide	*none available*		*none available*
Alfacalcidol (1-hydroxycholecalciferol)	*none available*		*none available*
Alfentanil	*none available*	Targeted in a single study but not reported (Fakhari et al., 2011).	*none available*
Aliskiren	*none available*		*none available*

Alosetron	*none available*	Restricted use in the US.	*none available*
Alprenolol (alfeprol, alpheprol, alprenololum)	STPs targeted in a few studies but not detected. Reported occurrence in river sediments.	Levels ranged from not detected to low ng/L.	(Basheer et al., 2010; Chen et al., 2013b; Lee et al., 2007; Salem et al., 2012)
Ambrisentan	*none available*		*none available*
Ambroxol	Surface waters and STP effluents.	Very low ng/L levels or not detected.	(BLAC, 2003; Sadezky et al., 2008)
Amifostine	*none available*		*none available*
Amoxapine	*none available*		*none available*
Amsacrine	*none available*		*none available*
Anastrozole	Sub-ng/L levels in STP influents and one effluent (single study).		(Liu et al., 2010)
Anhydrovinblastine (anhydrovincaleukoblastine)	*none available*		*none available*
Apomorphine	*none available*	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b).	*none available*
Asenapine	*none available*		*none available*
Atomoxetine (formerly tomoxetine)	*none available*		*none available*
Azathioprine	Only targeted in two studies: 19 ng/L in STP influent; low ng/L levels in STP effluents.	Prodrug of 6-mercaptopurine and rapidly metabolized.	(Ferrando-Climent et al., 2013; Yin et al., 2010a)
Bambuterol	*none available*		*none available*
Benazepril	*none available*	Prodrug ester of benazeprilat. Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b).	*none available*
Bendamustine	*none available*	Sorption to sewage sludge likely (Booker et al., 2014).	*none available*
Benidipine (benidipinum)	*none available*	Licensed for use only in Japan and certain Southeast Asian countries.	*none available*
Benserazide	*none available*		*none available*
Benznidazole	*none available*		*none available*
Bepridil	Solitary report of detection in passive sampling of rivers.		(Liscio et al., 2014)
Beraprost	*none available*		*none available*
Bimatoprost	*none available*	Ophthalmic and topical drug	*none available*
Bopindolol	*none available*	Prodrug ester of pindolol, which has abundant occurrence data.	*none available*
Bortezomib	*none available*	Not detected in various waters and sediments (Schlabach et al., 2009).	*none available*
Brimonidine	*none available*	Ophthalmic drug.	*none available*

Bromocriptine (bromocriptin)	Low ng/L levels (or targeted but not detected) in STP influent but not other matrices.	Low usage levels. Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b). Generally not detected in wetlands (Breitholtz et al., 2012). Possibly displays strong sorption (Hörsing et al., 2011).	(Fick et al., 2011; Woldegiorgis et al., 2007)
Bromperidol	*none available*		*none available*
Buflomedil	Solitary report of levels in STP influent and effluent: 360 and 90 ng/L.	Use suspended in EU; not approved in the US.	(Saussereau et al., 2013)
Bupivacaine	Solitary study of levels in river up to 0.69 µg/L; levels approaching undetectable in nearly all samples in rivers, lake, and sediments.	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b).	(Bernard and Arnold, 2011; Bernard et al., 2012; Edder et al., 2008; Ortelli et al., 2009)
Busulfan (busulphan)	*none available*		*none available*
Butabarbital	Solitary study. Contaminated groundwater below legacy landfill: maximum values of 0.7-2.2 µg/L* and median values approaching 1 µg/L*.		(Stuart et al., 2014)
Butorphanol	*none available*		*none available*
Capecitabine	Solitary report of STP influent levels up to 27 ng/L; comports with PECs (Besse et al., 2012; Johnson et al., 2013; Straub, 2010).	Prodrug of 5-fluorouracil (see separate entry). Environmental transformation studied for first time (Kosjek et al., 2013). Oral chemotherapeutic. European PECs in STP effluent range from 8.5-87 ng/L (Booker et al., 2014; Johnson et al., 2008; Johnson et al., 2013)	(Negreira et al., 2013)
Carbidopa	*none available*	Instability may be an issue since this is a hydrazine-class drug.	*none available*
Carmustine (BCNU: bis-chloroethylnitrosourea)	*none available*		*none available*
Caspofungin acetate	*none available*	PEC: 1 ng/L (Kostich and Lazorchak, 2008).	*none available*
Cefoperazone	Solitary report of up to 940 and 530 ng/L in STP influent and effluent.	Not detected in hospital effluent or in STP influent or effluent (Galletti, 2010).	(Wang et al., 2011)
Cerivastatin	*none available*	Withdrawn from market in 2001.	*none available*
Cetrorelix	*none available*		*none available*
Cevimeline	*none available*		*none available*
Chloral hydrate	*none available*	Not approved for use in US or EU but still used medically. A common byproduct from chlorination reactions in wastewater.	*none available*
Chlorambucil	*none available*	Unstable in wastewaters (possibly due to hydrolysis) (Negreira et al., 2014).	*none available*
Chlordiazepoxide	Levels in STP influents and effluents range from a single study reporting infrequent and low ng/L to another study showing frequent and high (6 µg/L*) levels. Source water for	Rapidly hydrolyzed to demoxepam, for which data is also lacking. Withdrawn from some markets. Reported but not quantified in one study at very low levels in river sediments	(Baker et al., 2013; Baker and Kasprzyk-Hordern, 2011a, b, 2013; Huerta-Fontela et al., 2011)

	drinking: 54 ng/L mean and 265 ng/L max.	(Chen et al., 2013b). Not detected during 7-day sampling of STP influent (Baker et al., 2013) or in influent or effluent from 5 STPs (Borova et al., 2014).	
Chlormethiazole (clomethiazole)	*none available*	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b). Targeted but not reported in rivers and lakes (Ortelli et al., 2011).	*none available*
Chlorpheniramine (chlorphenamine)	*none available*	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b). Not detected in rivers or STP effluents (Al-Odaini et al., 2010; Al-Odaini et al., 2013a; K'oreje et al., 2012).	*none available*
Cisplatin (*cis*-diamminedichloroplatinum; CDDP)	Emission estimated only for hospitals.	Cisplatin undergoes hydrolysis (e.g., yielding mono- and di-aquacisplatin) (Hann et al., 2005). Little monitoring data exist, even for hospital wastewaters (Lenz et al., 2007a; Lenz et al., 2007b), and despite that residues are continually excreted into domestic sewage after infusion treatment.	(Kümmerer and Helmers, 1997; Kümmerer et al., 1999)
Clemastine (meclastin)	One study reporting levels generally below 10 ng/L in sewage influent and effluent. Second study reporting levels in 5 of 6 STP effluents: 0.9-14 ng/L.	Not detected in EU STP effluents (Loos et al., 2013). Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b). Possibly displays strong sorption (Hörsing et al., 2011). Unstable in wastewaters (Fedorova et al., 2014a).	(Fick et al., 2011; Grabic et al., 2012)
Clobazam	*none available*	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b).	*none available*
Clomiphene citrate (clomifene)	Solitary study reporting 1 of 3 STP influent samples at 0.18 ng/L.		(Liu et al., 2010)
Clorazepate	Level in influent and sludge from 1 of 5 STPs: 6,227 ng/L* and 181 ng/g. Daily STP influent, effluent, and sludge loads: 0.71-1.83, 0-1.62, and 0-0.78 g/day. STP influent range: 0-3,332 ng/L* with daily means of 0-416 ng/L.	Prodrug metabolized to desmethyldiazepam and then to oxazepam.	(Salgado et al., 2012; Salgado et al., 2011; Salgado et al., 2010)
Colchicine	*none available*	Detected only in hospital effluents at median level of 9 ng/L (Lin et al., 2008). Reported but not quantified in STP influents (Lin et al., 2009). Natural product.	*none available*
Cyclizine	*none available*	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b).	*none available*
Cyclobenzaprine	*none available*	Unsuitable analytical methodology; targeted but	*none available*

		possibly thermally unstable (Bisceglia et al., 2010b).	
Cytarabine (cytosine arabinoside; Ara-C)	Mean levels in STP influent, effluent, and rivers: 9.2, 14, and 13 ng/L. Present in 48 of 48 influent and effluent samples from four STPs: 44.4-464 ng/L (mean 151 ng/L) and 9.90-190 ng/L (mean 65.1 ng/L)		(Martín et al., 2014; Martín et al., 2011b)
Dabigatran etexilate	*none available*		*none available*
Dantrolene	*none available*		*none available*
Darifenacin	*none available*		*none available*
Debrisoquine	*none available*		*none available*
Desalkylflurazepam	Targeted in only two studies, one which detected presence in STP effluent and other did not detect in either influent or effluent.	Also the major active metabolite (N-desalkyl) of flurazepam (see separate entry) and quazepam.	(Hogenboom et al., 2009; van der Aa et al., 2011)
Desipramine (desmethylimipramine)	*none available*	Major active metabolite of imipramine (see separate entry). Not detected in canal water (Ge and Lee, 2013).	*none available*
Desogestrel	A single study reported levels up to 46 and 7 ng/L in STP influent and effluent, and up to 18.6 µg/kg in STP biosolids samples.	Inactive prodrug of etonogestrel (see separate entry). Studies reported non-detection in river (Emery et al., 2010), lake samples (Ferrey, 2013), and STP influents (USEPA, 2009).	(Gottschall et al., 2013; Lubliner et al., 2010)
Dexmethylphenidate (d-threo-methylphenidate)	*none available*	Enantiomer of methylphenidate (see separate entry), for which considerable occurrence data has been published.	*none available*
Dextromethorphan	Low levels detected in rivers in one study; limited other studies report absence in various matrices.	Detected levels are an order of magnitude lower than metabolites.	(Nakada et al., 2007; Thurman and Ferrer, 2012)
Dezocine	*none available*	Not used in the US or Canada.	*none available*
Dihydroquinidine (hydroquinidine; dihydrochinidin; hydroconquinine)	*none available*	Natural product.	*none available*
Dobutamine hydrochloride	*none available*		*none available*
Dolasetron	*none available*		*none available*
Doxazosin	Two studies reported absence in STPs but levels in raw drinking water lower than 10 ng/L.		(Huerta-Fontela et al., 2010, 2011)
Doxorubicin (hydroxydaunorubicin)	One study: STP influent and effluent mean levels: 4.5 ng/L and <LOD; second study of 48 samples from four STPs: influent and effluent: <LOD and 20.3-42.4 ng/L in only two effluent samples. Levels in STP sludge	Not detected in STP effluents, receiving waters, or sediments (Schlabach et al., 2009). Most studies focus on hospitals or STPs receiving hospital effluent (e.g., Lenz et al., 2007b; Mahnik et al., 2007; Yin et al., 2010a). Paucity	(Martín et al., 2014; Martín et al., 2011b; Schlabach et al., 2009)

	(but receiving hospital effluent): 1.45-5.6 µg/g* dw.	of data for ambient waters.	
Eletriptan hydrobromide	*none available*		*none available*
Enfuvirtide	*none available*	Biomimetic polypeptide; injectable. Low manufactured quantity.	*none available*
Epirubicin	*none available*	Epimer of doxorubicin, which is also lacking data. Generally not reported in STP influent or effluent (Martín et al., 2014; Martín et al., 2011b; Rabii, 2012; Rabii et al., 2014) except for a single high level of 24.8 µg/L (Gómez-Canela et al., 2012). Investigated primarily in hospital effluents (e.g., Lenz et al., 2007b; Mahnik et al., 2007).	*none available*
Ergonovine (ergometrine)	*none available*	Natural product.	*none available*
Ergotamine tartrate	*none available*	Natural product; dihydroergotamine is the semi-synthetic form. Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b).	*none available*
Esmolol	*none available*	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b). Targeted in rivers but not reported (Varga et al., 2011). Rapidly hydrolyzed.	*none available*
Esomeprazole	*none available*	Active enantiomer (eutomer) of omeprazole (see separate entry), for which abundant occurrence data has been published.	*none available*
Eszopiclone	*none available*	Active enantiomer (eutomer) of zopiclone (see separate entry), for which limited occurrence data (negative) has been published. Not detected in STPs (González, 2012; Woldegiorgis et al., 2007) or drinking water (Helmfrid and Eriksson, 2010); zopiclone-N-oxide (a zopiclone metabolite) has been reported in STPs (Woldegiorgis et al., 2007).	*none available*
Ethosuximide	Tentatively identified in landfill leachates and in recycled water used for irrigation.		(Heaven et al., 2012; Jernberg et al., 2013)
Etonogestrel	*none available*	Active metabolite of the prodrug desogestrel, which is inactive itself. Not detected in STPs or surface waters (Fick et al., 2011; Grabic et al., 2012; K'oreje et al., 2012; Loos et al., 2013).	*none available*
Everolimus	*none available*		*none available*
Exenatide	*none available*	Synthetic polypeptide hormone.	*none available*
Famciclovir	*none available*	Prodrug of penciclovir, for which very limited occurrence data has been published, such as: STP influent (42.8 and 19.5 ng/L) but not	*none available*

		detected in effluent (Prasse et al., 2010).	
Fesoterodine	*none available*	Prodrug of 5-hydroxymethyl tolterodine (see separate entry), which is the primary active metabolite of tolterodine.	*none available*
Fludarabine	*none available*		*none available*
Fludrocortisone acetate (9α-fluorocortisol)	*none available*		*none available*
Flumazenil (flumazepil)	*none available*		*none available*
Flurazepam	*none available*	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b). The metabolite desalkyl-flurazepam reported in STPs and surface waters (Hogenboom et al., 2009).	*none available*
Formoterol (eformoterol)	*none available*	Sole study - not detected in STP influent or effluent (Schröder et al., 2010).	*none available*
Fosfluconazole	*none available*	Phosphate prodrug of fluconazole, for which occurrence data has been published (e.g., Chen et al., 2012; Loos et al., 2013; Peng et al., 2012).	*none available*
Frovatriptan	*none available*		*none available*
Galantamine	*none available*	Natural product (alkaloid). Also available OTC.	*none available*
Gemcitabine	Up to 9.3 ng/L in STP influents, and also present in effluents and surface water. In only 4 of 48 samples from four STPs: influent and effluent: 39.3–52.1 and 64.6–88.4 ng/L.	Not detected in STP influent or effluent (Rabii, 2012; Rabii et al., 2014). Up to 38 ng/L in hospital effluent (Kovalova et al., 2009).	(Martín et al., 2014; Martín et al., 2011b; Weissbrodt et al., 2009)
Glibornuride	*none available*	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b).	*none available*
Goserelin	*none available*	Decapeptide luteinizing hormone releasing hormone (LHRH) agonist.	*none available*
Granisetron	*none available*		*none available*
Guanabenz	*none available*		*none available*
Hexobarbital (hexobarbitone)	*none available*	Not detected in surface waters, drinking water, or STPs (Boleda et al., 2013; Peschka et al., 2006).	*none available*
Hydralazine hydrochloride (apresoline)	*none available*		*none available*
Hydromorphone (dihydromorphinone)	*none available*	Metabolite of hydrocodone, for which abundant monitoring data exist (see separate entry). Common practice in hospitals is to dispose of unused doses to sewers.	*none available*
Hydroxychloroquine	*none available*	Limitations in analysis (Bisceglia et al., 2010b); chloroquine has been widely studied (Zurita et	*none available*

		al., 2005).	
Ibutilide	*none available*		*none available*
Idarubicin (4-demethoxydaunorubicin)	*none available*		*none available*
Iloprost	*none available*		*none available*
Imidapril	*none available*	Prodrug ester of imidaprilat.	*none available*
Imipramine (melipramine)	Only two positive studies: five time-course samples from STP influent and effluents ranging from 29-48 ng/L, and levels from three STPs ranging from 10.6-10.9 ng/L.	Not detected in STP effluent, surface waters, canal waters, or drinking water (Borova et al., 2014; Ge and Lee, 2013; Nakada et al., 2007; Rabiet et al., 2006; Sadezky et al., 2008; Togola and Budzinski, 2008).	(Sheng et al., 2014; Unceta et al., 2010)
Imiquimod	*none available*	Topical drug.	*none available*
Inamrinone (amrinone)	*none available*	Intravenous only.	*none available*
Indapamide	Levels below detection limits in STPs. Two isolated studies reported sporadic levels in STP influents up to 1.2 and 15.4 µg/L*.	Sorbed to sewage sludge (Salgado et al., 2012).	(Salgado et al., 2011; Salgado et al., 2010; Sousa et al., 2011)
Irinotecan	Solitary study reporting levels below detection limits in STPs and rivers.	Intravenous only. Detected in hospital wastewater (Schlabach et al., 2009). Activated via enzymatic hydrolysis to produce an inhibitor of topoisomerase I. Not detected in STP influent or effluent (Rabii, 2012; Rabii et al., 2014).	(Martín et al., 2014; Martín et al., 2011b)
Isoniazid (isonicotinylhydrazine)	*none available*	Prodrug requiring enzymatic activation. In one study, very low levels reported but not quantified in river sediments (Chen et al., 2013b). Not detected in STPs (Gagne et al., 2006). Biodegradation examined (Sasu et al., 2013).	*none available*
Isosorbide (2- and 5-mononitrate); also isosorbid	Solitary report of occurrence in STPs.	Prodrug when coupled with nitrate. Not targeted because of short anticipated half-life (Batt et al., 2008) and extensively metabolized.	(Paxéus, 2011)
Isosorbide dinitrate	*none available*		*none available*
Ivabradine	*none available*		*none available*
Letrozole	Solitary study reporting range in STP influents and effluents: 0.27-0.8 ng/L.		(Liu et al., 2010)
Leuprolide (leuprorelin)	*none available*	Implant or SC/IM injection only. GnRH analog (polypeptide).	*none available*
Levobupivacaine	*none available*	S-enantiomer of racemic bupivacaine (see separate entry), for which occurrence data is also lacking.	*none available*
Levodopa (L-DOPA)	Solitary study reporting maximum and median levels in STPs: 2,888 and 1,374 ng/L*.	Endogenous biochemical.	(Huerta-Fontela et al., 2010)

Linezolid	Level of 720 µg/kg in sludge from one STP but levels below detection limit in five other STPs. Sporadic levels up to 6 µg/L* in STP effluents and reported occurrence in other matrices (high levels probably resulting from manufacture).		(Møskeland, 2006; Sundstøl Eriksen et al., 2009)
Liraglutide	*none available*	GLP-1 analog (polypeptide).	*none available*
Lorcainide	*none available*	The N-dealkylated derivative (noriorcainide) is an active metabolite.	*none available*
Maraviroc	*none available*		*none available*
Melphalan	*none available*		*none available*
Meperidine (pethidine)	*none available*	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b). Sole study: not detected in STPs or rivers, but hospital wastewaters: 89-1,500 ng/L (Lin et al., 2014).	*none available*
Mesna (2-mercaptoethane sulfonate sodium)	*none available*	Primarily intravenous.	*none available*
Methohexital (methohexitone)	*none available*	Primarily hospital use only.	*none available*
Methylergonovine (methylergometrine, methylergobasin, methergine)	*none available*		*none available*
Mexiletine	*none available*	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b).	*none available*
Micafungin	*none available*		*none available*
Midazolam	Solitary study reporting levels below LOD in various surface waters and one STP effluent.	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b). Not detected in 33 STPs (Östman et al., 2014). Low levels in extracts from passive sampling in 9 of 21 surface waters (Fedorova et al., 2014b).	(Roberts and Bersuder, 2006)
Minoxidil	*none available*	Topical use. Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b).	*none available*
Misoprostol	*none available*		*none available*
Molindone	*none available*	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b). Manufacture discontinued in 2010.	*none available*
Nafarelin	*none available*	Decapeptide.	*none available*
Nalbuphine	*none available*	Injectable only in US.	*none available*
Nalmefene (nalmetrene)	*none available*		*none available*
Naloxone	Levels up to 26 ng/L in STP effluents; 9 ng/L in wetlands.	Reported but not quantified in one study at very low levels in river sediments (Chen et al.,	(Breitholtz et al., 2012; Grabic et al., 2012)

		2013b). Negligible sorption to sewage sludge (Hörsing et al., 2011).	
Naltrexone	*none available*	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b).	*none available*
Nefopam	*none available*		*none available*
Nicardipine	*none available*	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b).	*none available*
Nicorandil	*none available*		*none available*
Nitroglycerin	*none available*	Not targeted possibly because of short anticipated half-life (Batt et al., 2008). Medication use would also only represent one of several potential sources for nitroglycerin in the environment. Major topical usage.	*none available*
Nortilidine	*none available*	Active metabolite of tilidine (see separate entry), for which published occurrence data is also lacking.	*none available*
Octreotide acetate	*none available*	Octapeptide mimic of somatostatin. Injectable.	*none available*
Olmesartan medoxomil	*none available*	Prodrug ester of olmesartan. Possibly transformed to an intermediate (valsartan acid) also shared by transformation of other sartans (Nödler et al., 2010).	*none available*
Ondansetron	*none available*	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b).	*none available*
Oxaliplatin	*none available*	Intravenous only. Not detected in hospital wastewater (Lenz et al., 2007a; Lenz et al., 2007b). Unstable in wastewaters) (Negreira et al., 2014).	*none available*
Oxybutynin	*none available*		*none available*
Oxymorphone	Absence or median levels in STP influent and effluent: 14.8-19.9 ng/L and 8.4 ng/L. STP loadings up to 31 mg/day/1,000 people.	Also a metabolite of oxycodone.	(Baker et al., 2013; Baker and Kasprzyk-Hordern, 2011a, b, 2013; Baker et al., 2012)
p-Aminosalicylic acid (PAS; 4-aminosalicylic acid)	*none available*		*none available*
Pentamidine	*none available*		*none available*
Perindopril	Median levels up to 35.6 ng/L in STP effluent and up to 6.1 ng/L in receiving waters. Maximum reported in STP influent is 71 ng/L.	Prodrug ester of perindoprilat.	(Al-Odaini et al., 2012; Al-Odaini et al., 2010; Al-Odaini et al., 2013a; Tarcomnicu et al., 2011)
Phenylephrine	Ranges of 0.9–4.5 µg/L* in STP influent, 0.5-2 µg/L* in effluent, and 200-480 ng/L in rivers. Not detected in recycled water but consistently present in groundwater. Of 11	Metabolite of ephedrine.	(Estévez et al., 2012; Martínez Bueno et al., 2011; Robles-Molina et al., 2014)

	river samples, 27% had mean and maximum levels: 27.9 and 47.7 ng/L.		
Pimozide	*none available*		*none available*
Pramlintide acetate	*none available*	Analog of peptide hormone amylin.	*none available*
Prazosin	Solitary study: STP influent (10 of 12 samples: average 117 ng/L; maximum: 326 ng/L) and effluent (3 of 12 samples: average 33 ng/L; maximum: 77 ng/L); surface water (5 of 6 samples): average (13 ng/L); maximum: (30 ng/L).	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b).	(Al-Qaim et al., 2014)
Primaquine	*none available*		*none available*
Prochlorperazine	Solitary study reporting levels below detection limits in surface waters and STP effluent.		(Roberts and Bersuder, 2006)
Proguanil (chlorguanide, chloroguanide)	*none available*	Prodrug of cycloguanil, for which occurrence data is also lacking.	*none available*
Promazine (sparine)	*none available*	In the US, veterinary use only. Occurrence data available for the many related promazine derivatives (e.g., see chlorpromazine). Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b). Not detected in influent or effluent from 5 STPs (Borova et al., 2014).	*none available*
Propantheline bromide	*none available*		*none available*
Propylthiouracil (PTU)	*none available*		*none available*
Protriptyline	*none available*	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b).	*none available*
Pyrazinamide	*none available*		*none available*
Quetiapine fumarate	Levels up to 6 and 4 ng/L in STP influent and effluent. Levels in 15 of 16 STP sludges: up to 17.3 with mean of 5.41 ng/g dw.	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b).	(Subedi et al., 2013; Yuan et al., 2013b)
Quinacrine (mepacrine)	Solitary study reporting 814 µg/kg in 1 of 7 sewage sludges.		(Peysson and Vulliet, 2013)
Quinidine	*none available*	Stereoisomer of quinine.	*none available*
Rabeprazole	Solitary study reporting consistent absence from STPs and surface waters.		(Van De Steene et al., 2010)
Ramelteon	*none available*		*none available*
Reboxetin	*none available*		*none available*
Remifentanil	*none available*		*none available*
Reserpine	*none available*	Natural product.	*none available*

Ribavirin	*none available*	One study reporting below LOQ in STP influent and another study reporting non-detection in influent and effluent.	(Peng et al., 2014; Prasse, 2012; Prasse et al., 2010)
Ridogrel	*none available*		*none available*
Riluzole	*none available*		*none available*
Rimantadine	*none available*	Not detected in STPs (Haeck, 2013; Vergeynst et al., 2014).	*none available*
Rivastigmine	*none available*		*none available*
Rizatriptan	*none available*		*none available*
Ropinirole	*none available*		*none available*
Ropivacaine	*none available*	Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b).	*none available*
Rosiglitazone maleate	*none available*	Withdrawn from market or restricted in some countries.	*none available*
Rotigotine	*none available*	Transdermal.	*none available*
Roxatidine acetate	*none available*	Prodrug of roxatidine.	*none available*
Scopolamine (levo-duboisine; hyoscine)	Solitary report of tentative identification in river water.	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b). Solitary study reporting non-detection in a river (Nakada et al., 2007). Natural product.	(Masiá et al., 2014)
Selegiline (L-deprenyl)	*none available*	Yields L-methamphetamine as a metabolite, which has abundant published monitoring data.	*none available*
Sibutramine	*none available*	Withdrawn from many markets, including the US and UK. But sill used as an illegal additive to certain consumer supplements (Phattanawasin et al., 2012).	*none available*
Solifenacin succinate	*none available*		*none available*
Sparfloxacin	Reported levels in STP influent and effluent: 4.4 and 3.9 ng/L; raw sewage sludge: 10 µg/kg. Reported in coastal waters at maximum of 0.79 ng/L.	Withdrawn from US market. Reported but not quantified in one study at very low levels in river sediments (Chen et al., 2013b). Also veterinary use.	(Jia et al., 2012; Na et al., 2011)
Sufentanil	*none available*	Not detected in STPs (Fakhari et al., 2011; Lin et al., 2014). Also formulated in transdermal patches.	*none available*
Sumatriptan succinate	*none available*		*none available*
Sunitinib	*none available*	Expected to partition to solids (Booker et al., 2014).	*none available*
Tamsulosin	Levels in STP influent and effluent (ng/L): 0.781-1.37 and <MQL-0.872. Single study reports non-detection in STPs, surface waters, drinking water.	Targeted by not reported in STPs and various other waters (Petrović et al., 2014).	(Gros et al., 2012; Santos et al., 2013)

Temocapril (temocaprilum)	*none available*	Not approved for use in the US. Prodrug ester of temocaprilat.	*none available*
Temsirolimus	*none available*	Intravenous only.	*none available*
Tenoxicam	Single study reporting non-detection in STPs. Single study reporting sporadic levels of 9-19 ng/L in STPs. Average levels in STP influent and effluent: 325 and 238 ng/L.	Not detected in rivers (Collado et al., 2014). Targeted by not reported in STPs and various other waters (Petrović et al., 2014).	(Collado et al., 2014; Gros et al., 2012; Santos et al., 2013)
Terazosin	*none available*		*none available*
Thioguanine (tioguanine)	*none available*		*none available*
Thiopental (thiopentone)	*none available*	No monitoring data but discussed in (Peschka et al., 2006). Not detected in influent or effluent from 5 STPs (Borova et al., 2014). Use in the US has dropped because of controversy regarding use in executions. A major metabolite is pentobarbital, for which abundant occurrence data has been published.	*none available*
Ticlopidine	Solitary monitoring program reports both presence and absence in yearly surveys of a river.		(Bernard et al., 2012; Ortelli et al., 2011)
Tilidine (tilidate)	*none available*	Schedule I narcotic in US. Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b). Nortilidine (see separate entry) is the active metabolite.	*none available*
Tinidazole	*none available*		*none available*
Tolterodine	*none available*		*none available*
Toremifene	Solitary study reporting 0.58 ng/L in 1 of 3 STP influents and non-detection in effluents.		(Liu et al., 2010)
Tranylcypromine sulfate	*none available*		*none available*
Triazolam	*none available*	Reported but not quantified in one study at low levels in river sediments (Chen et al., 2013b).	*none available*
Trifluoperazine	*none available*		*none available*
Trimetrexate glucuronate	*none available*		*none available*
Tropisetron	*none available*	Not available in the US.	*none available*
Urapidil	*none available*	Not approved in the US.	*none available*
Valacyclovir (valaciclovir)	Solitary study reporting high levels in STP influents and effluents: 2.83-5.66 µg/L* and 0.33-0.67 µg/L.	Prodrug ester of acyclovir. Occurrence of acyclovir in STPs includes: 1,780 ng/L (influent) and 27-53 ng/L (effluent) (Prasse et al., 2010), and 1,800-1,990 (influent) and 121-140 ng/L (effluent) (Prasse et al., 2011); STP data also reported (Peng et al., 2014). Review of acyclovir data in Jain et al. (2013; also see data for acyclovir in Supplemental Table S-2	(Ottmar et al., 2013)

		(BDDCS Category IV).	
Valganciclovir	*none available*	Prodrug ester of ganciclovir, which has not been detected in STP influent but has been reported in landfill leachate (418-1,131 ng/L) (Peng et al., 2014).	*none available*
Valproic acid (valproate)	STP influent and effluent: 140-150 ng/L and non-detection. Some reported values for a wide range of matrices in a single study: STP influent and effluent (10-1,820* and 34-117 ng/L) and STP suspended solids (67-9,287 µg/kg*).	Negative occurrence data may be a consequence of high MDLs (e.g., 199 ng/L, Palmer et al., 2008).	(Borova et al., 2014; Schneider, 2005; Yu et al., 2012; Yu et al., 2006)
Vinblastine	*none available*	Intravenous only. Natural product. Not detected in hospital wastewater, STPs, or surface waters (Lin et al., 2014).	*none available*
Vincristine (leurocristine)	Solitary study reporting 22.9 ng/L in 1 of 23 STP influents.	Intravenous only. Natural product. Not detected in hospital wastewaters (Yin et al., 2010a). Intravenous only. Natural product. Not detected in hospital wastewater, STPs, or surface waters (Lin et al., 2014). Relatively unstable in wastewaters as a function of various conditions (Negreira et al., 2014).	(Ferrando-Climent et al., 2013)
Vinorelbine	Solitary study reporting mean level for 3 STP effluents of 9.1 ng/L and non-detection for influent and receiving water. In 48 samples from four STPs: influent and effluent: <LOD and 44.1-170 ng/L in only three effluent samples.	Relatively stable in wastewaters as a function of various conditions (Negreira et al., 2014).	(Martín et al., 2014; Martín et al., 2011b)
Vorozole	*none available*	Not approved for use.	*none available*
Zidovudine (azidothymidine, AZT)	Single study reporting extremely high levels in 6 of 8 sampling sites in the Nairobi River basin, ranging from 2-9 µg/L*. Single study reporting ranges for influent and effluent from two STPs: 310-380 and 98-564 ng/L; range 4.5-170 ng/L for 12 sampling sites of receiving waters.		(K'oreje et al., 2012; Prasse, 2012; Prasse et al., 2010)
Zolmitriptan	*none available*		*none available*
Zonisamide	*none available*		*none available*

[1] From Benet et al. (2011, see Table I therein) a total of 322 APIs were selected from BDDCS Category I ; a limited number (21) of Category I APIs were excluded from evaluation because they have little toxicological relevance in the environment or they have major alternative contributory sources other than from bona fide human consumption of pharmaceuticals, such as from: endogenous biosynthesis (such as 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). The published occurrence data (as of 8 May 2014) for these 322 APIs resulted in the following subtotals within the three subjective data categories: Abundant data (57; 18% of total), Limited data (41; 13% of total), and Paucity of data (224; 69% of total).

[2] Focus of data is on API occurrence in STPs and environmental matrices, while attempting to exclude data from locations biased with contributions from hospitals and other healthcare facilities. Units of concentration are not standardized between the equivalent terms ng/L and µg/L, or between ng/g and µg/kg. Published literature has been searched up through 8 May 2014 using the bibliographic database of Daughton and Scuderi (2014).

[3] 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 depending on the quantity of drug locally prescribed or consumed. Numerous additional supporting references exist beyond the few examples cited, which were selected primarily from the more recent literature. Asterisks in the column "Reported occurrence data" denote that published occurrence data supports API's presence at substantial levels (e.g., levels in STPs exceeding 1 µg/L, or levels in sludges or sediments exceeding 1 mg/kg or 1 µg/g).

[4] 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.

[5] Paucity of occurrence data - possible MEOCs: 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.

Abbreviations: API: active pharmaceutical ingredient; BDDCS: Biopharmaceutics Drug Classification System (see: Benet et al., 2011); CAFO: confined animal feeding operation; dw: dry-weight basis; LOD: analytical limit of detection; LOQ: analytical limit of quantitation; MEOC: Matthew Effect Orphaned Chemical (see: Daughton, 2014)]; ND: not detected; OTC: Over-the-Counter drug; MQL: method quantitation limit; PEC: predicted environmental concentration; STP: sewage treatment plant (intended to be equivalent to MWWTP: municipal wastewater treatment plant); ww: wet-weight basis.

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Table S-2. Published environmental occurrence data for 52 APIs in BDDCS Class IV [1]

API (alternate name)	Reported occurrence data	Examples	Selected references [2]
Abundant occurrence data [3]			
Ciprofloxacin [4] [85721-33-1] [5]	Substantial levels in wide range of matrices; frequently detected.	***Up to 10 µg/kg on streambed sediments; 638 ng/L in STP effluent; 17-304 ng/L in rivers; 2.2-3.5 mg/kg sewage sludges.	(Gibs et al., 2013; Golet et al., 2003; Leung, 2012; Tong et al., 2011; Verlicchi et al., 2013; Yang et al., 2013; Zhou et al., 2013)
Enoxacin [4] [74011-58-8]	Mixed occurrence in a wide range of matrices; frequently detected.	***Up to 1.3 µg/L in STP primary settling tank; 24-75 ng/L in groundwater; mean of 27-36 ng/L in rivers; 61 ng/L in STP effluent; mean of 62 ng/L in bay.	(Dorival-García et al., 2013; López-Serna et al., 2013; López-Serna et al., 2011; Verlicchi et al., 2013; Zhang et al., 2012a)
Erythromycin stearate [4] [643-22-1] (as anhydroerythromycin)	Mixed occurrence in a wide range of matrices; frequently detected.	***Up to 204 and 695 ng/L in STP effluent; up to 1 mg/kg in dewatered sludge. Also used in veterinary medicine.	(Estévez et al., 2012; Fick et al., 2011; Michael et al., 2013; Tylová et al., 2013; Uslu et al., 2013; Verlicchi et al., 2013; Zhou et al., 2012; Zhou et al., 2013)
Fleroxacin [4] [79660-72-3]	Mixed occurrence in a wide range of matrices. Appreciable levels in a few studies.	***Up to 1.84 mg/kg in STP sludge; mean level of 13.6 µg/kg in mollusks; up to 60 ng/L in surface waters; low levels in marine waters.	(Chen et al., 2010; Gao et al., 2012a; Jia et al., 2012; Jiang et al., 2011; Li et al., 2012a, b, 2013a; Na et al., 2011; Zhang et al., 2013; Zhou et al., 2012)
Furosemide [54-31-9]	Substantial levels in wide range of matrices; frequently detected.	***Levels exceeding 1 µg/L (up to 3.2-3.8 µg/L) in rivers downstream of STPs. Up to 755 ng/L in STP sludge liquid phase.	(Gonçalves et al., 2013; Grabic et al., 2012; Narumiya et al., 2013; Rodríguez-Navas et al., 2013; Valcárcel et al., 2013; Valcárcel et al., 2011; Verlicchi et al., 2013)
Levonorgestrel [797-63-7]	Wide range of matrices (including fish tissue) but at comparatively low levels (higher levels from CAFOs).	Levels up to 199 ng/L in surface waters (as summarized in: Svensson et al., 2013). Level up to 213 ng/L in river water but not STP effluent (Al-Odaini et al., 2013b).	(Al-Odaini et al., 2013b; Fick et al., 2010; Gottschall et al., 2013; Liu et al., 2012a; Liu et al., 2012b; Reddy, 2013; Viglino et al., 2011; Vulliet and Cren-Olivé, 2011; Wang and Gardinali, 2013)
Norfloxacin [4] [70458-96-7]	Wide range of matrices but especially appreciable levels in sewage sludge.	***Levels up to 5.6 mg/kg in sewage sludge. Infrequently detected in surface waters (Hoerger et al., 2013).	(Chen et al., 2013a; Haiba et al., 2013; Leung, 2012; Li et al., 2013b; Tong et al., 2011; Verlicchi et al., 2014; Wei et al., 2013; Yan et al., 2014a; Zhou et al., 2013)
Penicillin V [4] (phenoxymethylpenicillin) [87-08-1]	Many reports, some frequently detecting at low levels in STPs; many other reports with negative occurrence data. In some countries, may originate from use in industry. Also used in veterinary medicine.	***Maximum of 13.8 µg/L in STP influent (Watkinson et al., 2009). Maximum of 64 ng/L in STP influent and 27 ng/L in STP effluent (Guerra et al., 2014).	(Chen et al., 2012; Christian et al., 2003; Gros et al., 2013; Guerra et al., 2014; Hirsch et al., 1999; Watkinson et al., 2007; Watkinson et al., 2009; Zhu and Chen, 2014; Zhu et al., 2013)
Roxithromycin [4] [80214-83-1]	Frequent occurrence at appreciable levels in many matrices.	***Levels exceeding 1 µg/L in rivers and sometimes 1 to 5 mg/kg in river sediments. Levels 2.8–15.1 ng/L in 7% of Chinese tap water samples (Leung et al., 2013).	(Chen et al., 2013a; Hu et al., 2012; Leung, 2012; Li et al., 2013b; Yan et al., 2014a; Yang et al., 2011; Zhou et al., 2013)

Sulfadiazine [4] [68-35-9]	Frequent occurrence at appreciable levels in many matrices. Frequently used in veterinary medicine.	Levels up to 1.68 µg/kg in coastal sediments. 21-42 ng/L in 8% of 36 STP influents but not detected in effluents or biosolids (García-Galán et al., 2013; Guerra et al., 2014). Levels from 5-25.6 mg/kg DW in chicken manure (Ho et al., 2012; Ho et al., 2013) and 91 mg/kg in turkey manure (Martinez-Carballo et al., 2007). Not detected in STP sludge (Nieto et al., 2007).	(Chang et al., 2008a; Dan et al., 2013; Díaz-Cruz et al., 2008; Gao et al., 2012b; Iglesias et al., 2014; Li, 2011; Lietz and Meyer, 2006; López-Serna et al., 2012; Na et al., 2013; Qi et al., 2014; Yan et al., 2013; Yan et al., 2014a; Yan et al., 2014b; Yang et al., 2011; Yuan et al., 2014; Zhang et al., 2012b; Zhou et al., 2013); also see references cited in review (Hruska and Franek, 2012).
Sulfamethizole [4] (sulfamethiazole) [144-82-1]	Frequent occurrence at wide spectrum of levels in many matrices; also data of absence. Frequently used in veterinary medicine.	***Up to 5.2 µg/L in STP effluents (Nordic Council of Ministers, 2012). Not detected in receiving waters (Glassmeyer et al., 2005).	(Díaz-Cruz et al., 2008; García-Galán et al., 2013; Gros et al., 2013; Guerra et al., 2014; Iglesias et al., 2012; Jensen et al., 2012; Klosterhaus et al., 2013; Miao et al., 2004; Møskeland, 2006; Na et al., 2013; Nordic Council of Ministers, 2012; Schaider et al., 2014; Shimizu et al., 2013; Yuan et al., 2014)
Sulfisoxazole [4] (sulphafurazole, sulfafurazole) [127-69-5]	Frequent occurrence but preponderance of data indicates low levels; also data of absence.	Not detected in STP effluents or receiving waters (Sosiak and Hebben, 2005). Also see summarized published data (Bu et al., 2013).	(García-Galán et al., 2013; Gros et al., 2013; Li et al., 2013a, b; Miao et al., 2004; Na et al., 2013; Spongberg and Witter, 2008; Zhang and Li, 2011)
Valsartan [137862-53-4]	Frequent occurrence at appreciable levels in many matrices.	***Up to 1.3 µg/L in source drinking waters and over 5 µg/L in STPs. A possibly common transformation product of valsartan - and possibly other sartan antihypertensives - is "valsartan acid" (Nödler et al., 2013).	(Gracia-Lor et al., 2012; Gros et al., 2012; Huerta-Fontela et al., 2011; Ibáñez et al., 2013; Klosterhaus et al., 2013; Kostich et al., 2014; Margot et al., 2013; Oosterhuis et al., 2013; Petrović et al., 2014)
Limited occurrence data [6]			
Acyclovir (aciclovir, acycloguanosine) [59277-89-3]	Appreciable levels but few reports.	***Also derives from the active form of its prodrug valacyclovir (see data for valacyclovir in Supplemental Table S-I, BDDCS Category I), which can itself occur at high levels in STPs (Ottmar, 2010). Levels in STP influents can exceed 1 µg/L (up to 1.76 µg/L); even higher levels of transformation product, carboxy-acyclovir (Prasse et al., 2012). Levels in surface waters 190 ng/L; levels in landfill leachate up to 2.4 µg/L. Frequently detected in many other matrices; does not partition to solids. Not detected in Nairobi River basin (Kenya) (K'oreje et al., 2012). Review of acyclovir data (Jain et al., 2013). Major topical usage.	(Peng et al., 2014; Prasse, 2012; Prasse et al., 2010; Prasse et al., 2011; Yu et al., 2012)
Chlorothiazide [58-94-6]	Appreciable levels but few reports.	***First reports – frequent occurrence in STP effluents and surface waters; some levels exceed 1 µg/L (maximum of 8.9 µg/L). Transformation	(Al-Odaini et al., 2010; Al-Odaini et al., 2013a; Al-Odaini et al., 2013b)

		product of hydrochlorothiazide (Brigante et al., 2005; Li et al., 2014), for which data is more abundant.	
Chlorthalidone (chlortalidone) [77-36-1]	Very limited data.	***Freshwater sediments: 20.1 µg/g.	(Terzic and Ahel, 2011; Zaja et al., 2013)
Cinoxacin [4] [28657-80-9]	Discontinued in US and UK. Predominantly negative occurrence data for STP wastewaters and sludge.	Measurement may sometimes be hindered by low analytical recoveries and high LODs.	(Dorival-García et al., 2013; Gros et al., 2013; Jia et al., 2012; Shao et al., 2009; Turiel et al., 2003; Xiao et al., 2008)
Cloxacillin [4] [61-72-3]	Mixed occurrence in a wide range of matrices. Predominantly negative data but appreciable levels in a few reports.	Generally not found with high frequency. 11-50 ng/L in 17% of 36 STP influents and 5-50 ng/L in 58% of 36 STP effluents (Guerra et al., 2014). Not detected in reclaimed water for irrigation or groundwater (Estévez et al., 2012). Not detected in raw drinking water (Stackelberg et al., 2007).	(Cha et al., 2006; Finnegan et al., 2010; Hirsch et al., 1999; Lin et al., 2010; Michael et al., 2013; Pozo et al., 2006; Watkinson et al., 2007; Watkinson et al., 2009)
Eprosartan [133040-01-4]	Appreciable levels but few reports.	***In wetlands receiving treated STP effluent, up to 1.2 µg/L incoming and 0.87 µg/L outgoing; river sediments; up to 1.7 µg/L in STP influent; up to 6.8 µg/L in STP effluent; up to 14 µg/kg in dewatered sludge; up to 50 ng/L in surface waters and 5 ng/L in drinking waters. Not detected in river bank filtrate (Huntscha et al., 2012).	(Breitholtz et al., 2012; Fick et al., 2011; Grabic et al., 2012; Hörsing et al., 2011; Loos et al., 2013; Margot et al., 2013)
Medroxyprogesterone acetate [71-58-9]	Frequently targeted but little occurrence data above LOD. Medroxyprogesterone is the metabolite of the acylated form: medroxyprogesterone acetate (MPA). This causes confusion in the published literature.	MPA: 13-31 ng/g in sediments, soils, biosolids; mean of 41 ng/L in STP influent (greatly reduced in effluent); reported in STPs and rivers. More data exists for the metabolite, medroxyprogesterone (e.g., Grabic et al., 2012; Kolodziej et al., 2003; Kolodziej et al., 2004).	(Chang et al., 2009; Chang et al., 2011; Fan et al., 2011; Tabak et al., 1981)
Megestrol acetate [595-33-5]	Comparatively low levels (mainly absence of occurrence; two positive-data reports). Megestrol is the metabolite of the acylated form: megestrol acetate (MTA). This causes confusion in the published literature.	MTA: Mean of 6 ng/L in STP influent (greatly reduced in effluent). STP receiving waters up to 3.03 ng/L. Megestrol not detected in STP effluents (Grabic et al., 2012).	(Chang et al., 2009; Chang et al., 2011; Chang et al., 2008b; Guedes-Alonso et al., 2013; Gust et al., 2014; Zhang et al., 2011)
Paucity of occurrence data - possible MEOCs [7]			
Acetazolamide [59-66-5]	*none available*	Photolabile (Vargas et al., 1998). Mentioned as a target analyte for a planned monitoring project (Botta et al., 2012).	*none available*
Amisulpride [71675-85-9]	*none available*	Not approved for use in the US. Photolabile (Skibiński, 2011). Only identified in wastewater collected during a music festival (Reid et al., 2014).	*none available*

Atovaquone (atavaquone) [95233-18-4]	*none available*		*none available*
Auranofin [34031-32-8]	*none available*		*none available*
Azapropazone (apazone) [13539-59-8]	*none available*		*none available*
Candesartan [139481-59-7]	Only two studies.	Active form of prodrug cilexetil ester (candesartan cilexetil, for which little occurrence data has been published; see entry below). One isolated study reporting levels in STPs: sludge (49.7 ng/g dw), influent (up to 60.3 ng/L), and effluent (up to 111 ng/L). Detection in river sediments. A possibly common transformation product of sartan antihypertensives is "valsartan acid" (Nödler et al., 2013).	(Chen et al., 2013b; Nordic Council of Ministers, 2012)
Candesartan cilexetil (145040-37-5]	*none available*	Ester prodrug form of candesartan, for which little occurrence data has been published (see entry above). A possibly common transformation product of sartan antihypertensives is "valsartan acid" (Nödler et al., 2013).	*none available*
Cefdinir [4] [91832-40-5]	Targeted but not detected in two studies.	MDL in drinking water reported in one study at roughly 250 ng/L (Padhye et al., 2014).	(Padhye et al., 2014; Rao et al., 2008)
Cefditoren [4] [104145-95-1]	*none available*		*none available*
Cefixime [4] [79350-37-1]	*none available*		*none available*
Cefpodoxime [4] [80210-62-4]	Not detected in 2 bottled waters.	Active form of prodrug cefpodoxime proxetil, for which occurrence data is also lacking. PECs estimated in France as 170-212 ng/L (Besse, 2008).	(Dévier et al., 2013)
Cefprozil [4] (cefproxil) [92665-29-7]	Mentioned in one study.	PECs for U.S. STPs: 1-1.7 µg/L (Sedlak and Pinkston, 2001).	(Rao et al., 2008)
Ceftibuten [4] [97519-39-6]	*none available*		*none available*
Clodronic acid (clodronate disodium) [10596-23-3]	*none available*		*none available*
Dalfopristin [4] [112362-50-2]	*none available*	All published literature focuses on occurrence and transmission of bacterial resistance. Note: dalfopristin is usually administered in combination with quinupristin (marketed under the trade name Synercid).	*none available*
Daunorubicinol [28008-55-1]	*none available*	13-Hydroxy metabolite of daunorubicin (daunomycin), for which occurrence data is also lacking.	daunorubicin monitored only in hospital wastewater (Lenz et al., 2007; Mahnik et al., 2007)

Felbamate [25451-15-4]	*none available*	Restricted use in US (Stepan et al., 2011); not widely used, but the daily dose is over 1gram.	*none available*
Fosinoprilat [95399-71-6]	*none available*	Active form of fosinopril, for which occurrence data is also lacking.	*none available*
Iopanoic acid (iodopanoic acid; iopodate or ipodate salts) [96-83-3; 1221-56-3]	Solitary report of occurrence above LODs in surface waters and wastewaters but not ground waters.	Not detected in STP effluent or surface waters.	(Sadezky et al., 2008; Wolf et al., 2012)
Lenalidomide [191732-72-6]	*none available*	Possible teratogen - derivative of thalidomide. PEC: 0.05 µg/L (Schreiber et al., 2011).	*none available*
Levocabastine [79516-68-0]	Solitary report of detection in river sediments.		(Chen et al., 2013b)
Meropenem [4] [96036-03-2]	Few reports (data of absence: STP effluent, sewage sludge, receiving waters, and sediments). Administered intravenously.	Most studies do not report occurrence data. PECs for hospitals: up to 15.8-22.8 µg/L (Al-Ahmad et al., 1999; de Souza et al., 2009; McArdell et al., 2011). PECs for STPs (up to 0.3 µg/L) and sewage sludge (up to 29 µg/kg) (Sundstøl Eriksen et al., 2009).	(Schlabach et al., 2009); detected in hospital sewage (Jarnheimer et al., 2004)
Niclosamide [50-65-7]	*none available*		*none available*
Nitrofurantoin [4] [67-20-9]	Solitary report - negative data for STPs.	Possibly photolabile (Edhlund et al., 2006). PEC in sewage sludge: 42 µg/kg (Sundstøl Eriksen et al., 2009).	(Hogenboom et al., 2009)
Orlistat (tetrahydrolipstatin) [96829-58-2]	Only two reports - negative data for STPs and surface waters. Monitoring data conflict with PECs.	Also available OTC. Sewage sludge not yet examined (extensively excreted in feces); possibly widely used as an active adulterant in other OTC weight-loss preparations (Yu et al., 2010).	(Boxall et al., 2012; Garcia-Ac et al., 2009; Garcia-Ac et al., 2011; Garcia Ac, 2010)
Paliperidone (9-hydroxyrisperidone) [144598-75-4]	*none available*	9-Hydroxyrisperidone is the primary active metabolite of risperidone, for which data exist for the latter's measurement in STP influent, lakes, and drinking water (e.g., Fedorova et al., 2014; Loos et al., 2013; Snyder et al., 2008; Yuan et al., 2013).	*none available*
Phenazopyridine hydrochloride [136-40-3]	*none available*		*none available*
Quinupristin [4] [120138-50-3]	*none available*	All published literature focuses on occurrence and transmission of bacterial resistance. Note: quinupristin is usually administered in combination with dalfopristin (marketed under the trade name Synercid).	*none available*
Rifaximin [4] [80621-81-4]	*none available*	Used in veterinary medicine (Kools et al., 2008).	*none available*
Trandolaprilat	*none available*	Trandolaprilat is the active metabolite of the ethyl	*none available*

[83601-86-9; 87679-71-8]		ester prodrug trandolapril, for which occurrence data is also lacking.	
Triclabendazole sulfoxide [100648-13-3]	*none available*	Triclabendazole sulfoxide is the initial active metabolite of triclabendazole, for which occurrence data is also lacking but claimed to not enter the environment because of extensive metabolism (Boxall et al., 2006); isolated report of triclabendazole in 1 of 11 river water samples at 2.38 ng/L (Zrnčić et al., 2013). Also used in veterinary medicine.	*none available*

[1] From Benet et al. (2011; see Table IV therein) a total of 52 APIs were selected for BDDCS Category IV. The published occurrence data (as of 8 May 2014) for these 52 APIs resulted in the following subtotals within the three subjective data categories: Abundant data (13; 25% of total), Limited data (8; 15% of total), and Paucity of data (31; 60% of total). Focus of data is on API occurrence in STPs and environmental matrices, while attempting to exclude data from locations biased with contributions from hospitals and other healthcare facilities. Units of concentration are not standardized between the equivalent terms ng/L and µg/L, or between µg/g and mg/kg.

[2] Published literature searched as of 8 May 2014 using the bibliographic database of Daughton and Scuderi (2014).

[3] 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 depending on the quantity of drug locally prescribed or consumed. Numerous additional supporting references exist beyond the few examples cited, which were selected primarily from the more recent literature. Asterisks (***) in the “examples” column denote that published occurrence data supports API’s presence at substantial levels (e.g., levels in STPs or waters exceeding 1 µg/L, or levels in sludges or sediments exceeding 1 mg/kg or 1 µg/g).

[4] API is an antibiotic - a total of 23 of the 52 APIs listed; some are also used in veterinary medicine and agriculture.

[5] Chemical Abstracts Service Registry Numbers [CASRN] listed in square brackets after API generic names.

[6] 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. Asterisks (***) in the “examples” column denote that published occurrence data supports API’s presence at substantial levels (e.g., levels in STPs exceeding 1 µg/L, or levels in sludges or sediments exceeding 1 mg/kg).

[7] Paucity of occurrence data - possible MEOCs: 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.

Abbreviations: API: active pharmaceutical ingredient; BDDCS: Biopharmaceutics Drug Classification System (see: Benet et al., 2011); CAFO: confined animal feeding operation; LOD: analytical limit of detection; MEOC: Matthew Effect Orphaned Chemical (see: Daughton, 2014)]; OTC: Over-the-Counter drug (no prescription required); PEC: predicted environmental concentration; STP: sewage treatment plant.

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Table S-3. Examples of "apparent increased concentrations" (negative removals), de-conjugation, or presence of conjugates of various non-steroidal[1] APIs during sewage treatment

API	Reference
Alfuzosin	(Fick et al., 2011)
Amitryptiline	(Fick et al., 2011)
Atenolol	(Terzic et al., 2008)
Azithromycin	(Fick et al., 2011; Terzic et al., 2008)
Bezafibrate	(Sui et al., 2011)
Budesonide	(Kosma et al., 2014)
Carbamazepine	(Calisto et al., 2011; Kosma et al., 2014; Lacey et al., 2012; Langford and Thomas, 2009; Lubliner et al., 2010; Martínez Bueno et al., 2012; Olofsson, 2012; Sui et al., 2014; Vieno et al., 2007; Yuan et al., 2013)
Cetirizine	(Wennmalm and Gunnarsson, 2009)
Citalopram	(Yuan et al., 2013)
Ciprofloxacin	(Plósz et al., 2010)
Clindamycin	(Fick et al., 2011)
Clotrimazole	(Lacey et al., 2012)
Dehydronifedipine	(Lubliner et al., 2010)
Diclofenac	(Kosma et al., 2014; Lacey et al., 2012; Lee et al., 2012; Pérez and Barceló, 2008; Sui et al., 2011; Terzic et al., 2008; Zorita et al., 2009)
Dihydrocodeine	(Wick et al., 2009)
Doxepin	(Wick et al., 2009)
Erythromycin	(Gulkowska et al., 2008; Terzic et al., 2008)
Fentanyl	(Fick et al., 2011; van der Aa et al., 2013)
Furosemide	(Lacey et al., 2012)
Gemfibrozil	(Sui et al., 2011)
Glibenclamide	(Fick et al., 2011)
Ibuprofen	(de Graaff et al., 2011)
Ketamine	(Baker and Kasprzyk-Hordern, 2013; van der Aa et al., 2013)
Ketoprofen	(Langford and Thomas, 2009)
Lamotrigine	(Ferrer and Thurman, 2010)
Loperamide	(Fick et al., 2011)
Lorazepam	(Yuan et al., 2013)
Mefenamic Acid	(Lacey et al., 2012; Nakada et al., 2008)
Metoprolol	(Lacey et al., 2012; Sui et al., 2011; Wennmalm and Gunnarsson, 2009; Wick et al., 2009)
Nefazodone	(Fick et al., 2011)
Nimesulide	(Lacey et al., 2012)
Nordazepam	(Bijlsma et al., 2012; van der Aa et al., 2013)
Ofloxacin	(Lee et al., 2007)
Oxazepam	(Bijlsma et al., 2012; Fick et al., 2011; Yuan et al., 2013)
Pentoxyfylline	(Metcalfe et al., 2003)
Propranolol	(Hashim, 2012)
Risperidone	(Fick et al., 2011)
Ritalin	(van der Aa et al., 2013)

Roxithromycin	(Tewari et al., 2013)
Sulfamethoxazole	(Plósz et al., 2010; Reungoat et al., 2011; Tewari et al., 2013)
Sulpiride	(Sui et al., 2014)
Temazepam	(Bijlsma et al., 2012)
Tetracycline	(Gulkowska et al., 2008)
Thiabendazole	(Lubliner et al., 2010)
Tramadol	(Wennmalm and Gunnarsson, 2009)
Trimethoprim	(Gulkowska et al., 2008; Plósz et al., 2010; Sui et al., 2011; Terzic et al., 2008) (Senta et al., 2013, references cited therein)
Negative STP removals compiled for many APIs	(Onesios et al., 2009; Verlicchi et al., 2012)
Various illicit drugs	(van Nuijs and Covaci, 2012)

[1] Most research on the occurrence of API conjugates in sewage has been done on estrogenic steroids; examples of these works are not provided here.

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