Science of the Total Environment 562 (2016) 391–426

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Review

Pharmaceuticals and the Environment (PiE): Evolution and impact of the published literature revealed by bibliometric analysis

Christian G. Daughton

Environmental Futures Analysis Branch, Systems Exposure Division, National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, 944 East Harmon Avenue, Las Vegas, NV 89119, USA

HIGHLIGHTS

- Pharmaceuticals in the environment (PiE) as a field of research has displayed exponential growth since the late 1990s.
- As a highly transdisciplinary field of research, PiE crosscuts many topics, concerns, and disciplines.
- The historical emergence of some of the many facets of PiE's was examined using bibliometric analysis.
- Some facets span over 70 years of publishing, raising questions regarding research priorities and resource allocation.
- A definitive, core list of PiE's most highly cited papers was compiled (385), together with a wide range of other metrics.

GRAPHICAL ABSTRACT

ARTICLE INFO

Article history:
Received 16 February 2016
Received in revised form 15 March 2016
Accepted 15 March 2016
Available online 19 April 2016

Editor: D. Barcelo

Keywords:
Pharmaceuticals
Environmental contaminants
History
Bibliometrics
Most cited

ABSTRACT

The evolution and impact of the published literature surrounding the transdisciplinary, multifaceted topic of pharmaceuticals as contaminants in the environment is examined for the first time in an historical context. The preponderance of literature cited in this examination represents the earlier works. As an historical chronology, the focus is on the emergence of key, specific aspects of the overall topic (often termed PiE) in the published literature and on the most highly cited works. This examination is not a conventional, technical review of the literature; as such, little attention was devoted to the more recent literature.

The many dimensions involved with PiE span over 70 years of published literature. Some articles began to appear in published works in the 1940s and earlier, while others only began to receive attention in the 1990s and later. Decades of early research on what at the time seemed to be disconnected topics eventually coalesced in the mid-to-late 1990s around a number of interconnected concerns and issues that now comprise PiE. Major objectives are to provide a new perspective to the topic, to facilitate more efficient and effective review of the literature by others, and to recognize the more significant, seminal contributions to the advancement of PiE as a field of research. Some of the most highly cited articles in all of environmental science now involve PiE. As of April 2015, a

Abbreviations: API, active pharmaceutical ingredient; CECs, contaminants of emerging concern; EDC, endocrine disrupting chemical; EPA, U.S. Environmental Protection Agency; EPR, extended producer responsibility; FDA, U.S. Food and Drug Administration; GS, Google Scholar; MDR, multidrug resistance; MXR, multixenobiotic resistance; PiE, pharmaceuticals in the environment; PhACs, pharmaceutically active compounds; PPCPs, pharmaceuticals and personal care products; TPs, transformation products; TrOC (TOrC), trace organic chemical.

E-mail address: daughton.christian@epa.gov.

http://dx.doi.org/10.1016/j.scitotenv.2016.03.109

core group of 385 PiE articles had each received at least 200 citations; one had received 5424 citations. But hundreds of additional articles also played important roles in the evolution and advancement of the field.

Contents

1. Introduction

A perspective is presented on the early history surrounding the evolution of the topic of pharmaceuticals as contaminants in the environment. This perspective is derived from examining key words and the metadata associated with a comprehensive database of articles relevant to this multi-faceted topic. The articles in this database were published in an array of resources, but primarily journals, books, reports, and dissertations:

Daughton and Scuderi, 2016b "Pharmaceuticals and Personal Care Products (PPCPs): Relevant Literature".

[*Note*: *the non-standard format used in this paper to cite references is discussed at the end of Section 3* (*Approach*).]

The wide spectrum of issues surrounding this complex, multi-faceted topic span over 70 years of published literature. Some articles began to appear in published works in the 1940s and earlier. Other aspects did not begin to receive attention until the 1990s and continuing to this day. With decades of research on what at the time seemed to be disconnected topics, a discrete field of research eventually coalesced in the mid-1990s around a number of interconnected concerns and issues related to the environmental occurrence of the active ingredients in drugs (known as active pharmaceutical ingredients, APIs). Among a number of terms used over the years, this field of research is frequently referred to as Pharmaceuticals in the Environment — often abbreviated PiE.

This examination is not a review of the literature. It is not an examination of the technical content of the PiE published literature or an attempt to distill new knowledge regarding the PiE topic. Rather, it began simply as an attempt to see whether new insights might emerge when trying to examine from some new perspectives a very large body of published literature surrounding a complex and expansive facet of environmental science. While this examination of PiE tries to show the historical trajectory of PiE and to place some events in an historical context, it does not attempt to summarize or critique what has been learned or to proffer where its future should aim; as such, it is important to keep in mind that the focus is on the older, pioneering literature rather than newer literature. To my knowledge, such an assessment has not been attempted before — nor has one been specifically called for. This effort was partly motivated by the fact that PiE comprises an extremely large body of disparate published literature, contributed from many different and usually disconnected technical disciplines. At the least, this examination tried to document some of the history behind the evolution or emergence of PiE as a field of study. As such, errors and omissions are inevitable — sometimes casualties of the subjective nature of defining the actual scope of PiE as a dedicated field of research.

This article could be partly viewed as an historical bibliometric examination of PiE. Surprisingly, very few bibliometric examinations

have been performed for PiE, and they have focused specifically on wastewater treatment and drinking water; they have also not examined the literature prior to 1992. Here are two examples:

Fu et al., 2013 "Mapping of drinking water research: A bibliometric analysis of research output during 1992–2011".

Qian et al., 2015 "A bibliometric analysis of global research progress on pharmaceutical wastewater treatment during 1994–2013".

Many of the terms and concepts that have surrounded or intersected with the PiE field of research were examined with respect to their historical emergence in the literature. Some large-scale bibliographic citation analysis was also performed to try and locate the most influential journals, articles, and authors. Whether anything of use will emerge from this journey can only be judged by the reader; this is especially the case given the necessarily disjointed and uneven array of topics covered. But a working hypothesis could be whether it is important to assess the evolution of a still-growing area of research that has emerged over the course of decades. An obvious question, however, is whether the sizeable investment in resources represented by this body of published works has been most effectively allocated, whether it has been overly redundant or unnecessarily incremental, and whether its data and insights might be more effectively mined and organized to yield useful new knowledge. Although some of the issues briefly touched upon here are germane to other topics or concerns in environmental science, they either originated from PiE or intersect with PiE. Some issues and concerns are unique to PiE, and others represent new areas that have been catalyzed or fostered by PiE research.

2. Scope of the PiE issue

In referring to "the environment" with respect to PiE, it must be emphasized that there are two dimensions that are often compartmentalized but which really form a continuum — the immediate, built (human-made) environment and the so-called natural environment. Drugs can have adverse – and sometimes profound – consequences after entering either. Transit into the immediate, surrounding built environment involves short, direct upstream pathways that can result in high exposure levels leading to acute – and sometimes fatal – toxicity for exposed humans, domestic animals, and wildlife. These upstream pathways involve imprudent storage and disposal practices for medications, as well as certain types of occupational practices such as those resulting from insufficiently controlled pharmacy compounding of highly toxic pharmaceuticals or from unprotected handling of contaminated laundry from those undergoing chemotherapy (Daughton and Ruhoy, 2009 "Environmental footprint of pharmaceuticals: The significance of factors beyond direct excretion to sewers"). In contrast, pathways leading to the natural environment involve downstream processes such as the introduction of drug residues to surface or ground waters via municipal or manufacturer wastewater discharge or from landfills. These downstream processes generally involve levels of exposure to active pharmaceutical ingredients (APIs) that are orders of magnitude lower than from upstream processes - often simply a result of dilution.

It is important to recognize that these two major pathways are the subjects of completely separate and distinct bodies of published literature that rarely cross-reference each other. The former is largely the domain of clinical medicine practitioners, toxicologists, and forensic specialists while the latter involves a host of disciplines within the environmental sciences. In reality, however, all of these processes and types of exposure are interrelated and comprise a complex network (see Fig. 1 in. Daughton, 2008 "Pharmaceuticals as environmental pollutants: the ramifications for human exposure") that reflects society's widespread, multi-faceted relationship with the expansive universe of therapeutic and lifestyle drugs, which comprises thousands of distinct APIs formulated into tens of thousands of different medicated products, as well as a largely separate galaxy of illicit drugs (see: Daughton, 2013 "Pharmaceuticals in the Environment: Sources and Their Management").

The persistent isolation of two distinct bodies of literature might seem surprising since both play major roles in defining the full scope of PiE and in seeking solutions for reducing or preventing a ubiquitous source of anthropogenic contamination of the environment. Drugs have been widely known to be involved in accidental, unintentional fatal human poisonings since the 1800s, with salicylates (particularly methyl salicylate) playing a major role. Formal case reports were being published as early as the 1930s; for example, see the references cited in the following:

Davis, 2007 "Are one or two dangerous? Methyl salicylate exposure in toddlers".

Shirreff and Pearlman, 1940 "Oil of wintergreen poisoning: (Report of Two Additional Fatal Cases)".

Troll and Menten, 1945 "Salicylate poisoning: report of four cases".

Hundreds of journal articles have been published since the 1940s on the unintentional and accidental, acute poisonings of children (drugs have long been a major cause of fatal poisonings among children) as a result of improperly stored or discarded medications. Other types of fatal poisonings from unintended exposures did not attract concerted attention until decades later. Accidental poisonings of pets did not begin attracting attention until the 1980s:

Fitzgerald et al., 2006 ""Over-The-Counter" Drug Toxicities in Companion Animals".

Murphy, 1994 "Toxin exposures in dogs and cats: drugs and household products".

Mass killings of raptors from scavenging improperly disposed carcasses of animals that had been euthanized with barbiturates began to attract attention in the 1990s:

Langelier, 1993 "Barbiturate poisoning in twenty-nine bald eagles".

USFWS, 2003 "Pentobarbital Poisoning of Eagles".

And the devastation of certain vulture populations from scavenging carcasses of animals that had been therapeutically treated with certain non-steroidal anti-inflammatories (notably diclofenac) emerged as a major ecological concern in 2004:

Green et al., 2004 "Diclofenac poisoning as a cause of vulture population declines across the Indian subcontinent".

Oaks et al., 2004 "Diclofenac residues as the cause of vulture population decline in Pakistan".

Shultz et al., 2004 "Diclofenac poisoning is widespread in declining vulture populations across the Indian subcontinent".

With acute "upstream" poisonings aside, the major concerns with regard to the presence of APIs in the environment result from chronic, low-level exposures for a broad spectrum of organisms ranging from microorganisms to mammalian wildlife. These downstream impacts can be subtle (such as modification to various behaviors), and their overall significance regarding species health at the population level continues to be scrutinized. Also important to note is that the issues surrounding APIs in the environment are closely intertwined with those involving other commonly used consumer chemicals, especially the myriad numbers of personal care products, nutritional supplements, and ever-expanding universe of illicit drugs - all of which may participate in complex interactions with biological receptors.

3. Approach

This examination of the published literature – covering all facets of pharmaceuticals in relationship to the environment – relied on a specialized, curated bibliographic database that houses the digitized full text for over 97% of the journal articles it contains (Daughton and Scuderi, 2016b "Pharmaceuticals and Personal Care Products (PPCPs): Relevant Literature"). Two different versions of the database are available to the public — a simple text listing of the bibliographic citations or an electronic database version of the citations together with abstracts; because of publisher copyright restrictions, the complete

electronic version with digitized reprints is available only to US EPA employees. Background and history regarding the database are provided here: https://sites.google.com/site/daughton/PPCPs-bibliographic_database. As of 6 August 2015, it contained over 22,600 records — over 16,900 of which were journal articles and over 1100 were book chapters. Only 14 (0.08%) of the nearly 17,000 journal articles had been retracted or withdrawn — half of these by the same author. A total of 192 articles (1%) were published in journals that some define as "predatory" (e.g., see: http://scholarlyoa.com/publishers/), while noting that this can be a contentious issue and one that is a function of how this evolving publishing niche is defined and how its ethics are perceived.

Important to recognize is that the decision process used for inclusion/exclusion of articles in any bibliographic database cannot avoid subjective judgments. The scope of each article must be evaluated for its relevance. With the database used in this study (Daughton and Scuderi, 2016b "Pharmaceuticals and Personal Care Products (PPCPs): Relevant Literature"), articles were included if they contained environmental data or discussion of pharmaceuticals and personal care products (PPCPs) relevant to the many facets of the PiE topic, including origins, sources, occurrence, transport, fate, exposure, effects, stewardship, disposal, pollution prevention, monitoring, waste and water treatment technologies, risk assessment, risk communication, acute poisoning, and others, as well as major articles on many aspects that are peripherally related (e.g., important references dealing with low-dose effects, mixture effects, and databases for medications, physicochemical properties, and toxicology, among others). Articles were excluded if the focus on PPCPs was judged to be minimal - requiring an admittedly subjective judgment. We believe the database houses the most extensive collection of curated articles focused solely on PiE and which is accessible to the public.

The topic of PiE is not suited to straightforward, conventional searches of commercial databases of the published literature because of the lack of definitive search terms, which results in extremely large numbers of irrelevant hits. Instead, many different types of searches (ranging from very specific to general) must be continually performed to locate new references to include in the database. Equally important is the role of citation analysis (both forward and backward - using both citing and cited articles) for locating new references. Citation analysis is also used in this examination as a proxy for the "impact" of specific articles. Google Scholar was used for obtaining citation counts on individual articles (recognizing its advantages and limitations compared with subscription citation services); these counts often contain self-citations, but these become unimportant in determining which articles are most highly cited since the overall contributions from self-citations become diminishingly small. A discussion of citation analysis is far beyond the scope of this examination; the reader is referred to a recent article (Harzing, 2014 "A longitudinal study of Google Scholar coverage between 2012 and 2013").

Finally, note that since the primary focus of this paper is on an historical chronology of the published literature, the decision was made to provide more emphasis than usual to the cited papers. To each in-text citation, which would normally use the conventional notation of author(s) and year, the complete title has also been added. This unconventional formatting style was intended to provide the reader a more ready understanding of what papers were being cited so that the full citations in the bibliography would not have to be frequently referred to. It was also intended to provide added recognition to the contributions of seminal works.

4. Findings

4.1. The trajectory of the published literature on PiE

This study made use of the articles in the PPCPs database as of April 2015. Of the total entries in the PPCPs database (22,676), 75% (16,918) were journal articles and 4% (918) were book chapters (96 were books). During the period 2000–2015, the numbers of articles published on PiE (in journals and books) had increased yearly — from a rate of 200 per year to a rate of 1800 per year; see Table 1, which also shows the yearly percentage increases in numbers of publications. Relative to the prior year, the largest yearly increases were 38% (2003), 36% (2006), and 30% (2012). The smallest increases were 3% (2010 and 2011) and 6% (2013). About 98% of the journal articles and book chapters in the database most directly relevant to PiE (excluding those devoted to accidental poisonings and disposal) were published in the last 20 years (after 1995, a total of 14,658); of the 14,936 spanning all years, only 278 (1.8%) were published before 1996. Compared with the respective prior decade, in the two decades spanning 1990–1999 and 2000–2009, the numbers of publications in journals and books have increased by 5- and 10-fold.

The sheer size of the continually expanding published literature surrounding PiE makes it readily apparent that huge challenges confront those who strive for a synoptic understanding of many individual facets of the topic. Such an understanding of the entire integrated field may no longer be possible. The proliferation of articles on PiE make it more time-consuming and onerous to not only ensure that the newly appearing articles (which takes place on a daily basis) are being comprehensively located, but also to discern which are the more important — to distinguish them from those that are redundant or that represent minor incremental additions. Synthesizing the expanding literature in a manner that creates new understandings or knowledge may only be possible for very specialized aspects of the topic. A fundamental question presents itself - at which point does unfettered addition of new articles to the published literature actually begin to impede advancements or the translation of new data into useful knowledge? The examination presented here does not pretend to address this important question — or the many other allied questions, such as whether continually diminishing research resources are being effectively targeted at the most pressing needs.

4.2. Distribution of journals publishing PiE-related articles

The distribution of journals that have published PiE-related work is highly skewed (see Supplementary Table S-1 and Supplementary Fig. S-1). Although a total of 16,580 PiE articles were distributed among 2295 different journals, 31% of all published articles (5186/16580) were distributed among just eight journals: *Environmental Science & Technology* (1083), *Chemosphere* (918), *Science of the Total Environment* (744), *Water Research* (687), *Journal of Chromatography A*

Table 1
Numbers of articles relevant to PiE in journals and books from 1980 to 2015.[a]

Decade or year	Number of articles	Percent increase
1980–1989	85	Percent increase over prior decade
1990–1999	500	488
2000–2009	5458	992
2010–2014	7308	(Half decade) 33.9
2000	181	Percent increase over prior year
2001	207	14.4
2002	242	16.9
2003	335	38.4
2004	421	25.7
2005	512	21.6
2006	697	36.1
2007	827	18.7
2008	925	11.9
2009	1111	20.1
2010	1146	3.2
2011	1184	3.3
2012	1541	30.2
2013	1635	6.1
2014	1802	10.2
2015	1524	Incomplete year (through 6 August 2015)

[a] Data compiled up until 6 August 2015.

(548), *Environmental Toxicology & Chemistry* (459), *Journal of Hazardous Materials* (384), and *Aquatic Toxicology* (363). The majority of PiE articles have been published in just 50 journals, which housed 58% of all published articles (9549 of 16,580). There were 23 journals that had published at least 100 articles each. In contrast, 1403 different journals had each published only a solitary article.

Notable aspects of the types of journals that have published the world's literature on PiE include the following. The field is predominantly published in journals outside the fields of medicine and health care. The most active journals have focused on environmental science (especially aquatic and marine sciences), environmental toxicology, analytical chemistry (11 journals), environmental monitoring, water chemistry, waste treatment, water treatment, and human toxicology. See the word cloud graphic comprising the journal-title words (excluding generic words such as journal, science, and nature) for the 65 journals that have each published at least 25 articles (see Supplementary Fig. S-2. As one might expect, higher-impact journals published fewer articles than many other journals; for example, *Science* was 27th with 87 articles, and *Nature* was 43rd with 59 articles.

In contrast, comparatively little has been published in journals devoted to the fields of medicine, health care, or pharmacology. Of the 65 journals that have published more than 25 articles each, only 3 are devoted to the fields of medicine or applied pharmacology: *The Pharmaceutical Journal* (33 articles), *New England Journal of Medicine* (32), and *The Lancet* (27). These journals account for only 92 articles (0.6% of the total number of articles in journals); many of these articles tend to focus on childhood accidental poisonings from drug waste, drug disposal (e.g., take-back programs for unwanted drugs), and environmental stewardship (e.g., prudent use of antibiotics and safe disposal of unwanted drugs).

4.3. Emergence of PiE as a discrete field of research in environmental science

Given the wide scope of environmental issues surrounding the topic of pharmaceuticals and personal care products (PPCPs), the examination presented here will focus primarily on concerns related to the occurrence of APIs in the natural environment. This topic is sometimes referred to as Pharmaceuticals in the Environment — or PiE. The examination tried to exclude from consideration articles that focused solely on the allied topic of personal care products, which is also captured in the PPCPs bibliographic database. These two large groups of consumer chemicals sometimes intersect (for example, with the use of biocides such as triclosan and triclocarban). The fact that ingredients in personal care products can establish a presence in the environment began to emerge in the early 1980s and mid-1990s with the identification of synthetic musks in various environmental matrices:

Eschke et al., 1994 "Untersuchungen zum Vorkommen polycyclischer Moschus-Duftstoffe in verschiedenen Umweltkompartimenten – Nachweis und Analytik mit GC/MS in Oberflässern und Fischen (1. Mitteilung) [Studies on the occurrence of polycyclic musk flavors in different environmental compartments — 1st Communication: Detection and analysis by GC/MS in surface and sewage waters and fish]".

Franke et al., 1995 "Organic compounds as contaminants of the Elbe River and its tributaries. Part II: GC/MS screening for contaminants of the Elbe water".

Rimkus et al., 1994 "Nitro musks in human adipose-tissue and breast-milk".

Yamagishi et al., 1981 "Identification of musk xylene and musk ketone in freshwater fish collected from the Tama River, Tokyo".

Yamagishi et al., 1983 "Synthetic musk residues in biota and water from Tama River and Tokyo Bay (Japan)".

This was preceded with identification of the biocide triclosan in the late 1970s and its environmental transformation product methyl triclosan in 1984:

Hites and Lopez-Avila, 1979 "Identification of organic compounds in an industrial waste water"; Jungclaus et al., 1978 "Organic compounds in an industrial Wastewater: a case study of their environmental impact"; Lopez-Avila and Hites, 1980 "Organic compounds in an industrial wastewater. Their transport into sediments".

Jungclaus et al., 1978 "Organic compounds in an industrial Wastewater: a case study of their environmental impact".

Lopez-Avila and Hites, 1980 "Organic compounds in an industrial wastewater. Their transport into sediments".

Miyazaki et al., 1984 "Residues of 4-chloro-1-(2,4-dichlorophenoxy)-2-methoxybenzene(triclosan methyl) in aquatic biota".

These were all preceded in 1975 with study of the degradation in sewage of the biocide trichlorocarbanilide (triclocarban):

Gledhill, 1975 "Biodegradation of 3,4,4′-trichlorocarbanilide, TCC®, in sewage and activated sludge".

One aspect of PiE that has caused long-time confusion is the question of what is meant by a pharmaceutical, drug, or API — or even how large the super set of APIs might even be. This topic was not covered in the PiE literature until 2013:

Daughton, 2013 "Pharmaceuticals in the Environment: Sources and Their Management".

It still appears, however, that no authoritative estimate yet exists for the number of medicinal, small molecular APIs in current use worldwide; estimates for the US seem to currently range up to 2500, even though a recent study shows that the cumulative total ever approved in the US (through 2013) is 1453. And it is even more difficult to estimate the numbers of illicit and designer drugs in current use, although the numbers continue to grow:

Kinch et al., 2014 "An overview of FDA-approved new molecular entities: 1827–2013".

The question often arises as to when the topic of PiE first emerged and established itself as a discrete field of study. There is no definitive date that marks the emergence of the PiE field. Rather it is a topic that gradually coalesced from a number of isolated progenitor studies over the course of several decades, especially in the 1970s and early 1980s. But a concerted and rapidly expanding focus on the larger scope of the many environmental issues that surround pharmaceuticals as environmental contaminants (especially human-use drugs) began in earnest several decades later, notably marked by the 2-year period 1998–1999. This becomes clear when examining a select series of 93 articles published up through 1999, which are listed in chronological order in Supplementary Table S-2; of these articles, 37 are highlighted as among those most highly cited from all years, with each attracting a minimum of 200 citations (as of April 2015) according to Google Scholar. These articles were selected to represent many of the numerous facets that play interacting roles in the questions and concerns surrounding the PiE topic.

The 2-year period 1998–1999 witnessed an initial explosion of 26 articles that would later become highly cited. As of April 2015, the citation counts for these 26 articles spanned the range of 203 to 3064; notable is that these articles continue to attract citations over 15 years later. While this is more than twice the number of the 12 highly cited papers over the prior 20 years (1977–1997), it is overshadowed by the total of 348 highly cited papers during the ensuing 13-year period 2000–2012, which have attracted citation counts spanning the range from 200 to 5424 (see Supplementary Table S-3). In total, there have been 378 highly cited papers on PiE (each with at least 200 citations as of April 2015). Many of these articles continue to display very long citation half-lives. The disproportionate abundance of highly cited articles concentrated in the 2-year period 1998–1999 can be viewed as a point in time at which PiE emerged in the literature as a discrete field of research.

Briefly discussed below are some specific aspects to PiE that deserve highlighting with respect to their emergence in the literature.

4.3.1. Brief history prior to 2000

Prior to 1998, comparatively few papers had directly addressed environmental issues regarding isolated pharmaceuticals. Absent was a

widespread recognition that the larger universe of pharmaceuticals may pose environmental risks. The earlier published work tended to focus on very specific aspects involving agriculture and aquaculture and indirectly related issues involving public health and safety (e.g., accidental poisonings involving ingestion by children and wildlife of leftover or imprudently disposed drugs).

Not yet recognized was how expansive, interconnected, and complex the larger issue would eventually become (see Fig. 1 in. Daughton, 2008 "Pharmaceuticals as environmental pollutants: the ramifications for human exposure") — one that would eventually bring together many disciplines and areas of investigation within science, social science, engineering, and healthcare – including analytical and environmental chemistry, environmental and human toxicology, veterinary sciences, animal husbandry, aquatic and marine sciences, agricultural and plant sciences, hydrology, pharmacology, pharmacy science and practice, medical science and practice, healthcare practice, nursing, social and behavioral sciences, civil and sanitary engineering, waste treatment, water treatment, water reuse, and risk assessment and communication – as well as the need to inform policy, legislation, and regulation.

Concerns surrounding the potential for endogenous and synthetic steroids from human and domestic animals to enter the environment and drinking water via sewage were being voiced in the 1950s–1970s (and probably earlier):

Kirchner et al., 1973 "Fluoreszenzspektroskopische Bestimmung ovulationshemmender Steroide aus Wasser und Abwassern auf der DC-Platte [Fluorescence spectroscopic determination of anti-ovulatory steroids in water and waste water on thin layer chromatography plate]".

Norpoth et al., 1973 "Untersuchingen zur ovulationshemmender Steroide Frage des Loslichkeit und Stabilitat in Wasser, Abwassern und Belebtschlamm [Studies on the problem of solubility and stability of steroid ovulation inhibitors in water, waste water, and activated sludge]".

Stob, 1956 "Fecal Elimination of Hormones in Sheep and Cattle Treated with Synthetic Estrogens".

Stumm-Zollinger and Fair, 1965 "Biodegradation of steroid hormones".

Tabak and Bunch, 1970 "Steroid hormones as water pollutants I. Metabolism of natural and synthetic ovulation-inhibiting hormones by microorganisms of activated sludge and primary settled sewage".

von Rathner and Sonneborn, 1979 "Biologisch wirksame Östrogene in Trink- und Abwasse [Biologically active oestrogens in portable water and effluents]".

Wilson, 1976 "Steroids as water pollutants: a literature survey of synthetic and natural hormonal steroids and the analytical methods for their determination" <as cited by others>.

Wilson, 1978 "Contraceptive steroids in water supplies".

Stumm-Zollinger and Fair may have been the first (in 1965) to voice the possibility that residues of drugs or hormones "may occur in our drinking waters," albeit "under the most unfavorable conditions." This concern did not seem to be resurrected until the mid-1970s with the work of:

Daughton, 2010b "Pharmaceutical Ingredients in Drinking Water: Overview of Occurrence and Significance of Human Exposure" (see references cited therein).

Donaldson, 1977 "Trace organics in water".

Garrison, 1977 "Analysis of organic compounds in water to support health effects studies".

Garrison et al., 1976 "GC/MS Analysis of Organic Compounds in Domestic Wastewaters".

Hignite and Azarnoff, 1977 "Drugs and drug metabolites as environmental contaminants: Chlorophenoxyisobutyrate and salicylic acid in sewage water effluent".

Stumm-Zollinger and Fair, 1965 "Biodegradation of steroid hormones".

Significantly, the works of Garrison, Donaldson, and others in the 1970s on the characterization of low but measurable levels of known chemicals in treated wastewaters began to lead to the eventual widespread appreciation that sewage treatment may not be capable of fully removing the most hazardous pollutants and that when removed from the liquid phase, many of these pollutants concentrate in the sludge; for example, see:

Petrasek et al., 1983 "Fate of Toxic Organic Compounds in Wastewater Treatment Plants".

The potential environmental impact of pharmaceuticals began to attract some attention in the 1970s. This early literature (pre-1998) tended to focus on three limited aspects of what would only later become the field of PiE:

(i) certain drugs used in agriculture and aquaculture (primarily antibiotics, certain steroids, and agricultural antiparasitics, especially the macrocyclic lactones such as the avermectins); for example:

Coats et al., 1976 "Model ecosystem evaluation of the environmental impacts of the veterinary drugs phenothiazine, sulfamethazine, clopidol, and diethylstilbestrol".

Huber, 1971 "Antibacterial drugs as environmental contaminants".

Nessel et al., 1989 "Environmental fate of ivermectin in a cattle feedlot".

Samuelsen et al., 1991 "Fate and microbiological effects of furazolidone in a marine aquaculture sediment".

Wall and Strong, 1987 "Environmental consequences of treating cattle with the antiparasitic drug ivermectin".

(ii) the recognition that antibiotics could lead to resistance in the environment — a concern that extends at least back to the 1940s; for example:

Barber, 1947 "Staphylococcal Infection due to Penicillin-resistant Strains".

Demerec, 1945 "Production of Staphylococcus Strains Resistant to Various Concentrations of Penicillin".

Miller, 1948 "Bacterial resistance to antibiotics".

(iii) the various aspects of stewardship and sustainable use of pharmaceuticals — namely, the public health concerns posed by unused, unwanted drug waste (especially problems faced by consumer disposal of drugs, the need for unwanted-drug take backs, and the persistent hazard of childhood unintentional, accidental ingestions from improperly stockpiled or stored medications or imprudently disposed medications in the home). These were problems that had already begun to attract debate and discussion in the 1960s and 1970s; for example:

Bradley and Williams, 1975 "Evaluation of medicines returned in Manchester DUMP campaign".

Gunn and Lishman, 1967 "Letters to Editor regarding "Problem of Unused Drugs""

Hart and Marshall, 1976 "Wastage of Pharmaceuticals".

Overall, during the period predating the early 1990s, there were comparatively few papers that would later prove seminal in providing an early glimpse into the expansive scope of the PiE issue. Among these few that have discussed the prospects of APIs occurring in sewage or ambient waters or that established their actual presence were:

Aherne and Briggs, 1989 "The relevance of the presence of certain synthetic steroids in the aquatic environment".

Aherne et al., 1985 "The role of immunoassay in the analysis of microcontaminants in water samples".

Aherne et al., 1990 "Cytotoxic drugs and the aquatic environment: estimation of bleomycin in river and water samples".

Coats et al., 1976 "Model ecosystem evaluation of the environmental impacts of the veterinary drugs phenothiazine, sulfamethazine, clopidol, and diethylstilbestrol".

Garrison et al., 1976 "GC/MS Analysis of Organic Compounds in Domestic Wastewaters".

Gilbertson et al., 1990 "Environmental fate of ceftiofur sodium, a cephalosporin antibiotic. Role of animal excreta in its decomposition".

Hignite and Azarnoff, 1977 "Drugs and drug metabolites as environmental contaminants: Chlorophenoxyisobutyrate and salicylic acid in sewage water effluent".

Rurainski et al., 1977 "Über das Vorkommen von natürlichen und synthetischen Oestrogenen im Trinkwasser [Concerning the occurrence of natural and synthetic estrogens in drinking water]".

Tabak et al., 1981 "Steroid hormones as water pollutants II. Studies on the persistence and stability of natural urinary and synthetic ovulation-inhibiting hormones in treated and treated wastewaters".

Warman and Thomas, 1981 "Chlortetracycline in soil amended with poultry manure".

It is important to note that throughout this examination of the chronology of work on PiE, there could very well be even earlier articles in non-English journals. Much of this literature is very difficult to locate or access. Some of the articles in German or Dutch, for example, have numerous errors in how they are cited by others; this is also true for older reports and dissertations. For example, it is usually noted that the first instances of APIs being identified in water samples usually refer back to the mid-1970s:

Garrison et al., 1976 "GC/MS Analysis of Organic Compounds in Domestic Wastewaters".

Hignite and Azarnoff, 1977 "Drugs and drug metabolites as environmental contaminants: Chlorophenoxyisobutyrate and salicylic acid in sewage water effluent".

Rurainski et al., 1977 "Über das Vorkommen von natürlichen und synthetischen Oestrogenen im Trinkwasser [Concerning the occurrence of natural and synthetic estrogens in drinking water]".

But prior works on "micropollutants" had also identified chemicals that could be associated with APIs. One example, published in 1974, compiled data from the early 1970s where clofibric acid (as mecoprop), caffeine, some natural steroids/sterols, and other allied chemicals had been reported; this report, however, does not explicitly mention any connections with pharmaceuticals:

Water Research Centre, 1974 "A comprehensive list of polluting substances which have been identified in various fresh waters, effluent discharges, aquatic animals and plants, and bottom sediments. COST project 64b: Analysis of organic micropollutants in water".

Some background for this 1974 Water Research Centre project can be found here:

Penning et al., 1986 "Integration and Use of the List of Organic Micropollutants in the Aquatic Environment in the ECDIN Data Bank".

In 1988, the first papers to focus on environmental risk assessment for PiE began to appear. These articles, authored by the US FDA, presaged the eventual concerns regarding environmental impact. These included:

Matheson, 1988 "The Nuts and Bolts of Preparing an Environmental Assessment".

Bloom and Matheson, 1993 "Environmental assessment of avermectins by the US Food and Drug Administration".

Haley et al., 1993 "Requirements of the FDA for the environmental assessment of animal health products".

Vincent, 1993 "Environmental assessment: U.S. requirements in new drug applications".

As an aside, despite several decades of studies on a wide spectrum of APIs in the environment, the first official methods for monitoring a select group of chemicals often targeted for PiE studies (namely various steroids and hormones) was not published until December 2007, by the USEPA:

USEPA, 2007 "EPA Method 1698: Steroids and hormones in water, soil, sediment, and biosolids by HRGC/HRMS".

A concerted focus on the need for new analytical methods for APIs in environmental matrices was perhaps catalyzed in large part by the very first large-scale monitoring study involving PiE, which was published in 2002 and which has become one of the most highly cited articles in environmental science (with over 5700 citations in October 2015):

Kolpin et al., 2002 "Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999–2000: a national reconnaissance".

In 1993 and 1994, at least two seminal papers presented another toxicological concern – endocrine disruption – that would later become a major research area onto itself and prove important with respect to the potential for ecological impacts from PiE:

Colborn et al., 1993 "Developmental effects of endocrine-disrupting chemicals in wildlife and humans".

Purdom et al., 1994 "Estrogenic Effects of Effluents from Sewage Treatment Works".

Note, however, that this work was preceded in 1956 by that of Stob, who showed that synthetic hormones can be excreted by domestic animals, and in 1981 by that of Tabak et al., who identified and quantified a spectrum of steroid hormones in sewage:

Stob, 1956 "Fecal Elimination of Hormones in Sheep and Cattle Treated with Synthetic Estrogens".

Tabak et al., 1981 "Steroid hormones as water pollutants II. Studies on the persistence and stability of natural urinary and synthetic ovulation-inhibiting hormones in treated and treated wastewaters".

4.3.2. Multiple exposure and mixture toxicity

Another major area of research that has key relevance to PiE involves multiple exposure (sometimes also referred to as co-exposure) resulting in mixture toxicity (sometimes also referred to as combination effects, combined effects, or joint toxicity). This is one of the major challenges faced by toxicology today. The topic of aquatic mixture toxicity has been an area of research extending back to the 1960s, where its initial scope of interest regarding stressors was primarily inorganic species. A concerted focus on the toxicity of mixtures that included organic pollutants did not begin to coalesce until the 1970s–1980s, marked in 1987 by perhaps the first comprehensive collection of articles in a journal devoted to mixture effects, by Vouk et al. For examples, see the following and the references cited therein:

EIFAC, 1987 "Working party on Water Quality Criteria for European Freshwater Fish, Water quality criteria for European freshwater fish. Revised report on combined effects on freshwater fish and other aquatic life of mixtures of toxicants in water" (and its predecessor 1980 report).

Hermens and Leeuwangh, 1982 "Joint toxicity of mixtures of 8 and 24 chemicals to the guppy (*Poecilia reticulata*)".

Konemann, 1981 "Fish toxicity tests with mixtures of more than two chemicals: a proposal for a quantitative approach and experimental results".

Vouk et al., 1987 "Methods for assessing the effects of mixtures of chemicals".

Despite the decades of isolated articles, mixture toxicity did not begin to attract concerted attention until the mid-1990s and early 2000s:

Altenburger et al., 1996 "Regulations for Combined Effects of Pollutants: Consequences from Risk Assessment in Aquatic Toxicology".

Carpenter et al., 2002 "Understanding the Human Health Effects of Chemical Mixtures".

Escher and Hermens, 2002 "Modes of Action in Ecotoxicology: Their Role in Body Burdens, Species Sensitivity, QSARs, and Mixture Effects".

Kortenkamp and Altenburger, 1998 "Synergisms with mixtures of xenoestrogens: A reevaluation using the method of isoboles".

Kortenkamp and Altenburger, 1999 "Approaches to assessing combination effects of oestrogenic environmental pollutants".

Mehendale, 1994 "Amplified interactive toxicity of chemicals at nontoxic levels: mechanistic considerations and implications to public health".

Rajapakse et al., 2001 "Defining the Impact of Weakly Estrogenic Chemicals on the Action of Steroidal Estrogens".

Silva et al., 2002 "Something from "Nothing" - Eight Weak Estrogenic Chemicals Combined at Concentrations below NOECs Produce Significant Mixture Effects".

Specifically with respect to PiE issues, the toxicological challenges posed by exposure to multiple chemical stressors did not begin to receive attention until the early 2000s:

Backhaus et al., 2000a "Predictability of the toxicity of a multiple mixture of dissimilarly acting chemicals to *Vibrio fischeri*".

Backhaus et al., 2000b "The single substance and mixture toxicity of quinolones to the bioluminescent bacterium *Vibrio fischeri*".

Brain et al., 2004 "Microcosm evaluation of the effects of an eight pharmaceutical mixture to the aquatic macrophytes *Lemna gibba* and *Myriophyllum sibiricum*".

Cleuvers, 2002 "Aquatische Ökotoxikologie ausgewählter Arzneimittel - Algentest und akuter Daphnientest [Aquatic ecotoxicology of selected pharmaceutical agents - Algal and acute daphnia tests]".

Cleuvers, 2003 "Aquatic ecotoxicity of pharmaceuticals including the assessment of combination effects".

Richards et al., 2004 "Effects of pharmaceutical mixtures in aquatic microcosms".

Much of the concern and unknowns surrounding PiE results from the three hypotheses that: (i) chemical stressors such as APIs in the ambient environment often occur at individually low levels (perhaps at levels below the accepted no-effects levels), (ii) ambient exposure for humans and wildlife is often an ongoing process that results from simultaneous or sequential exposure to multiple stressors (aggregate exposure), and (iii) many APIs might impact aquatic species in subtle ways (such as modulation of behaviors) that could be difficult to discern. The possibility that multiple, coordinated exposures might reflect a reality of the exposure universe posed a serious obstacle to predicting toxicity based on individual levels of chemical stressors. These two realities of exposure greatly impede the ability to predict and regulate the risk incurred from ambient exposure; this is noteworthy in contrast with the much better defined conditions of occupational exposure.

One obstacle to readily locating the published literature on multiple exposure and mixture toxicity is the lack of a single, widely used term that reliably captures much of its scope. Required instead, are a mix of general terms (including multiple exposure and mixture toxicity) combined with specific terms describing the interactions between multiple stressors, such as joint action or various modifiers for toxicity (or effects), such as combined (combination), additive, interactive (such as antagonism), enhanced (synergism), cumulative, or amplified. The most commonly used general terms, however, might be multiple exposure and mixture toxicity (combined effects), whose usage extends back into the 1980s.

4.3.3. Inhibition of multidrug resistance

A specific type of mixture effect relates to the inhibition of the endogenous protective mechanism that promotes the cellular efflux of toxicants — multidrug resistance (MDR). The ability of certain APIs to inhibit MDR can enhance the aquatic toxicity of xenobiotics (including other APIs). The role of MDR and its inhibition in aquatic exposures was pioneered and reviewed by Kurelec in 1992, and was soon specifically termed multixenobiotic resistance (MXR) with respect to aquatic organisms by Toomey and Epel (1993):

Kurelec, 1992 "The multixenobiotic resistance mechanism in aquatic organisms".

Toomey and Epel, 1993 "Multixenobiotic Resistance in *Urechis caupo* Embryos: Protection from Environmental Toxins".

This initial work was further elaborated upon by research from Kurelec's and Epel's groups in the 1990s:

Kurelec, 1995 "Inhibition of multixenobiotic resistance mechanism in aquatic organisms: ecotoxic consequences".

Kurelec, 1997 "A new type of hazardous chemical: the chemosensitizers of multixenobiotic resistance".

Müller et al., 1996 "The multixenobiotic resistance mechanism in the marine sponge *Suberites domuncula*: its potential applicability for the evaluation of environmental pollution by toxic compounds".

Smital and Kurelec, 1997 "Inhibitors of the multixenobiotic resistance mechanism in natural waters: in vivo demonstration of their effects".

Smital and Kurelec, 1998 "The chemosensitizers of multixenobiotic resistance mechanism in aquatic invertebrates: a new class of pollutants".

Reviews of the importance of MXR for aquatic toxicity were first provided by Epel in 1998 and by Bard in 2000, followed by continued studies by Epel and Smital:

Bard, 2000 "Multixenobiotic resistance as a cellular defense mechanism in aquatic organisms".

Epel, 1998 "Use of multidrug transporters as first lines of defense against toxins in aquatic organisms".

Epel and Smital, 2001 "Multidrug — multixenobiotic transporters and their significance with respect to environmental levels of pharmaceuticals and personal care products".

Work by others followed in 2008:

Caminada et al., 2008 "Human pharmaceuticals modulate P-gp1 (ABCB1) transport activity in the fish cell line PLHC-1".

Luckenbach and Epel, 2008 "ABCB- and ABCC-type transporters confer multixenobiotic resistance and form an environment-tissue barrier in bivalve gills".

4.3.4. Subtle effects

Because the mechanisms of biological action (or adverse outcome pathways) for APIs can be distinctly different from those of conventional (legacy) pollutants, the potential for subtle effects (e.g., neurobehavioral; efflux pump inhibition) was first raised as a possibility in 1999:

Daughton and Ternes, 1999 "Pharmaceuticals and personal care products in the environment: Agents of subtle change?"

This hypothesis, which initially focused on selective serotonin reuptake inhibitors (SSRIs) and efflux pump inhibitors (MXR), was largely catalyzed by preexisting aquaculture research on the induction of spawning by the use of serotonin — in particular the work of Fong in 1998:

Fong, 1998 "Zebra mussel spawning is induced in low concentrations of putative serotonin reuptake inhibitors".

Interest and research on the potential for subtle effects – particularly from low-level exposure to SSRIs – began in the early 2000s, with work from Brooks, Fong, and others:

Brooks et al., 2003a "Aquatic ecotoxicology of fluoxetine".

Brooks et al., 2003b "Waterborne and sediment toxicity of fluoxetine to select organisms".

Fong, 2001 "Antidepressants in aquatic organisms: a wide range".

Research continues to expand the focus on subtle effects with respect to PiE:

Jeong et al., 2015 "Multi-generational effects of propranolol on *Daphnia magna* at different environmental concentrations".

Nunes, 2015 "How to Answer the Question — Are Drugs Real Threats to Biological Systems or Overrated Innocuous Chemicals?"

It should be noted, however, that the shift of focus from conventional aquatic toxicity end points (e.g., lethality) to more subtle and difficult-to-observe end points really began in the mid-1990s with the observation of subtle changes in fish intersexuality (and the emergence of the intersecting topic of endocrine disruption and EDCs):

Bortone and Davis, 1994 "Fish intersexuality as indicator of environmental stress".

Crisp et al., 1998 "Environmental endocrine disruption: an effects assessment and analysis".

Harries et al., 1996 "A survey of estrogenic activity in United Kingdom inland waters".

Isomaa and Lilius, 1995 "The urgent need for in vitro tests in ecotoxicology".

Sumpter and Jobling, 1995 "Vitellogenesis as a Biomarker for Estrogenic Contamination of the Aquatic Environment".

4.4. Gauging the emergence of PiE in the published literature

There are three major approaches for examining the chronology of PiE in its emergence as an issue attracting growing attention or concern. One is by chronicling the first scientific conferences devoted to PiE and the subsequent attention by news media. A second is by documenting the introduction to the published literature of new jargon and acronyms that are specific to – or closely allied with – the field. These can be viewed as landmarks or milestones for a field's development. The emergence of terms and acronyms is sometimes driven by the need to define new insights or perspectives deemed important or that require new ways to communicate. And the third major approach is by bibliographic citation analysis, which can reveal which published works are the most highly cited - possibly reflecting their value to the citing authors and their impact on the field or the general science community. Examples from each of these approaches are presented below.

4.4.1. First published articles on PiE

The first studies specifically focused on pharmaceuticals as environmental contaminants began to appear from 1976 to 1985, but there were comparatively few. Some of the more significant include:

Caballa et al., 1979 "A Terrestrial-Aquatic Model Ecosystem for Evaluating the Environmental Fate of Drugs and Related Residues in Animal Excreta".

Coats et al., 1976 "Model ecosystem evaluation of the environmental impacts of the veterinary drugs phenothiazine, sulfamethazine, clopidol, and diethylstilbestrol".

Richardson and Bowron, 1985 "The fate of pharmaceutical chemicals in the aquatic environment".

Rurainski et al., 1977 "Über das Vorkommen von natürlichen und synthetischen Oestrogenen im Trinkwasser [Concerning the occurrence of natural and synthetic estrogens in drinking water]".

Tabak et al., 1981 "Steroid hormones as water pollutants II. Studies on the persistence and stability of natural urinary and synthetic ovulation-inhibiting hormones in treated and treated wastewaters".

Waggott, 1981 "Trace organic substances in the River Lee".

Wilson, 1976 "Steroids as water pollutants: a literature survey of synthetic and natural hormonal steroids and the analytical methods for their determination" <as cited by others>.

Wilson, 1978 "Contraceptive steroids in water supplies".

For some context and perspective, these studies were being initiated at a time (the 1970s) when it was believed by some that what would years later become the PiE issue posed little concern, as reflected in the following excerpt (from: Peck, 1977 "The Environmental Impact of Drugs"):

"With few exceptions … drugs are not studied for their effects on the environment, i.e., birds, fishes, plants, since they are not intended to be used in such a way that there would be a significant impact on the environment."

The following, in particular, probably reflects much of the thinking at that time:

"The impact of drugs on the environment can be considered to be rather minimal because of the controlled manner in which most drugs are used …. As a rule the benefit/risk evaluation of drugs would indicate that even though there might be some impact on the environment, this should be small, and it is probable that the benefits would outweigh the risk."

4.4.2. Journal special issues devoted to PiE

The advent of a new concern is often marked by journals devoting a "special issue" to the topic. Four of the first journal special issues devoted to articles on PiE were published in 1999–2002: (i) a 1999 collection of 15 articles in *Science of the Total Environment* (TOC: http://www.sciencedirect.com/science/journal/00489697/225/1-2), (ii) a 2000 collection comprising 8 articles in *Chemosphere* (TOC: http://www.sciencedirect.com/science/journal/00456535/40/7), (iii) a 2001 collection, including 6 articles, in *Journal of Contemporary Water Research and Education* (TOC: http://opensiuc.lib.siu.edu/jcwre/vol120/iss1/), and (iv) a 2002 collection of upwards of 14 articles in *Toxicology Letters* (TOC: http://www.sciencedirect.com/science/journal/03784274/131/1-2):

Ternes, 1999 "Drugs and Hormones as Pollutants of the Aquatic Environment: Determination and Ecotoxicological Impacts".

Jørgensen and Halling-Sørensen, 2000 "Drugs in the environment".

Masters, 2001 "Pharmaceuticals and Endocrine Disruptors in Rivers and on Tap".

Dietrich et al., 2002a "Hot Spot Pollutants: Pharmaceuticals in the Environment".

An earlier special issue, in 1993, comprised roughly 30 papers and was devoted entirely to the topic of avermectins and the environment. It was published in *Veterinary Parasitology* (TOC: http://www.sciencedirect.com/science/journal/03044017/48; this effort was catalyzed by the earlier, highly cited work of Wall and Strong in 1987:

Herd and Wardhaugh, 1993 "Environmental Impact of Avermectin Usage in Livestock".

Wall and Strong, 1987 "Environmental consequences of treating cattle with the antiparasitic drug ivermectin".

4.4.3. Science conferences devoted to PiE

The advent of a new concern is also often reflected by science conferences that are dedicated in part or entirely to the topic. The first conferences and symposia devoted to PiE (in North America and Europe) were held within a 3-month period in 2000, marking a point at which widespread interest had crystallized within the environmental science arena. These initial conferences triggered numerous follow-on regional and local conferences on PiE. They were sponsored by the ACS, AWWARF, SETAC, and NGWA:

ACS, 2000 (27 March) "Special Symposium on 'Pharmaceuticals in the Environment'" (first-ever all-day symposium in North America on PiE).

AwwaRF, 2000 "Endocrine Disruptors & Pharmaceutically Active Chemicals in Drinking Water Workshop".

SETAC, 2000 (21–25 May) "Veterinary and human pharmaceuticals - fate and effects".

NGWA, 2000 (7–8 June) "Emerging Issues Conference – pharmaceuticals – endocrine disrupting chemicals - pesticides - arsenic and radon".

The first meeting on PiE that was organized by the USEPA was held in 2005:

USEPA, 2005 (23–25 August) "Session on Environmental Stewardship for Pharmaceuticals in the Environment".

Worth noting is that these conferences that focused on PiE were preceded decades earlier with several whose focus was on the predecessor issue of trace levels in waters of organic pollutants in general:

Keith, 1976b "Recent advances in the identification and analysis of organic pollutants in water".

Bjørseth and Angeletti, 1982 "Analysis of Organic Micropollutants in Water".

Angeletti and Bjørseth, 1984 "Analysis of Organic Micropollutants in Water: Proceedings of the Third European Symposium held in Oslo, Norway, September 19–21, 1983".

NRC, 1999 "Identifying Future Drinking Water Contaminants".

4.4.4. News media coverage of PiE

Stories in the news media are somewhat more difficult to locate, as the archiving and search utilities for news articles are not as

comprehensive or rigorous as those for academic publications. So there may well be news articles (especially in the non-English media) that predate those mentioned here. News articles, whether published in the lay press or in scientific journals, capture current activities in science (primarily conference presentations, press releases from research institutions, and select, newly published journal articles) when they are perceived as having the potential to capture public interest. A few news articles related to PiE began to appear in the late 1980s. But it was not until 10 years later – in the late 1990s – that an initial cascade of news articles began to appear.

One of the first news reports (in 1988) briefly covered some of the key concerns that would later fall within the future PiE issue. While disposal of unwanted medications to sewers had already been practiced for decades as a means of preventing accidental poisonings in children, this news report noted that the practice could lead to other problems, primarily (i) disposal of antibiotics to sewers could disrupt the action of microorganisms needed for efficient functioning of sewage treatment, and (ii) disposal to sewers of medications in general could lead to residues not removed during sewage treatment making their way into the environment and drinking water (Anon., 1988 "Disposal of pharmaceutical waste"). There was also considerable discussion surrounding the reasons that so many drugs would go unused and later require disposal (e.g., Wilson, 1991 "Forum: Too much of a good thing — John Wilson wonders how many people even start taking the tablets") and that charitable donations of medications could cause a host of other, unanticipated problems (e.g., Purvis, 1996 "The goodwill pill mess").

Perhaps it was the early media attention related to endocrine disruption ("hormone mimics") – especially the "environmental estrogens and androgens" – that drove the subsequent attention for PiE that soon followed. The following chronology of news articles serve as early examples (1998–2000) from the flurry of initial media interest in the PiE issue:

Montague, 1998 "Drugs in the water".

Raloff, 1998 "Drugged waters — Does it matter that pharmaceuticals are turning up in water supplies".

Reuters, 1998 (8 October) "Researchers find estrogen-like chemicals in toiletries".

Raloff, 1999 "Medicinal waters: where ibuprofen goes — the finding of clofibric acid and diclofenac in the water of Swiss lakes, leads to the question of why ibuprofen was not being found".

Bowman, 2000 "Medicines, Chemicals Taint Water: Contaminants Pass Through Sewage Plants".

Carr, 2000 "Flush with drugs: Waterways examined for potential risks posed by medicines released down drains".

Chui, 2000 "Tainted waters: Trace amounts of medicine, lotions and household products are showing up in waterways".

Dobson, 2000 "Anti-depressants get into water system".

Dunne, 2000 "Pharmaceutical pollution: Traces of medicines found in N.O.-area water".

Hall, 2000 "Makeup, medication may pollute waterways".

Manning, 2000 "Traces of drugs found in LV Wash".

Mansur and Martellaro, 2000 "Rivers face new threat: Medicines".

Montague, 2000 "Pay dirt from the human genome".

Potera, 2000 "Drugged drinking water".

Raloff, 2000a "Excreted drugs: Something looks fishy".

Raloff, 2000b "More waters test positive for drugs".

Woods, 2000 "Researchers warn of drug pollution: Drug, chemical residue found in waterways".

Zuer, 2000 "Drugs down the drain: Surprisingly little research exists on the potential environmental effects of pharmaceuticals and personal care products".

A major contributor of these early articles was Janet Raloff, who wrote perhaps the first major news expose on PiE ("Drugged waters"), published on 21 March 1998. An article by Peter Montague, which followed in September 1998, also generated considerable attention. But the press article that eventually attracted the most attention was not published until 8 years later - by the Associated Press:

Donn et al., 2008 "Pharmaceuticals found in drinking water, affecting wildlife and maybe humans".

The Associated Press article was widely distributed and fostered a series of follow-up articles on PiE by the Associated Press: see:

Associated Press, 2008 "An AP Investigation: Pharmaceuticals Found in Drinking Water".

Some of these news stories paralleled the early scientific conferences. PiE became a topic for cover stories (in 2008) in *Chemical & Engineering News*, including:

Halford, 2008a "Don't Flush: What to Do with Your Unused Pharmaceuticals".

Halford, 2008b "Side Effects: Pharmaceuticals have been finding their way into our environment for a long time, but just what are they doing there?"

Rouhi, 2008 "Drug Pollution".

4.4.5. The first web site devoted to PiE (PPCPs)

Largely because of the news attention that began in 1998, the first web site devoted to the larger topic of PPCPs was created in April 2000 by Daughton at the US EPA. Its now-defunct URL was: http://www.epa.gov/nerlesd1/chemistry/pharma/index.htm); 7 years later (on 18 July 2007), this web site was subsumed by the US EPA/ORD's PPCPs web site: http://www.epa.gov/ppcp. The ORD site was then terminated (8 years later, on 1 October 2015), with plans to initiate a new US EPA PPCPs web site in 2016.

4.4.6. First books devoted to PiE

Books, review articles, and university dissertations are excellent indicators of when a field of investigation has reached a critical level of interest or sustained level of research activity. The first books to focus on aspects of PiE began to appear in 2001, although they were preceded by some whose focus was on what would later be called endocrine disruption and which would have relevance to PiE (e.g., Committee on Hormonally Active Agents in the Environment et al., 1999 "Hormonally Active Agents in the Environment"). The major initial books devoted to PiE appeared from 2001 to 2006 and included:

Daughton and Jones-Lepp, 2001 "Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues".

Kümmerer, 2001b "Pharmaceuticals in the environment — Sources, fate, effects and risks".

Weyer and Riley, 2001 "Endocrine disruptors and pharmaceuticals in drinking water".

Williams, 2005 "Human pharmaceuticals: Assessing the impacts on aquatic ecosystems".

Bengtsson et al., 2006 "Environment and pharmaceuticals".

Kümmerer's 2001b book was followed by a 2nd edition in 2004 and a 3rd edition in 2008:

Kümmerer, 2004a "Pharmaceuticals in the environment — Sources, fate, effects, and risks".

Kümmerer, 2008 "Pharmaceuticals in the environment — Sources, fate, effects, and risks".

4.4.7. First comprehensive review articles devoted to PiE

The earliest review articles relevant to PiE focused on antibiotics in the environment, beginning in the 1970s; examples include:

Huber, 1971 "Antibacterial drugs as environmental contaminants".

Addison, 1984 "Antibiotics in sediments and run-off waters from feedlots".

The first comprehensive reviews dedicated to the larger issue of PiE did not appear until over a decade later (in 1985) and then again not until 13 years later, during 1998–2000:

Ayscough et al., 2000 "Review of Human Pharmaceuticals in the Environment".

Blok and Wösten, 2000 "Source and environmental fate of natural oestrogens".

Christensen, 1998 "Pharmaceuticals in the Environment—A Human Risk?"

Daughton and Ternes, 1999 "Pharmaceuticals and personal care products in the environment: Agents of subtle change?"

Halling-Sorensen et al., 1998 "Occurrence, fate and effects of pharmaceutical substances in the environment — A review".

Jørgensen and Halling-Sørensen, 2000 "Drugs in the environment".

Richardson and Bowron, 1985 "The fate of pharmaceutical chemicals in the aquatic environment".

Stahlschmidt-Allner et al., 1997 "Endocrine disrupters in the aquatic environment".

Velagaleti, 1997 "Behavior of pharmaceutical drugs (human and animal health) in the environment".

Wilken et al., 2000 "Pharmaceuticals in sewage, surface and drinking water in Germany".

Five of the first reviews that were published in journals have each received citations from other works ranging from 209 to 3064. In contrast, the first two reviews published in a book and the two as reports had fewer than 11 citations each. This probably just reflects the greater ease of access to journal articles.

4.4.8. First academic dissertations devoted to PiE

The topic of PiE did not begin to serve as a concerted focus for Doctoral and Masters dissertations until 1996. Four of the earliest examples were from 1996 to 2000:

Hagan, 1996 "An examination of acute environmental toxicity of pharmaceutical compounds using quantitative structure-activity relationships (*Daphnia magna*)".

Hartmann, 1998 "Drug load of hospital wastewater and its ecotoxicological relevance".

Holten Lützhöft, 2000 "Environmental risk assessment of antimicrobials".

Jiménez-González, 2000 "Life Cycle Assessment in Pharmaceutical Applications".

Note, however, that these were preceded two decades earlier by at least one other:

Wilson, 1978 "Contraceptive steroids in water supplies".

4.4.9. Illicit drugs

Although the focus of PiE has tended to be on prescription (legend) and over-the-counter pharmaceuticals, the parallel galaxy of so-called illicit drugs shares many of the same concerns. The two directly overlap where legal controlled substances are illegally diverted for recreational use and abuse. Drugs designated as controlled substances with no recognized medical use (Schedule I in the U.S.) and designer drugs (e.g., illegal analogs of registered pharmaceuticals) also pose the same concerns as do licit pharmaceuticals with regard to ecological risk. So the study of PiE actually covers the full gamut of substances that are used as drugs in any capacity.

The extent to which the universe of licit and illicit drugs can become convoluted is illustrated by the practice of adulteration. Adulteration is used in the preparation of counterfeit drugs, which can contain legal drugs but with illegal substances added as adulterants. It is also practiced in the preparation of illicit drugs, which are sometimes adulterated with otherwise legal drugs - an example being the addition of large quantities of the cytotoxic veterinary anthelmintic levamisole to cocaine (Daughton, 2011 "Illicit Drugs: Contaminants in the Environment and Utility in Forensic Epidemiology"). Both licit and illicit drugs can therefore serve as sources for each other in the environment.

Interest in illicit drugs in the environment was catalyzed by a concept proposed by Daughton in 2001 (Daughton, 2001 "Illicit drugs in municipal sewage: Proposed new non-intrusive tool to heighten public awareness of societal use of illicit/abused drugs and their potential for ecological consequence"), where residues of illicit drugs in sewage could be used to back-calculate community-wide consumption, and by the work of Zuccato et al. 4 years later – the first to reduce the concept to practice (Zuccato et al., 2005 "Cocaine in surface waters: A new evidence-based tool to monitor community drug abuse"); it should be noted, however, that the concept of monitoring sewage for controlled substances was first mentioned 9 years prior to Daughton's concept in a patent application (McClellan and Castorani, 1990 "Continuous (flexible) sewage monitoring machine for sampling building effluent to measure for certain controlled substances") on the continuous monitoring of wastewater from buildings for the presence of controlled substances (as a lower-cost streamlined approach for collective urinalysis). No further discussion will be provided here regarding the history behind the published literature regarding the environmental concerns regarding illicit drugs. This history has been captured in the following review (see Table 1, therein):

Daughton, 2011 "Illicit Drugs: Contaminants in the Environment and Utility in Forensic Epidemiology".

4.4.10. Pollution prevention, stewardship, pharmEcovigilance, disposal, collection take-backs, EPR

The many problems posed by the fact that significant portions of many medications go unused collectively constitute an integral aspect of the overall PiE issue. Unused, leftover, unwanted medications have played a number of roles in the evolution of the PiE published literature. Although there are few unique words to this facet of PiE, its relevant published literature can often be located with various combinations of the search words: disposal (or disposed) with drug (or pharmaceutical or medication); searches can be further narrowed with special terms such as pollution prevention, stewardship, pharmEcovigilance (or ecopharmacovigilance), and take-backs.

In the 1940s and earlier, the fact that small doses of certain medications can be lethal to children raised awareness of the acute hazards posed by medications that have been improperly stored or disposed:

Shirreff and Pearlman, 1940 "Oil of wintergreen poisoning: (Report of Two Additional Fatal Cases)".

Troll and Menten, 1945 "Salicylate poisoning: report of four cases".

This concern later expanded in the 1990s once it was recognized that many common medications can be fatal for children in very small doses — sometimes a single adult dose – posing major concerns regarding the storage, handling, and disposal of these medications:

Koren, 1993 "Medications which can Kill a Toddler with One Tablet or Teaspoonful".

Liebelt and Shannon, 1993 "Small doses, big problems: a selected review of highly toxic common medications".

Fatal accidental ingestions were partly responsible for a growing focus in the 1960s on the practices of stockpiling and disposal of unwanted, leftover medications in the home — a concern that continues to grow and which has been greatly exacerbated today by the newer problems of drug diversion, misuse, and abuse — for example:

Ferguson, 2014 "Keeping Families Safe Around Medicine".

Lewis et al., 2014 "What Do Patients Do with Unused Opioid Medications?"

Lovegrove et al., 2014 "Emergency Hospitalizations for Unsupervised Prescription Medication Ingestions by Young Children".

The need for prudent collection and disposal of leftover, unwanted drugs was recognized as a means for reducing childhood poisonings and fatalities as early as the 1960s:

Gunn and Lishman, 1967 "Letters to Editor regarding "Problem of Unused Drugs""

Nicholson, 1967 "Collection of unwanted drugs from private homes".

A decade later, the recognition that medications often went unused and served as a major cause of childhood poisonings drove efforts to improve prescribing practices, reduce drug leftovers (which are often subsequently disposed to sewers), and reduce the storage of unwanted drugs in the home. These led to various organized disposal programs,

which led to today's formal, consumer take-back programs in the US (e.g., Glassmeyer et al., 2009 "Disposal practices for unwanted residential medications in the United States"):

Harris et al., 1979 "Returned-medicines campaign in Birmingham".

Leach and White, 1978 "Use and wastage of prescribed medicines in the home".

Sixsmith and Smail, 1978 "Evaluation of medicines returned in Glasgow DUMP campaign".

Taylor, 1978 "Towards better prescribing".

Formal consumer take-back programs date back to 1975 with the Manchester unwanted drug collection campaign (also known as a "take-back") dubbed "DUMP": Disposal of Unused Medicines and Pills. DUMP later became a generic acronym used in other take-back programs.

Bradley and Williams, 1975 "Evaluation of medicines returned in Manchester DUMP campaign".

Implementation of consumer take-backs in the U.S. (primarily implemented at local levels) did not take hold until the mid-2000s, delayed partly because of complexities associated with the handling of controlled substances under the Controlled Substances Act (DEA, 2014 "Disposal of Controlled Substances 21 CFR Parts 1300, 1301, 1304, 1305, 1307, and 1317"). These obstacles were largely overcome once the U.S. Drug Enforcement Administration (DEA) published its final rule implementing the Secure and Responsible Drug Disposal Act of 2010 (Senate and House of Representatives of the United States of America in Congress, 2010 "Secure and Responsible Drug Disposal Act of 2010"). Consumer take-back events received greater recognition from the public once the DEA's National Take-Back Initiative was established in 2010:

DEA, 2010 "Press release: DEA Heads First-ever Nationwide Prescription Drug Take-back Day".

The importance of take-backs (for preventing drug diversion and accidental poisonings) received its greatest endorsement when take-backs were highlighted in a weekly public address by the President of the United States on 26 September 2015:

Office of the Press Secretary, 2015 "Weekly Address: Dispose of Your Expired and Unwanted Prescription Drugs".

It is useful to point out that the frequent U.S. news coverage beginning in the early 2000s regarding the need for "prudent" disposal of unwanted drugs was driven largely by the still unsubstantiated presumption that reducing the disposal of unwanted drugs to sewers could significantly reduce the levels of corresponding APIs in the environment. Such a connection, however, has never been documented. Rather, the need for prudent disposal is primarily driven by the imperative to reduce accidental poisonings (especially those leading to serious morbidity or fatalities):

Daughton, 2010a "Drugs and the Environment: Stewardship & Sustainability".

Daughton and Ruhoy, 2008 "The afterlife of drugs and the role of pharmEcovigilance".

Daughton and Ruhoy, 2009 "Environmental footprint of pharmaceuticals: The significance of factors beyond direct excretion to sewers".

Worth mentioning is a specific type of drug take-back that is a mandatory program designed around extended producer responsibility (EPR). EPR places responsibility for product life-cycle management on the manufacturer, in contrast to consumer take-backs, which are voluntary and funded by the public. The adoption of EPR in the U.S. for the collection of unused drugs was first suggested in 2001:

Daughton, 2001 "Pharmaceuticals and personal care products in the environment: Overarching issues and overview".

In the years following, a number of states and local governments proposed EPR for unused drug take-backs. But it was not until July 2012 that the first EPR legislation in the U.S. for unwanted drugs was enacted — by Alameda County, California:

Alameda County, 2012 "New County Policy Requires Drug Makers to Pick Up Disposal Costs".

The adoption of EPR models in the U.S. for unwanted drugs has been a rather contentious issue - and one with a complex history:

Karst, 2015 "U.S. Supreme Court is Asked to Review First-in-the-Nation Safe Drug Disposal Ordinance".

Whalen, 2015 "U.S. Supreme Court Decides Not to Hear Pharmaceutical Industry Case Against Drug Disposal Law".

Wick, 2014 "Comment: Mandatory Drug Take-Back Programs: Will They Survive the Dormant Commerce Clause Challenge?"

Formal consumer take-back collection programs were becoming established in the 1970s, as well as studies examining economic costs to hospitals of leftover medications and studies aimed at consumer education to improve household safety:

Bradley and Williams, 1975 "Evaluation of medicines returned in Manchester DUMP campaign".

Dershewitz and Williamson, 1977 "Prevention of childhood household injuries: a controlled clinical trial".

Hart and Marshall, 1976 "Wastage of Pharmaceuticals".

Leach and White, 1978 "Use and wastage of prescribed medicines in the home".

Numerous studies have built on the areas summarized above; these areas remain active as fields of investigation, primarily because accidental childhood poisonings and drug diversion and abuse have not declined as public health issues. This is reflected by the growing size of the literature associated with the many facets of leftover, unwanted drugs. This literature currently comprises thousands of articles and has been compiled here:

Daughton and Scuderi, 2016a "Drug Disposal and Environmental Stewardship: Relevant Literature".

These studies served as the prelude to the much later recognition, in the mid-1990s, that the practice of medicine plays a major role in the entry of APIs to the immediate and natural environments and that healthcare providers and drug manufacturers should therefore play major roles in ways to reduce or minimize the problem:

Eckerman and Martineus, 1997 "Medicines and the environment — what do we know today?"

Menicucci and Coon, 1993–1994 "Environmental Regulation of Health Care Facilities: A Prescription for Compliance".

USEPA, 1994 "Guides to Pollution Prevention. Selected Hospital Waste Streams".

Concerns regarding the potential for environmental effects may have been expressed several years earlier (in 1991) by Vaarkamp with respect to the practice of veterinary medicine:

Vaarkamp, 1991 "De veterinaire praktijk en het milieu: wat te doen en wat te laten [Veterinary practice and the environment: what to do and what to omit]".

Note, however, that these articles were preceded by interest in the engineered treatment of waste streams from the manufacture of pharmaceuticals, which emerged in the 1950s and 1960s; see the many references cited in the 1975 U.S. EPA report:

Struzeski, 1975 "Waste treatment and disposal methods for the pharmaceutical industry".

That consumer drug waste disposal has environmental connections was first formally recognized in Canada in 1995 with the rebranding of an existing drug collection program under the EnviRx name:

Cameron, 1996 "Study by Alberta pharmacists indicates drug wastage a "mammoth" problem".

But it was not until 1999–2002, that connections between the disposal of unwanted, leftover drugs and the environment were noted and suggestions to adopt preventative measures made:

Campbell, 2002 "Pharmaceuticals in the environment: Regulatory and nonregulatory approaches".

Daughton, 2002 "Environmental stewardship and drugs as pollutants".

Daughton and Ternes, 1999 "Pharmaceuticals and personal care products in the environment: Agents of subtle change?"

Grayling, 1999 "Guidelines for safe disposal of unwanted pharmaceuticals in and after emergencies".

One of the first dedicated discussions in a pharmacy journal of the need to understand the connection between drug waste and the environment appeared in 2002:

Smith, 2002 "Managing Pharmaceutical Waste: What Pharmacists Should Know".

The concept of the "Green Pharmacy" was introduced in 2003 as the first comprehensive approach combining environmental stewardship, pollution prevention, and waste reduction for reducing the entry of APIs to the environment:

Daughton, 2003a "Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. I. Rationale for and avenues toward a green pharmacy".

Daughton, 2003b "Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. II. Drug disposal, waste reduction, and future directions".

This work has served as the foundation for a number of subsequent works on environmental stewardship targeted at PiE:

Daughton, 2014a "Drug Disposal & Stewardship: Ramifications for the Environment and Human Health".

The concept of pharmEcovigilance (as an integrative term for aligning the existing, conventional process of pharmacovigilance for tracking and ensuring the safety of medications with the parallel need for environmental protection) was introduced in 2008. One intention of pharmEcovigilance was to link protection of the environment with improved quality and reduced cost of medical care:

Daughton and Ruhoy, 2008 "The afterlife of drugs and the role of pharmEcovigilance".

Other terms also emerged in the 2006–2008 time frame, including: ecopharmacovigilance, ecopharmaco-stewardship, and pharmaco-environmentology:

Keck, 2006 "Teaching environmental toxicology for veterinary students and veterinarians: some new trends".

Rahman et al., 2007 "Pharmacoenvironmentology — a component of pharmacovigilance".

Kampa, 2008 "Proceedings of the expert workshop on the design of instruments to limit pollution from PPs".

Debate exists, however, as to whether these multiple terms are needed:

Rahman, 2015 "Do we really need multiple terms for a single concept in the field of Environmental Pharmacovigilance?"

Another major work to focus on the sustainable use of medications was published in 2009:

Bengtsson et al., 2009 "A Healthy Future - Pharmaceuticals in a Sustainable Society".

4.4.11. Risk and environmental assessment

The first articles to focus on the process of assessing environmental risk of pharmaceuticals predated the field of PiE. They were published by the US FDA, first in 1988 and later in 1993 [some were in the form of Environmental Impact Statements (EISs) and others in the form of Findings of No Significant Impact (FONSIs)], and by others beginning in 1994:

Matheson, 1988 "The Nuts and Bolts of Preparing an Environmental Assessment".

Bloom and Matheson, 1993 "Environmental assessment of avermectins by the US Food and Drug Administration".

Haley et al., 1993 "Requirements of the FDA for the environmental assessment of animal health products".

Vincent, 1993 "Environmental assessment: U.S. requirements in new drug applications".

Sager and Williams, 1994 "Environmental Assessment and Finding of No Significant Impact for TOPAMAX® (Topiramate)".

These articles were largely preceded by a number of unconnected articles (1970–1990) that began to hypothesize or examine the potential for various environmental impacts from specific APIs, years before any sense of the larger PiE issue had begun to coalesce. Noteworthy is the seminal review in 1985 by Richardson and Bowron:

Aherne and Briggs, 1989 "The relevance of the presence of certain synthetic steroids in the aquatic environment".

Aherne et al., 1990 "Cytotoxic drugs and the aquatic environment: estimation of bleomycin in river and water samples".

Hignite and Azarnoff, 1977 "Drugs and drug metabolites as environmental contaminants: Chlorophenoxyisobutyrate and salicylic acid in sewage water effluent".

Richardson and Bowron, 1985 "The fate of pharmaceutical chemicals in the aquatic environment".

Tabak and Bunch, 1970 "Steroid hormones as water pollutants I. Metabolism of natural and synthetic ovulation-inhibiting hormones by microorganisms of activated sludge and primary settled sewage".

Tabak et al., 1981 "Steroid hormones as water pollutants II. Studies on the persistence and stability of natural urinary and synthetic ovulation-inhibiting hormones in treated and treated wastewaters".

Even earlier studies focused on the potential impacts on soil of antibiotics and steroids present in manure resulting from medicated feed. These began in the 1950s and 1960s; see the references cited in:

Warman and Thomas, 1981 "Chlortetracycline in soil amended with poultry manure".

Gregers-Hansen, 1964 "Decomposition of diethylstilboestrol in soil".

Knight, 1980 "Estrogens administered to food producing animals: environmental considerations".

Broom et al., 1961 "The stability of hexoestrol in soil and its uptake by plants".

Coordinated responses in Europe to PiE began in the early 2000s:

CSTEE, 2001 "Opinion on: Draft CPMP Discussion Paper on Environmental Risk Assessment of Medicinal Products for Human Use [Non-Genetically Modified Organism (Non-GMO) Containing]".

The first formal coordinated examination of PiE in the U.S. was the Federal Interagency Working Group on Pharmaceuticals in the Environment (PiE), which was formed in September 2004 (but not formally chartered until 2006) under the Toxics and Risk Subcommittee, Committee on Environment and Natural Resources (CENR), National Science and Technology Council (NSTC). An external report, however, was not released; see reference cited in:

USGAO, 2011 "Environmental Health: Action Needed to Sustain Agencies' Collaboration on Pharmaceuticals in Drinking Water".

4.5. Milestones and landmarks involving jargon, terms, and acronyms pertinent to PiE

This section presents some of the terms that are unique to PiE (or that have become closely associated with PiE). These are useful in facilitating better-targeted literature searches. Summarized here is a chronology of the emergence of these terms in the published literature, which serve as milestones marking the evolution of the field.

4.5.1. Expressions and acronyms

The many technical facets, issues, and concerns surrounding the expansive topic of PiE cannot be cleanly retrieved from the published archived and gray literatures because it is entangled with numerous other fields of investigation that share most of the same technical vernacular and jargon. This problem was a major driver for creation of the curated USEPA PPCPs bibliographic database that was used for this study. To ensure wide but pertinent coverage by literature searches, a major strategy is to use search terms that are relatively unique to the PiE topic or that deal with issues that intersect with PiE. Summarized below is a brief history behind the emergence of some of these terms and expressions in the published literature - while recognizing that there are many others:

PiE (or PIE) [pharmaceuticals in the environment]

PPCPs (or PPCP) [pharmaceuticals and personal care products]

PhACs [pharmaceutically active compounds]; PhCs (pharmaceuticals)
EDC [endocrine-disrupting compound]
TrOC (also TOrC) [trace organic chemical]
Micro-contaminant, micro-pollutant, micro-constituent
Emerging (e.g., Contaminants of emerging concern [CECs], Emerging contaminants, Emerging pollutants)
Non-target (or non-targeted) — in reference to chemical analysis or environmental monitoring
Pseudo-persistent (or pseudo-persistence)

4.5.1.1. The expression "pharmaceuticals in the environment". The first articles to use the expression "pharmaceuticals in the environment" (or the German "Arzneimittel in der Umwelt" or "Arzneimittelwirkstoffe in der Umwelt") appeared in 1998–2000, including:

Ayscough et al., 2000 "Review of Human Pharmaceuticals in the Environment".

BLAC, 1999 "Arzneimittel in der Umwelt: Konzept für ein Untersuchungsprogramm [Pharmaceuticals in the environment — plan for a study program]".

Christensen, 1998 "Pharmaceuticals in the Environment–A Human Risk?"

Daughton and Ternes, 1999 "Pharmaceuticals and personal care products in the environment: Agents of subtle change?"

Kratz et al., 2000 "Arzneimittelwirkstoffe in der Umwelt [Medication Active Ingredients in the Environment]".

Landesumweltamt Brandenburg (LUA), 1999 "Humanarzneimittel in der Umwelt: Erhebung von Humanarzneimittelmengen im Land Brandenburg 1999 [Human pharmaceuticals in the environment: Collection of human medicinal amounts in the state of Brandenburg in 1999]".

Schecker et al., 1998 "Arzneimittel in der Umwelt: Elimination des Zytostatikums Ifosfamid während der simulierten Zersetzung von Hausmüll im Labormaßstab [Pharmaceuticals in the Environment: Elimination of the antineoplastic agent ifosfamide in a laboratory-scale waste bioreactor]".

4.5.1.2. PiE (or PIE). The first paper to use the acronym PiE (or PIE) appeared in 2002:

Dietrich et al., 2002b "Hot Spot Pollutants: Pharmaceuticals in the Environment".

The term was used in a number of conference presentations and reports as early as 2005, for example:

Mastrocco, 2005 "Pharmaceuticals in the Environment (PIE): Assessing Risk to Human Health".

Park, 2005 "Pharmaceuticals in the Environment and Management Approaches in Korea".

Buzby, 2006 "Pharmaceuticals in the environment — a review of PhRMA initiatives".

Buzby and Meyerhoff, 2007 "Pharmaceutical Research and Manufacturers of America: Research on Pharmaceuticals in the Environment".

Daughton and Ruhoy, 2007 "Pharmaceuticals in the Environment — Why Should Anyone Care?"

But after 2002, PiE was not really used again in the peer reviewed literature until 2007:

Khetan and Collins, 2007 "Human Pharmaceuticals in the Aquatic Environment: A Challenge to Green Chemistry".

Robinson et al., 2007 "Trends in the detection of pharmaceutical products, and their impact and mitigation in water and wastewater in North America".

And showing its continued use, PiE has appeared in many articles, such as more recently in:

Rastogi et al., 2015 "A sustainable chemistry solution to the presence of pharmaceuticals and chemicals in the aquatic environment - the example of re-designing β-blocker Atenolol".

Straub, 2016 "Aquatic environmental risk assessment for human use of the old antibiotic sulfamethoxazole in Europe".

Note, however, that outside the published literature, the term PiE was already in use as early as the late 1990s. For example, the Pharmaceutical Research and Manufacturers of America (PhRMA) had created its internal "Task Force on Pharmaceuticals in the Environment (PIE)" in 1999; see discussions in:

Buzby, 2006 "Pharmaceuticals in the environment — a review of PhRMA initiatives".

Buzby and Meyerhoff, 2007 "Pharmaceutical Research and Manufacturers of America: Research on Pharmaceuticals in the Environment".

Goldhammer, 2008 "Pharmaceuticals in the Nation's Drinking Water: assessing potential risks and actions to address the issue".

It was also used by the U.S. Federal Interagency Working Group on Pharmaceuticals in the Environment (PiE), which was formed in September 2004 (but not formally chartered until 2006) under the Toxics and Risk Subcommittee, Committee on Environment and Natural Resources (CENR), National Science and Technology Council (NSTC); see the discussion in:

USGAO, 2011 "Environmental Health: Action Needed to Sustain Agencies' Collaboration on Pharmaceuticals in Drinking Water".

4.5.1.3. PPCPs. The term "pharmaceuticals and personal care products" (PPCPs) was introduced to the literature in 1999, when it was first coined:

Daughton and Ternes, 1999 "Pharmaceuticals and personal care products in the environment: Agents of subtle change?"

Its use by others in the published literature began 2 years later, in 2001:

Boyd and Grimm, 2001 "Occurrence of Pharmaceutical Contaminants and Screening of Treatment Alternatives for Southeastern Louisiana".

Drewes et al., 2001 "Occurrence of iodinated X-ray contrast media in domestic effluents and their fate during indirect potable reuse".

Osemwengie and Steinberg, 2001 "On-site solid-phase extraction and laboratory analysis of ultra-trace synthetic musks in municipal sewage effluent using gas chromatography-mass spectrometry in the full-scan mode".

Clearly, PPCPs cover a more expansive spectrum of consumer chemicals since it includes personal care products.

4.5.1.4. PhACs. The term PhACs (pharmaceutically active compounds) first appeared in 1998 and 2000, followed by several other uses in 2001:

Sedlak, 1998 "Transport and Transformation of Antibiotics and Hormones in the Aquatic Environment".

Sedlak et al., 2000 "Understanding Microcontaminants in Recycled Water".

Heberer et al., 2001b "Occurrence and Fate of Pharmaceuticals During Bank Filtration – Preliminary Results from Investigations in Germany and the United States".

Heberer et al., 2001a "Removal of pharmaceutical residues and other persistent organics from municipal sewage and surface waters applying membrane filtration".

Sedlak and Pinkston 2001 "Factors Affecting the Concentrations of Pharmaceuticals Released to the Aquatic Environment".

Other variants have been coined but are infrequently used. One example is "PhCs" (pharmaceuticals), which was first used in a poster presentation in 2007 and for the first time in the published literature in 2010:

Kleywegt et al., 2007 "Pharmaceuticals and personal care products in the Canadian environment: research and policy directions".

Verlicchi et al., 2010 "Management of hospital wastewaters: the case of the effluent of a large hospital situated in a small town".

4.5.2. Aspects of PiE shared with other, unrelated groups of chemicals

A number of other terms and acronyms serve to classify chemical contaminants according to a variety of parameters or characteristics, such as according to biological effects (e.g., "endocrine-disrupting compound/chemical" — EDC), relative concentration in the environment (e.g., trace levels), or novelty (e.g., any of the various expressions using the adjective "emerging"). These aspects of chemical contaminants in the environment often involve pharmaceuticals.

4.5.2.1. EDCs. EDCs (or the initially less controversial "hormonally active agent" — HAA) as an acronym for the discrete field of study made its entry to the general literature after the Wingspread Conference in Wisconsin (1991):

Arizona Water Resource, 2000 "Endocrine disrupters in water: What are EDs? What risks do they pose?"

Hotchkiss et al., 2008 "Fifteen Years after "Wingspread"—Environmental Endocrine Disrupters and Human and Wildlife Health: Where We are Today and Where We Need to Go".

EDCs serve as one of the many links between PPCPs and other classes of pollutants. Note, however, that the concerns with EDCs have their roots with research that extends back into the 1930s when estrogenic or androgenic activity was noted for various synthetic chemicals, for example:

Dodds et al., 1938 "OEstrogenic Activity of Certain Synthetic Compounds".

Schueler, 1946 "Sex Hormonal Action and Chemical Constitution".

Stob, 1956 "Fecal Elimination of Hormones in Sheep and Cattle Treated with Synthetic Estrogens".

4.5.2.2. Uptake and bioconcentration by biota. There are examples of other properties of drugs that were noted many decades before PiE began to emerge as a cohesive, discrete concern of its own. One example is the fact that drugs (i.e., antibiotics and veterinary hormones) can be taken up from the soil by plants, translocated through their tissues, and sometimes bioconcentrated. This was shown several decades before concerns with the environmental fate of drugs emerged:

Pramer, 1953 "Observations of the uptake and translocation of five actinomycete antibiotics by cucumber seedlings".

Stokes, 1954 "Uptake and translocation of griseofulvin by wheat seedlings".

Crowdy et al., 1956 "The Translocation of Antibiotics in Higher Plants: II. The movement of griseofulvin in broad bean and tomato".

Crowdy and Jones, 1956 "The Translocation of Sulphonamides in Higher Plants: I. Uptake and Translocation in Broad Beans".

Gregers-Hansen, 1964 "The uptake by plants of diethylstilboestrol and of its glucuronide".

Similarly, the uptake and tissue distribution of APIs had been long studied in fish but primarily with respect to their therapeutic use (e.g., aquaculture). It was not until the mid-2000s that attention began to emerge regarding the possibility of uptake and bioconcentration of trace levels of APIs in the aquatic environment by aquatic organisms (see: Daughton and Brooks, 2011 "Active pharmaceutical ingredients and aquatic organisms" and references cited therein). Also, since the linkage of vulture extirpations with exposure to veterinary use of diclofenac in the mid-2000s, interest has been growing regarding exposure to API residues in the environment by raptors and the possible use of biomonitoring as a means of estimating the scope of PiE distribution and magnitude of API levels in the environment (e.g., see: Espín et al., 2016 "Tracking pan-continental trends in environmental contamination using sentinel raptors—what types of samples should we use?" and references cited therein).

4.5.2.3. Partitioning to biosolids. A topic closely allied with uptake by plants is the partitioning of APIs to biosolids, which can then be applied to agricultural soils. The earliest studies regarding the fate of APIs in biosolids were published in 1996, followed by other early articles beginning in the period 1999–2002:

Rogers, 1996 "Sources, behaviour and fate of organic contaminants during sewage treatment and in sewage sludges".

Wilson et al., 1996 "Screening the environmental fate of organic contaminants in sewage sludges applied to agricultural soils: 1. the potential for downward movement to groundwaters".

Ternes et al., 1999 "Behaviour and occurrence of estrogens in municipal sewage treatment plants — II. Aerobic batch experiments with activated sludge".

Layton et al., 2000 "Mineralization of steroidal hormones by biosolids in wastewater treatment systems in Tennessee USA".

Holbrook et al., 2002 "Estrogen receptor agonist fate during wastewater and biosolids treatment processes: A mass balance analysis".

Jjemba, 2002 "The potential impact of veterinary and human therapeutic agents in manure and biosolids on plants grown on arable land: a review".

Khan and Ongerth, 2002 "Estimation of pharmaceutical residues in primary and secondary sewage sludge based on quantities of use and fugacity modelling".

Among these early articles were concerns expressed by the U.S. FDA regarding environmental assessments for drugs (1998) and an NRC report (2002), where biosolids are discussed in both:

USFDA, 1998 "Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application".

Committee on Toxicants and Pathogens in Biosolids Applied to Land et al., 2002 "Biosolids applied to land: Advancing standards and practices".

4.5.2.4. Trace analysis. The expression "trace organic chemical" (or "trace organics") appeared in the peer-reviewed literature as early as 1975–1977; the usage of "trace organic" (or "trace levels") is difficult to determine because it had been used for quite some time outside of the PiE literature, and because it often occurs in PiE articles only in the references-cited section. Among the earlier articles using this term are:

Heller et al., 1975 "Trace organics by GC/MS".

Keith, 1976a "Identification and Analysis of Organic Pollutants in Water".

Donaldson, 1977 "Trace organics in water".

Sievers et al., 1977 "Environmental trace analysis of organics in water by glass capillary column chromatography and ancillary techniques: Products of ozonolysis".

Initially, the term was infrequently used with respect to PiE issues, appearing briefly only in the early 1980s:

Waggott, 1981 "Trace organic substances in the River Lee".

Drewes et al., 2001 "Occurrence of iodinated X-ray contrast media in domestic effluents and their fate during indirect potable reuse".

Patterson et al., 2002 "Application of U.S. EPA methods to the analysis of pharmaceuticals and personal care products in the environment: Determination of clofibric acid in sewage effluent by GC-MS".

The literature on trace organics is also intermixed with that which focused on identifying "non-volatiles" (because non-volatiles had long received little attention prior to the advent of high-performance liquid chromatography):

Watts et al., 1984 "Identification of non volatile organics in water using field desorption mass spectrometry and high performance liquid chromatography".

"Trace organic chemicals" was followed years later by its acronym, "TOrCs," an acronym that first appeared in a series of reports published in 2008 by the Water Environment Research Foundation (WERF); see:

Anderson, 2008 "Technical brief: trace organic compounds and implications for wastewater treatment".

A definition for TOrCs was proposed in 2010:

WERF, 2010 "Workshop Proceedings: Diagnostic tools to evaluate impacts of trace organic compounds on aquatic populations and communities".

The term was first used in several journal articles, also in 2010:

Hoppe-Jones et al., 2010 "Attenuation of total organic carbon and unregulated trace organic chemicals in U.S. riverbank filtration systems".

Rauch-Williams et al., 2010 "The Role of Organic Matter in the Removal of Emerging Trace Organic Chemicals during Managed Aquifer Recharge".

Confusingly, a variant of the acronym (i.e., TrOCs) first appeared in 2010 and was subsequently widely adopted by others beginning in 2012:

Chiu and Westerhoff, 2010 "Trace Organics in Arizona Surface and Wastewaters".

Hübner et al., 2012 "Optimized removal of dissolved organic carbon and trace organic contaminants during combined ozonation and artificial groundwater recharge".

Reungoat et al., 2012 "Ozonation and Biological Activated Carbon Filtration of Wastewater Treatment Plant Effluents".

4.5.2.5. Micro-contaminant, micro-pollutant, micro-constituent. Perhaps to place more emphasis on the reality that chemical contaminants are reported at extremely low levels in environmental matrices (made possible by detection levels being pushed ever lower by continual advances in analytical chemistry), new terms continued to emerge that reiterated the idea of "trace organics".

Of these three terms using iterations of "micro", *micro-pollutant* (micropollutant, micro pollutant) is the most common, first occurring in 1974–1985:

Water Research Centre, 1974 "A comprehensive list of polluting substances which have been identified in various fresh waters, effluent discharges, aquatic animals and plants, and bottom sediments. COST project 64b: Analysis of organic micropollutants in water".

Waggott, 1981 "Trace organic substances in the River Lee".

Fielding et al., 1981 "Organic micropollutants in drinking water".

Micro-contaminant (microcontaminant, micro contaminant) emerged in the PiE literature in 1985 but was not used again for over a decade:

Aherne et al., 1985 "The role of immunoassay in the analysis of microcontaminants in water samples".

Richardson and Bowron, 1985 "The fate of pharmaceutical chemicals in the aquatic environment".

Hirsch et al., 1998 "Determination of antibiotics in different water compartments via liquid chromatography-electrospray tandem mass spectrometry".

Sedlak et al., 2000 "Understanding Microcontaminants in Recycled Water".

For the third variant, *micro-constituent* (microconstituent, micro constituent), its usage began much later (in 2004) and is much less common than the other two:

Petrovic et al., 2004 "Endocrine disrupting compounds and other emerging contaminants in the environment: A survey on new monitoring strategies and occurrence data".

Singh, 2006 "Assessing the sources, quantities, and trends on human waste contamination along protected south Florida ecosystem: A chemical tracer based study".

WEF, 2007 "Effects of Wastewater Treatment on Microconstituents".

A series of European conferences in the early 1980s focused on the larger topic of micro-pollutants in general:

Bjørseth and Angeletti, 1982 "Analysis of Organic Micropollutants in Water".

Angeletti and Bjørseth, 1984 "Analysis of Organic Micropollutants in Water: Proceedings of the Third European Symposium held in Oslo, Norway, September 19–21, 1983".

4.5.2.6. Non-target pollutants (previously unmonitored unknowns). The repeated discoveries of expanding numbers of chemical contaminants at ever-lower levels in environmental matrices (especially waters) introduced a quandary as to which contaminants to target for monitoring. While making this determination inevitably prompts many questions surrounding the assessment of risk and assignment of overall priorities, it also leads to questions regarding what other contaminants might still be present but have escaped notice or detection. The desire to obtain a more complete understanding of the chemical composition of the world to which all life is exposed eventually led to an emphasis on "nontarget" contaminants — analytes that had not been previously monitored or whose presence was noticed in screenings but their identification was not attempted or was unsuccessful.

The term "non-target" (or non-targeted) has direct relevance to the issue of PiE in that a growing number of APIs are detected and identified in monitoring studies when they have not been among the suite of chemicals specifically targeted. Non-targeted analysis has grown in use largely because of advancements in mass spectrometry; for example see:

Ferrer and Thurman, 2003 "Liquid chromatography/time-of-flight/mass spectrometry (LC/TOF/MS) for the analysis of emerging contaminants".

Ferrer and Thurman, 2003 "Analysis of Emerging Contaminants".

The desire and ability to perform non-targeted analyses (to identify unknowns) really began in the 1970s, although it was not specifically referred to as such — but rather as "chemical characterization":

Keith, 1976b "Recent advances in the identification and analysis of organic pollutants in water".

Kleopfer and Fairless, 1972 "Characterization of organic components in a municipal water supply".

Grob, 1973 "Organic substances in potable water and in its precursor: Part I. Methods for their determination by gas-liquid chromatography".

These early studies were catalyzed by the growing inventories of trace organic chemicals (primarily of industrial and agricultural origin) reported in ambient waters; for example, see the 1970 report prepared for the US EPA:

Davis et al., 1970 "Organic Chemical Pollution of Freshwater".

These studies involving non-targeted analysis (which were forced to rely on mass spectral libraries that were not sufficiently comprehensive) were also limited by insufficient mass resolution, spectral acquisition speed (required for full-spectrum scanning), and data acquisition, processing, and storage. A later example (in 1994) is:

Hendriks et al., 1994 "Monitoring response of XAD-concentrated water in the Rhine delta: A major part of the toxic compounds remains unidentified".

These early chemical characterization studies attempted to identify some of the many unknown chemicals that became evident with the advent of high-resolution GC and LC; many of these unmasked substances that had been noted in prior analyses simply as unknowns (and never suspected to be present) started to become labeled as "tentatively identified compounds". One such study (in 1976) was among the first to establish the presence of a drug metabolite (i.e., clofibric acid) in wastewater:

Garrison et al., 1976 "GC/MS Analysis of Organic Compounds in Domestic Wastewaters".

Garrison, 1977 "Analysis of organic compounds in water to support health effects studies".

Note that the work of Garrison et al. was preceded the year before by several studies focused on the occurrence of radionuclides used in nuclear medicine, reflecting the emerging realization that drug substances could enter sewers as a result of their routine use:

Dielman, 1978 "A report on hospital effluent problems with low level radionuclides".

Gesell et al., 1975 "Nuclear medicine environmental discharge measurement. Final report".

Sodd et al., 1975 "Concentrations of the Medically Useful Radionuclides, Technetium-99m and Iodine-131 at a Large Metropolitan Waste Water Treatment Plant".

Of course, much more comprehensive targeted analysis is now possible because of the continual advancements in mass spectral analysis (e.g., see: Wode et al., 2015 "Search for over 2000 current and legacy micropollutants on a wastewater infiltration site with a UPLC-high resolution MS target screening method"). The ease and speed of compound identification made possible by the growing power of mass spectrometry now serves to blur the distinction between targeted and non-targeted analysis.

Non-targeted monitoring or screening of waters was being performed more routinely in the 1990s and early 2000s for a variety of chemicals, including the non-target identification of pharmaceuticals and personal care products:

Franke et al., 1995 "Organic compounds as contaminants of the Elbe River and its tributaries. Part II: GC/MS screening for contaminants of the Elbe water".

Paxéus, 1996 "Organic pollutants in the effluents of large wastewater treatment plants in Sweden".

Bester et al., 1998 "Results of non target screening of lipophilic organic pollutants in the German bight II: Polycyclic musk fragrances".

Weigel et al., 2001 "New method for rapid solid-phase extraction of large-volume water samples and its application to non-target screening of North Sea water for organic contaminants by gas chromatography-mass spectrometry".

Dsikowitzky et al., 2002 "Distribution of polycyclic musks in water and particulate matter of the Lippe River (Germany)".

Oros et al., 2003 "Surveillance for previously unmonitored organic contaminants in the San Francisco Estuary".

These studies were partly catalyzed by a growing recognition that a large fraction of the organic contaminants that occur in waters had yet to be identified by targeted analysis; for example, see:

Hendriks et al., 1994 "Monitoring response of XAD-concentrated water in the Rhine delta: A major part of the toxic compounds remains unidentified".

Daughton, 2003a "Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. I. Rationale for and avenues toward a green pharmacy".

Daughton, 2005 "Emerging chemicals as pollutants in the environment: a 21st century perspective".

Recognition of an "iceberg" scenario emerged, where growing numbers of unique but previously unrecognized chemicals may occur in the environment at ever-lower (and previously unmeasurable concentrations). Suspicions also continue to emerge that those chemical contaminants that remain unidentified may be responsible for significant portions of unexplained stress in biological systems:

Daughton, 2013 "Pharmaceuticals in the Environment: Sources and Their Management".

The utility of non-targeted analysis for PiE did not begin to receive concerted attention until the early 2000s. But identification of non-target analytes was intentionally omitted from the first large-scale monitoring study involving PiE, published by the USGS in 2002. Nonetheless, this seminal study was probably largely responsible for catalyzing heightened interest in non-targeted monitoring:

Kolpin et al., 2002 "Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999–2000: a national reconnaissance".

The first studies to stress the value of non-targeted analysis and to begin showing its application in identifying certain non-targeted APIs began to appear only in 2002–2003:

Khan, 2002 "Occurrence, behaviour and fate of pharmaceutical residues in sewage treatment".

Pedersen et al., 2003 "Xenobiotic organic compounds in runoff from fields irrigated with treated wastewater".

Ricking et al., 2003 "Molecular markers of anthropogenic activity in sediments of the Havel and Spree Rivers (Germany)".

Kronimus et al., 2004 "Anthropogenic organic contaminants in sediments of the Lippe river, Germany".

Soliman et al., 2004 "Rapid gas chromatography-mass spectrometry screening method for human pharmaceuticals, hormones, antioxidants and plasticizers in water".

Pedersen et al., 2005 "Human Pharmaceuticals, Hormones, and Personal Care Product Ingredients in Runoff from Agricultural Fields Irrigated with Treated Wastewater".

Non-targeted analysis began to receive attention for use in biological effects-directed characterization of wastewaters in 2004:

Heisterkamp et al., 2004 "Bioassay-directed chemical analysis utilizing LC–MS: A tool for identifying estrogenic compounds in water samples?"

Over the last 10 years, the application of non-target analysis to more comprehensive characterization of environmental samples for pharmaceuticals (as well as other emerging chemicals) has grown dramatically — often catalyzed by the concerns surrounding PiE:

Bletsou et al., 2015 "Targeted and non-targeted liquid chromatography-mass spectrometric workflows for identification of transformation products of emerging pollutants in the aquatic environment".

Diaz et al., 2012 "Target and non-target screening strategies for organic contaminants, residues and illicit substances in food, environmental and human biological samples by UHPLC-QTOF-MS".

Herrera-Lopez et al., 2014 "Simultaneous screening of targeted and non-targeted contaminants using an LC-QTOF-MS system and automated MS/MS library searching".

Hogenboom et al., 2009 "Accurate mass screening and identification of emerging contaminants in environmental samples by liquid chromatography-hybrid linear ion trap Orbitrap mass spectrometry".

Hug et al., 2014 "Identification of novel micropollutants in wastewater by a combination of suspect and nontarget screening".

Ibáñez et al., 2008 "Rapid non-target screening of organic pollutants in water by ultraperformance liquid chromatography coupled to time-of-light mass spectrometry".

Martínez Bueno et al., 2007 "Application of Liquid Chromatography/Quadrupole-Linear Ion Trap Mass Spectrometry and Time-of-Flight Mass Spectrometry to the Determination of Pharmaceuticals and Related Contaminants in Wastewater".

Schwarzbauer and Ricking, 2010 "Non-target screening analysis of river water as compound-related base for monitoring measures".

Schymanski et al., 2015 "Non-target screening with high-resolution mass spectrometry: critical review using a collaborative trial on water analysis".

Zedda and Zwiener, 2012 "Is nontarget screening of emerging contaminants by LC-HRMS successful? A plea for compound libraries and computer tools".

4.5.2.7. Transformation products (TPs). An important aspect of PiE is that the chemical products of various transformation processes can often possess biological activity of their own, with many of these products being more potent than their parent structures. While this might be obvious for drugs designed as pro-drugs (where the parent drug might require metabolic transformation to produce the active form), this can also be true for various process pathways in the environment (both biotic and abiotic) that can structurally transform parent structures, including microbial action (biotransformation, biodegradation), sunlight (photolysis, photodegradation, phototransformation), and chemical (e.g., disinfection byproducts created by oxidative treatment). The study of transformation processes and pathways has long been an integral aspect of environmental toxicology. So tracing its roots within the PiE literature is not straightforward, primarily because of the numerous aspects of transformation and the fact that transformation has many distinct threads throughout the published PiE literature.

Study of the transformation of APIs was originally directed at its relevance in reducing the biological activity of the parent structures. This served as a focus in the study of waste treatment and in studies

of environmental fate. Only later did transformation attract attention as a process that held potential to create new and sometimes more toxic and persistent byproducts and yet further complicate the assessment of risk (Escher and Fenner, 2011 "Recent Advances in Environmental Risk Assessment of Transformation Products"). This eventually became yet another aspect of the expansive topic of emerging contaminants (see Section 4.5.3.1). Also note that the topic of API metabolic conjugation (see Section 4.5.3.2) is related to transformation in the sense that API glucuronides are excreted as endogenous products of metabolism and can then undergo transformation back to their parent APIs.

Perhaps the key concern posed by the various transformation processes and their actions on an already large galaxy of APIs is the large uncertainty imposed on assessing risk because of the potential for one or multiple byproducts from each individual API. And the vast majority of these byproducts have yet to be characterized. This, in turn, has served to catalyze yet more interest in non-targeted monitoring.

The concerns regarding transformation products (often abbreviated TPs) began to attract attention in 2007–2008:

Barceló, 2007 "Pharmaceutical-residue analysis".

Farré et al., 2008 "Fate and toxicity of emerging pollutants, their metabolites and transformation products in the aquatic environment".

Kosjek et al., 2007 "Mass spectrometry for identifying pharmaceutical biotransformation products in the environment".

Kosjek and Heath, 2008 "Applications of mass spectrometry to identifying pharmaceutical-transformation products in water treatment".

Kümmerer, 2007 "Sustainable from the very beginning: rational design of molecules by life cycle engineering as an important approach for green pharmacy and green chemistry".

Sharma, 2008 "Oxidative transformations of environmental pharmaceuticals by Cl_2, ClO_2, O_3, and Fe(VI): Kinetics assessment".

Use of the acronym "TPs" began in 2004–2005:

Oppel et al., 2004 "Leaching behaviour of pharmaceuticals in soil-testing-systems: a part of an environmental risk assessment for groundwater protection".

Agüera et al., 2005 "Application of time-of-flight mass spectrometry to the analysis of phototransformation products of diclofenac in water under natural sunlight".

Loffler et al., 2005 "Environmental Fate of Pharmaceuticals in Water/Sediment Systems".

Reviews dedicated to TPs only began to appear in the last couple of years:

Evgenidou et al., 2015 "Occurrence and removal of transformation products of PPCPs and illicit drugs in wastewaters: A review".

Hübner et al., 2015 "Evaluation of the persistence of transformation products from ozonation of trace organic compounds — a critical review".

Petrie et al., 2015 "A review on emerging contaminants in wastewaters and the environment: current knowledge, understudied areas and recommendations for future monitoring".

Among the few, more specific and rather unique terms for TPs include "degradate," which became an alternative for "degradation product" in the early 1980s. But it did not begin experiencing more common usage until the 1990s:

Bull et al., 1984 "Fate of avermectin B_1a in soil and plants".

Bergh et al., 1990 "High-performance liquid chromatographic analysis of trimethoprim in the presence of its degradation products".

Gruber et al., 1990 "Mobility of avermectin B_{1a} in soil".

Halley et al., 1993 "Environmental effects of the usage of avermectin in livestock".

4.5.3. Concepts fostered by PiE

4.5.3.1. "Emerging" — emerging contaminants, emerging pollutants, contaminants of emerging concern (CECs). The term "emerging" has been frequently applied to PiE, primarily with the intention to frame it as a topic that has escaped prior notice or that has not been sufficiently recognized as a potential concern; an added motivation behind use of the term when discussing PiE may also be in attracting attention or eliciting concern. At times, the topics of emerging contaminants and PiE have been narrowly conflated as one and the same. The term "emerging" has also brought attention to the corollary that APIs as environmental contaminants have been largely unregulated. In the popular press, use of the word "emerging" has possibly sought to inject cause for some alarm, similarly to its use in describing the identification of "emerging" pathogens or pathogens with emerging resistance.

Perhaps the first article to use the term emerging with respect to chemical contaminants was published in 1999:

NRC, 1999 "Identifying Future Drinking Water Contaminants".

Brief mention of emerging was also made in:

Sedlak et al., 2000 "Understanding Microcontaminants in Recycled Water".

Perhaps the first formal research program devoted to emerging contaminants was launched by the USGS. It was first referenced in the published literature in 2000 as the "Emerging Contaminants Program":

Meyer et al., 2000 "Use of radioimmunoassay as a screen for antibiotics in confined animal feeding operations and confirmation by liquid chromatography/mass spectrometry".

The USGS also established a web page for their emerging contaminants program in the early 2000s; the current URL for this web page is: http://toxics.usgs.gov/regional/emc/.

The first conference whose focus was on emerging contaminants was organized by the National Ground Water Association, in 2000:

NGWA, 2000 (7–8 June) "Emerging Issues Conference - pharmaceuticals - endocrine disrupting chemicals - pesticides - arsenic and radon".

The first focused discussion and attempt to formally define "emerging" pollutants was published in 2001:

Daughton, 2001a "Emerging pollutants, and communicating the science of environmental chemistry and mass spectrometry: pharmaceuticals in the environment".

An historical perspective on emerging contaminants is presented by Halden:

Halden, 2015 "Epistemology of Contaminants of Emerging Concern and Literature Meta-analysis".

Use of "emerging" in the scientific literature was quickly followed by its adoption in the popular press, where the first news coverage appeared in 2000:

> "traces of 70 'emerging contaminants' — substances that are not now considered environmental hazards but are facing growing scrutiny …":

Carr, 2000 "Flush with drugs: Waterways examined for potential risks posed by medicines released down drains".

> "government agencies concerned with water quality in the United States and professional organizations serving the water and wastewater communities are beginning to acknowledge PPCPs as an emerging environmental issue …":

Greene, 2000 "Controversy swirls around toilet-to-tap project".

> "Organizers said it was the first time scientists have gathered to address the topic in North America — itself a sign of just how little attention has been paid to the emerging environmental concerns posed by products such as antibiotics, psychiatric drugs, hormones, animal-feed additives and synthetic fragrances …":

Hall, 2000 "Makeup, medication may pollute waterways".

> "Water pollution by drugs 'is a newly emerging issue …'":

Raloff, 2000b "More waters test positive for drugs".

Many other terms incorporating "emerging" have since been coined — some being more obscure, such as EPOCs ("emerging pollutants of concern"), whose use began in 2005:

Crook et al., 2005 "Status and Role of Water Reuse: An International View".

Daughton, 2006 "Emerging Pollutants - Questions, Challenges, and the Future".

Singh, 2006 "Assessing the sources, quantities, and trends on human waste contamination along protected south Florida ecosystem: A chemical tracer based study".

Daughton and Ruhoy, 2007 "Pharmaceuticals in the Environment — Why Should Anyone Care?"

Daughton and Ruhoy, 2010 "Pharmaceuticals in the Environment - Why Should We Care?"

Regardless of the original intentions of the descriptor "emerging", its continued use [now extending into 2016, e.g. see: Álvarez-Torrellas et al., 2016 "Comparative adsorption performance of ibuprofen and tetracycline from aqueous solution by carbonaceous materials"; Li et al., 2016 "Can environmental pharmaceuticals be photocatalytically degraded and completely mineralized in water using g-C_3N_4/TiO_2 under visible light irradiation?—Implications of persistent toxic intermediates"; Patiño et al., 2016 "Pre-concentration of nalidixic acid through adsorption-desorption cycles: adsorbent selection and modelling"; Rao et al., 2016 "Degradation of Ibuprofen by a synergistic UV/Fe(III)/Oxone Process"; Russo et al., 2016 "Direct photolysis of benzoylecgonine under UV irradiation at 254 nm in a continuous flow microcapillary array photoreactor"] poses questions regarding its meaning or utility given the sizeable pre-existing published PiE literature that now extends back decades. Does "emerging" still add value to this topic or should it be reserved for those environmental contaminants or concerns that meet the original intentions articulated in 2001:

Daughton, 2001a "Emerging pollutants, and communicating the science of environmental chemistry and mass spectrometry: pharmaceuticals in the environment".

Questions regarding the usefulness of the term become even more germane when published articles begin to refer to pollutants known for centuries as having been "emerging" during their time. With the escalating growth of journals, it was inevitable that "emerging contaminants" would eventually be used as the name for a journal (in December 2014): http://www.keaipublishing.com/en/journals/emerging-contaminants/

New ways to express the idea of "emerging" continue to appear. One communicates from the perspective of exposure rather than the stressor. An example is the expression "new" or "distinctive" exposure:

Klupinski et al., 2015 "Identification of New and Distinctive Exposures from Little Cigars".

4.5.3.2. Processes particularly important to the fate of APIs in the environment: pseudo-persistence and de-conjugation. Some new terms have emerged as a direct result of the PiE topic. One example is "pseudo-persistence." The fact that certain chemicals (even those with short environmental half-lives such as APIs) can nonetheless establish a continual presence in certain domains of the environment was a concept that was introduced in 2002–2003 and termed "pseudopersistence":

Daughton, 2002 "Environmental stewardship and drugs as pollutants".

Daughton, 2003a "Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. I. Rationale for and avenues toward a green pharmacy".

APIs serve as the prototypical example of pseudopersistent chemicals given that their major route of entry to the environment is via sewage, which serves as a means for continual replenishment of what would otherwise be continuously diminishing levels. APIs have therefore served to show that chemical half-life (as a measure of chemical stability and resistance to microbial degradation and other environmental transformation processes) is not the only driver that dictates the ubiquitous presence of chemicals in the environment (such as inherent resistance to chemical transformations).

This concept has since been discussed in more depth and a simpler alternative proposed (i.e., "continuously present" or, simply, "continuous presence"):

Mackay et al., 2014 "The role of persistence in chemical evaluations".

Other terms unique to PiE have also emerged. One in particular — "EPPP" (Environmental Persistent Pharmaceutical Pollutants) — was proposed at a 2010 meeting involving the Strategic Approach to International Chemicals Management (SAICM) by the International Society of Doctors for the Environment (ISDE):

International Society of Doctors for the Environment (ISDE), 2010 "Strategic Approach to International Chemicals Management: Nomination of emerging policy issues for consideration by the International Conference on Chemicals Management at its third session".

It is important to recognize that some new terms, such as EPPP, may only serve to add confusion to the literature. In this particular case, few APIs meet the conventional criteria for being environmentally persistent (one example being iodinated X-ray contrast agents). Creation of new acronyms can clearly be misleading. The long-established POPs (persistent organic pollutants) would seem to encompass EPPPs, even though their scopes would hardly intersect.

One process that has been particularly germane to PiE — and which can also play a secondary role in environmental persistence — is the process of metabolic conjugation, a pathway for detoxification and excretion of APIs from humans and animals. Some metabolic conjugates are reversible; these are sometimes also called interconvertible conjugates. The importance of reversible metabolic conjugates of APIs is that they can be recycled back to the parent API by hydrolysis or cleavage of particular bonds — a process called deconjugation. For drugs that are extensively excreted as reversible conjugates, the conjugates can possibly serve as hidden reservoirs of the parent APIs in the environment.

Assessing the magnitude or significance of conjugate excretion and subsequent deconjugation has proved difficult with respect to PiE and persistence. After arriving in the influent to sewage treatment plants in conjugated forms, subsequent deconjugation might be the cause of higher levels of free, unconjugated APIs in the treated effluent compared with those measured in the raw influent; for further discussion and many examples of this phenomenon see:

Daughton, 2014b "Eco-Directed Sustainable Prescribing: Feasibility for Reducing Water Contamination by Drugs" [see Table S-3 therein: Examples of "apparent increased concentrations" (negative removals), deconjugation, or presence of conjugates of various non-steroidal APIs during sewage treatment].

The possible role and importance of deconjugation in the regeneration of the parent API was first recognized for various steroid hormones — in a flurry of articles during 1998–2000, including:

Baronti et al., 2000 "Monitoring natural and synthetic estrogens at activated sludge sewage treatment plants and in a receiving river water".

Desbrow et al., 1998 "Identification of estrogenic chemicals in STW effluent. 1. Chemical Fractionation and in vitro biological screening".

Panter et al., 1999 "Transformation of a non-oestrogenic steroid metabolite to an oestrogenically active substance by minimal bacterial activity".

Ternes et al. 1999 "Behaviour and occurrence of estrogens in municipal sewage treatment plants – II. Aerobic batch experiments with activated sludge".

Tyler and Routledge, 1998 "Natural and anthropogenic environmental oestrogens: the scientific basis for risk assessment; Oestrogenic effects in fish in English rivers with evidence of their causation".

Wegener et al., 1999 "Vorkommen und Verhalten von natürlichen und synthetischen Östrogenen und deren Konjugate in der aquatischen

Umwelt [Presence and behaviour of natural and synthetic estrogens and their conjugates in the aquatic environment]".

The possible role of de-conjugation for non-steroidal, small-molecular drugs initially received comparatively less attention, with a few of the first articles also appearing in 1998–1999, including:

Möhle et al., 1999 "Untersuchungen zum Abbau von Pharmaka in kommunalen Kläranlagen mit HPLC-Electrospray-Massenspektrometrie [Examination of the degradation of drugs in municipal sewage plants using liquid chromatography-electrospray mass spectrometry]".

Sattelberger, 1999 "Arzneimittelrückstände in der Umwelt – Bestandsaufnahme und Problemdarstellung [Pharmaceutical residues in the environment — An inventory and problem representation]".

Ternes et al., 1998 "Methods for the determination of neutral drugs as well as betablockers and β_2-sympathomimetics in aqueous matrices using GC/MS and LC/MS/MS".

4.5.3.3. APIs as monitoring tools: source tracking of sewage and human activities (indicators, tracers, markers, surrogates, sentinel chemicals). Not until the late 1990s and early 2000s did APIs and their transformation/metabolic products become recognized for their possible utility as tools for tracking the origin and fate of sewage in the environment; this served to augment the long-established use of microorganisms (and their genetic materials), fecal sterols, consumer products (e.g., caffeine, polyethoxylates, fluorescent brighteners, and synthetic fragrances), and certain inorganic substances as extended indicators or proxies for detecting the presence of human waste in natural waters. Examples include:

Chen et al., 2002 "Determination of caffeine as a tracer of sewage effluent in natural waters by on-line solid-phase extraction and liquid chromatography with diode-array detection".

Heberer, 2002b "Tracking persistent pharmaceutical residues from municipal sewage to drinking water".

Möller et al., 2000 "Anthropogenic gadolinium as a conservative tracer in hydrology".

Seiler et al., 1999 "Caffeine and pharmaceuticals as indicators of waste water contamination in wells".

Concerted attention to the use of APIs as indicators, tracers, or tracking agents took several more years to develop — in the mid-2000s:

Fono and Sedlak, 2005 "Use of the Chiral Pharmaceutical Propranolol to Identify Sewage Discharges into Surface Waters".

Fono and Sedlak, 2007 "A simple method for the measurement of organic iodine in wastewater and surface water".

Glassmeyer et al., 2005 "Transport of Chemical and Microbial Compounds from Known Wastewater Discharges: Potential for Use as Indicators of Human Fecal Contamination".

Heim et al., 2004 "Monitoring of waste deposit derived groundwater contamination with organic tracers".

Katz and Griffin, 2007 "Using chemical and microbiological indicators to track the impacts from the land application of treated municipal wastewater and other sources on groundwater quality in a karstic springs basin".

Around the same time as the development of source tracking using APIs, another new application was proposed involving the monitoring of API levels in sewage. The monitoring of specific drug residues in sewage (initially, residues of illicit drugs) was proposed for reconstructing community-wide drug usage rates (Daughton, 2001 "Illicit drugs in municipal sewage: Proposed new non-intrusive tool to heighten public awareness of societal use of illicit/abused drugs and their potential for ecological consequence"); surprisingly, illicit drugs had been largely omitted from the PiE discussion, even with respect to their potential for ecological effects. This approach was first reduced to practice in 2005 by Zuccato et al. and continues to attract growing interest:

Zuccato et al., 2005 "Cocaine in surface waters: A new evidence-based tool to monitor community drug abuse".

The approach became known initially (in 2008) as "sewage epidemiology" or "sewage-based epidemiology" (Zuccato et al., 2008 "Estimating Community Drug Abuse by Wastewater Analysis"; Frost and Griffiths, 2008 "Introduction to sewage epidemiology and the wastewater system") and as "sewage forensics" (Kasprzyk-Hordern et al., 2010 "Enantiomeric analysis of drugs of abuse in wastewater by chiral liquid chromatography coupled with tandem mass spectrometry"), or sometimes as "community drug testing" or "community urinalysis". It later received a more formal name: "Forensic Epidemiology Using Drugs in Sewage" — FEUDS (Daughton, 2011 "Illicit Drugs: Contaminants in the Environment and Utility in Forensic Epidemiology"). The general approach made possible for the first time an evidence-based means for determining normalized per capita estimates of substance flows in sewage (Daughton, 2001 "Illicit drugs in municipal sewage: Proposed new non-intrusive tool to heighten public awareness of societal use of illicit/abused drugs and their potential for ecological consequence").

The history behind this new tool for gauging community-wide usage rates is presented here:

Daughton, 2011 "Illicit Drugs: Contaminants in the Environment and Utility in Forensic Epidemiology".

The chemical monitoring of sewage for the purpose of estimating human consumption (or for substance-flow analysis in general) has been steadily expanding to target more types of so-called "down-the-drain" chemicals. Surprisingly, this field has only more recently begun to target licit pharmaceuticals and their human metabolites as an additional approach for estimating (via back-calculation) population-wide consumption of therapeutic medicines:

ter Laak et al., 2014 "Different compositions of pharmaceuticals in Dutch and Belgian rivers explained by consumption patterns and treatment efficiency".

Likewise, this field is beginning to attract interest as a tool for estimating population-wide consumption of other substances of abuse, such as alcohol and nicotine:

Reid et al., 2011 "Analysis and Interpretation of Specific Ethanol Metabolites, Ethyl Sulfate, and Ethyl Glucuronide in Sewage Effluent for the Quantitative Measurement of Regional Alcohol Consumption".

Mastroianni et al., 2014 "Analysis of ethyl sulfate in raw wastewater for estimation of alcohol consumption and its correlation with drugs of abuse in the city of Barcelona".

Rodríguez-Álvarez et al., 2014 "Assessment of local tobacco consumption by liquid chromatography-tandem mass spectrometry sewage analysis of nicotine and its metabolites, cotinine and trans-3′-hydroxycotinine, after enzymatic deconjugation".

Tscharke et al., 2015 "Estimates of tobacco use by wastewater analysis of anabasine and anatabine".

In its most general sense, sewage analysis can be called "sewage chemical-information mining" (SCIM). One of the most recent potential applications of SCIM is the monitoring of endogenous biomarkers of human stress or disease for the purpose of estimating community-wide health status:

Daughton, 2012 "Using biomarkers in sewage to monitor community-wide human health: Isoprostanes as conceptual prototype".

Ryu et al., 2015 "Liquid chromatography–high resolution mass spectrometry with immunoaffinity clean-up for the determination of the oxidative stress biomarker 8-iso-prostaglandin F2alpha in wastewater".

API monitoring in sewage continues to evolve as a tool for addressing additional questions. One area receiving increasing attention is the monitoring of specific API enantiomers for the purpose of differentiating origins or sources. One of the first examples (in 1999) was the use of chiral analysis for determining the portion of API sewage loading originating from raw sewage versus treated sewage (as microbial degradation can result in alteration of enantiomeric ratios):

Buser et al., 1999 "Occurrence and Environmental Behavior of the Chiral Pharmaceutical Drug Ibuprofen in Surface Waters and in Wastewater".

Poiger et al., 2003 "Occurrence and fate of organic micropollutants in the environment: Regional mass balances and source apportioning in

surface waters based on laboratory incubation studies in soil and water, monitoring, and computer modeling".

Fono and Sedlak, 2005 "Use of the Chiral Pharmaceutical Propranolol to Identify Sewage Discharges into Surface Waters".

One question that has proved particularly refractory is determining the relative importance of direct disposal of leftover medications to sewerage versus excretion with respect to the levels of APIs in sewage. Since metabolism of racemic APIs can skew the relative ratios of optical isomers, the contribution of APIs in raw sewage that originate from disposal could possibly be differentiated from the portion resulting from excretion. This was first proposed in 2007, and studies beginning in 2012 have tried to show the utility of this approach:

Daughton, 2007 "Pharmaceuticals in the environment: sources and their management".

Kasprzyk-Hordern and Baker, 2012 "Estimation of community-wide drugs use via stereoselective profiling of sewage".

Emke et al., 2014 "Enantiomer profiling of high loads of amphetamine and MDMA in communal sewage: A Dutch perspective".

Petrie et al., 2016 "A new framework to diagnose the direct disposal of prescribed drugs in wastewater — a case study of the antidepressant fluoxetine".

4.6. The most-highly cited articles on PiE

4.6.1. Approach for bibliometrics

One of the most useful and direct ways to assess the emergence of PiE as a concerted field of investigation is by examining the citation trajectories of the peer-reviewed literature. Bibliographic citations reflect interest from the science community and therefore may serve as an indirect measure of the impact or significance of the cited papers. Citation analysis, as part of the field of scientometrics, will not be discussed here. The intent in this study was merely to identify those PiE articles that were the most highly cited at the time this paper was prepared. This compilation of most-cited articles relevant to PiE represents the first such attempt. The lack of prior, comprehensive compilations of most-cited articles on PiE might simply be a result of the surprising amount of time and effort required.

There was no intent to further interpret what the citation counts might mean; there are numerous limitations to the interpretation of citation counts, many resulting from biases introduced by errors in citing or by gratuitous citing practices. It is important, however, to recognize that the citation counts reported here represent only a point in time (April 2015). Over time, the citation rates of even the most highly cited individual articles will vary. One would expect that their overall relative rankings might change over time. Some articles currently categorized as highly cited could eventually be displaced by others that are currently less-cited if their rates of citation are increasing faster.

In this study, those articles that had been cited at least 200 times were categorized as highly cited. The citations were mined from Google Scholar (GS), recognizing the limitations of this database, which may be biased high compared with curated citation databases. Given that only articles with the most citations were of interest, self-citations were assumed to contribute proportionately less bias than for less-frequently cited articles. Also note that citation counts are much more reliable for journal articles than for book chapters. Books are problematic because of the variations in how citation counts are assigned by search engines; mis-assigned citations are common because of the confusion caused by the complexity and variance in the formatting of reference citations for books and because of confusion as to whether a citation belongs to an individual chapter or to the entire respective book.

Important to note is the difficulty in establishing which articles among the thousands published on PiE that have garnered the most citations. This is not a straightforward endeavor and is quite time-consuming. The bibliographic software application *Zotero* was used to download citation counts directly from GS using the Mozilla Firefox plug-in "Google Scholar Citations for Zotero" (https://addons.mozilla.org/en-us/firefox/addon/zotero-scholar-citations/). This was a time-consuming task because Google restricts the frequency of access for downloading; citation counts can only be downloaded for a limited number of references for each cycling of the plug-in before Google blocks all new queries (a feature designed by Google to block automated machine requests); the cycle can only be restarted within a time-out by deleting browser cookies, responding to repeated CAPTCHA requests, and restarting the GS plug-in. To cover all of the journal articles and books chapters in the EndNote database required the repeated querying of GS hundreds of cycles for all of the articles in the PPCPs bibliographic database.

The citation data in the PPCPs bibliographic database first had to be imported into Zotero. The final Zotero citation counts were then exported into Excel so that they could be easily sorted. Once the most-highly cited articles were identified, the counts for each article were directly verified by locating the reference in Google Scholar (GS). Extensive quality checks for comprehensiveness (to ensure that all of the highly cited articles were indeed captured) were made by performing a large number of searches in Google Scholar and examining them for the most highly cited articles. These searches were designed to represent a wide spectrum of facets of the overall topic of PiE to increase the probability that a large portion of the PiE literature was being accessed. When highly cited articles were located, the citing articles were also assessed for their citation counts. This repetitive, iterative process took quite a number of weeks to reach a point where no additional articles could be found that qualified as highly cited. Surprisingly, extensive forward and backward searching using a wide spectrum of key words and terms using GS failed to locate most of the most highly cited papers; extensive forward/backward citation searching using GS also did not locate any highly cited articles that were not already captured in the database. Some of the most-cited papers in the PPCPs database were only indirectly pertinent to the PiE issue. These papers tended to focus on antibiotic resistance and endocrine disruption and were therefore excluded from the core set of papers considered for being the most-cited for the PiE topic itself. An outline of the methodology used for all of the bibliometric analyses performed in this study is summarized in Supplementary Table S-4.

Note that many articles just missed the arbitrary cut-off minimum of 200 citations. Just months later, many of the articles residing below this cutoff would probably qualify as highly cited; some might have even received more citations that those currently ranked at the bottom of the most-cited. The relative rankings of the articles ranked at the top would be expected to remain consistent for considerably longer.

4.6.2. Results

The cumulative yearly totals of journal articles and book chapters relevant to the many facets of PiE are displayed in Supplementary Fig. S-3. Publishing activity can be clearly seen to begin escalating in the period 1998–2000. Through 2014, the rate of publication continued to increase each year.

A total of 385 PiE articles were identified as having from 200 to 5424 citation counts (as of April 2015). These comprised roughly 2% of the entire database. Only five book chapters or books were among the articles identified as most cited (ranging from 202 to 738 citations each); this must be tempered, however, by recognizing the problems faced by search engines compiling accurate citations for books:

Damstra et al., 2002 "Global assessment of the state-of-the-science of endocrine disruptors".

Jelić et al., 2012 "Pharmaceuticals in drinking water".

Joss et al., 2006 "Wastewater treatment"

Kümmerer, 2008 "Pharmaceuticals in the environment - Sources, fate, effects, and risks".

Sørensen, 2008 "Veterinary Medicines".

These 385 articles are listed in descending order of numbers of citations in the spreadsheet in Supplementary Table S-3. The following section examines some of the characteristics of these papers.

Important to note, however, is that hundreds of additional articles have also played important roles in the evolution and advancement of the field.

To highlight the top 100 most-cited papers, these are also shown in the scatter plot in Supplementary Fig. S-4, where the citation count for each article number is displayed against its year of publication; the arbitrary article IDs shown in the figure correspond to the numbers that precede each reference listed in Supplementary Fig. S-4a.

A distribution of the cumulative yearly numbers of the 64 most-cited articles is shown in Supplementary Fig. S-5. From this chart, it can be seen that the year 2003 has accounted for the greatest number of these most-cited papers — a total of 10. The fewest were seen in 1998 and 2001.

4.6.2.1. The top most-cited articles. There were 13 articles that were each cited more than 1000 times; the most highly cited articles are among the most highly cited articles in all of environmental science. These were published from 1994 to 2006; the four most highly cited articles had garnered over 2000 citations each and were published in the narrow window from 1998 to 2002:

Carballa et al., 2004 "Behavior of pharmaceuticals, cosmetics and hormones in a sewage treatment plant".

Daughton and Ternes, 1999 "Pharmaceuticals and personal care products in the environment: Agents of subtle change?"

Desbrow et al., 1998 "Identification of estrogenic chemicals in STW effluent. 1. Chemical Fractionation and in vitro biological screening".

Fent et al., 2006 "Ecotoxicology of human pharmaceuticals".

Halling-Sorensen et al., 1998 "Occurrence, fate and effects of pharmaceutical substances in the environment — A review".

Heberer, 2002a "Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data".

Hirsch et al., 1999 "Occurrence of antibiotics in the aquatic environment".

Kolpin et al., 2002 "Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999–2000: a national reconnaissance".

Purdom et al., 1994 "Estrogenic Effects of Effluents from Sewage Treatment Works".

Routledge et al., 1998 "Identification of estrogenic chemicals in STW effluent. 2. in vivo responses in trout and roach".

Sarmah et al., 2006 "A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment".

Ternes, 1998 "Occurrence of drugs in German sewage treatment plants and rivers".

Ternes et al., 1999b "Behaviour and occurrence of estrogens in municipal sewage treatment plants — I. Investigations in Germany, Canada and Brazil".

4.6.2.2. Distribution of journals where the 100 most-cited articles on PiE were published. Of the top 100 most-cited articles on PiE, the majority of them (62%) were published in just six journals. The remaining 38 top-cited articles were published in 31 different journals and books, each of which had only one or two top-cited articles:

Environmental Science & Technology	24
Water Research	12
Science of the Total Environment	11
Chemosphere	7
Environmental Toxicology and Chemistry	5
Science	3

Of the 53 most-highly cited papers, 7 were not published in any of the 50 journals that have published the majority of the PPCPs literature:

Baquero et al., 2008 "Antibiotics and antibiotic resistance in water environments".

Heberer, 2002b "Tracking persistent pharmaceutical residues from municipal sewage to drinking water".

Kemper, 2008 "Veterinary antibiotics in the aquatic and terrestrial environment".

Kidd et al., 2007 "Collapse of a fish population after exposure to a synthetic estrogen".

Kümmerer, 2004b "Resistance in the environment".

Richardson and Bowron, 1985 "The fate of pharmaceutical chemicals in the aquatic environment".

Snyder et al., 2003 "Pharmaceuticals, Personal Care Products, and Endocrine Disruptors in Water: Implications for the Water Industry".

Distribution of most-cited PiE articles among the journals that published the most articles on PiE.

Of the 386 PiE articles cited at least 200 times, an examination was made of their distribution among the journals that have published the most PiE articles. There were 23 journals that had published at least 100 articles each (Table 2); these did not include the two journals with the highest impact factors (*Science* and *Nature*). Together, these journals contributed 309 of the 386 articles that had been cited at least 200 times; the remainder of the 386 most-cited articles were interspersed among other journals (at most 2 per journal). The percentage of articles receiving at least 200 citations in *Science* and *Nature* were roughly the same as the top 6 journals specializing in environmental science that had published the most articles. After that, the percentage of top-cited articles began to decline with certain exceptions.

Those core PiE articles that had had received at least 250 citations each were primarily distributed among 21 journals; there were 38 journals that had each published a sole article having received at least 250 citations (Supplementary Fig. S-1).

Some of the journals with fewer articles had higher percentages of most-cited articles (versus total articles published in the respective journal) than did the six journals with the most total articles (as well as *Science* and *Nature*). These include *Environmental Health Perspectives* (5.5%), *Environment International* (6.9%), and *Analytical Chemistry* (10%). Some of the journals that could be considered much more specialized had very low percentages of highly cited articles, including *Environmental Science and Pollution Research*, *Chemical Engineering Journal*, and *Bioresource Technology*, none of which had any highly cited articles. Notably, *PLoS One* had 49 articles, none of which was highly cited.

4.6.2.3. Incidence of review articles among the 100 most-cited PiE articles. Review articles (those that provide a synthesis or critical examination of the published literature) often experience higher citation rates than original research articles. Indeed, of the top 100 most-cited articles on PiE, 21 could be considered reviews (either containing the word review in their titles or abstracts); 12 of these 21 articles were classified as reviews by the publishing journal. Of the 21 review articles, five were among the top 11 most-cited articles, each with over 1,000 citations.

Of the 100 most-cited PiE articles, 21 could be considered reviews of the literature:

Allen et al., 2010 "Call of the wild: antibiotic resistance genes in natural environments".

Boxall et al., 2003 "Are veterinary medicines causing environmental risks?"

Crisp et al., 1998 "Environmental endocrine disruption: an effects assessment and analysis".

Daughton and Ternes, 1999 "Pharmaceuticals and personal care products in the environment: Agents of subtle change?"

Fent et al., 2006 "Ecotoxicology of human pharmaceuticals".

Halling-Sorensen et al., 1998 "Occurrence, fate and effects of pharmaceutical substances in the environment — A review".

Table 2
The 23 journals that have published the most articles on PiE and their rates for articles cited at least 200 times (compared with PiE articles published in *Science* and *Nature*).

Journal	Number of papers with more than 200 citations each	Total number of papers[a]	Range of citations per paper	Percentage of papers that are highly cited
Science	2	61	454 and 835	3.3
Nature	2	44	249 and 773	4.5
Environmental Science & Technology	73	1074	203–5424	6.8
Chemosphere	33	951	202–2524	3.5
Science of the Total Environment	38	779	202–1577	4.9
Water Research	41	721	202–2142	5.7
Journal of Chromatography A	27	550	201–705	4.9
Environmental Toxicology and Chemistry	18	475	211–640	3.8
Journal of Hazardous Materials	7	398	203–544	1.8
Aquatic Toxicology	9	369	202–1415	2.4
Environmental Science and Pollution Research	0	276	NA	0
Environmental Pollution	8	265	217–380	3.0
Analytical and Bioanalytical Chemistry	4	235	233–334	1.7
Chemical Engineering Journal	0	206	NA	0
Environmental Health Perspectives	10	182	205–3064	5.5
Ecotoxicology and Environmental Safety	3	182	229–450	1.6
Analytica Chimica Acta	2	177	227 and 324	1.1
Water Science & Technology	1	175	257	0.6
Talanta	2	174	469 and 493	1.1
Bioresource Technology	0	133	NA	0
Environment International	9	131	220–625	6.9
Analytical Chemistry	12	120	204–601	10.0
TrAC Trends in Analytical Chemistry	5	111	218–428	4.5
Journal of Agricultural and Food Chemistry	1	111	320	0.9
Journal of Environmental Quality	2	100	246 and 273	2.0
TOTAL	309			

[a] Sorted in descending order of numbers of papers published by each journal.

Heberer, 2002a "Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data".

Johnson and Sumpter, 2001 "Removal of endocrine-disrupting chemicals in activated sludge treatment works".

Kemper, 2008 "Veterinary antibiotics in the aquatic and terrestrial environment".

Khetan and Collins, 2007 "Human Pharmaceuticals in the Aquatic Environment: A Challenge to Green Chemistry".

Klavarioti et al., 2009 "Removal of residual pharmaceuticals from aqueous systems by advanced oxidation processes".

Kümmerer, 2001a "Drugs in the environment: emission of drugs, diagnostic aids and disinfectants into wastewater by hospitals in relation to other sources — a review".

Kümmerer, 2009a "Antibiotics in the aquatic environment — A review — Part I".

Kümmerer, 2009b "Antibiotics in the aquatic environment — A review — Part II".

Santos et al., 2010 "Ecotoxicological Aspects related to the presence of Pharmaceuticals in the Aquatic Environment".

Sarmah et al., 2006 "A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment".

Schwarzenbach et al., 2006 "The challenge of micropollutants in aquatic systems".

Thiele-Bruhn, 2003 "Pharmaceutical antibiotic compounds in soils — a review".

Tolls, 2001 "Sorption of veterinary pharmaceuticals in soils: A review".

Tyler et al., 1998 "Endocrine Disruption in Wildlife: A Critical Review of the Evidence".

Ying et al., 2002 "Occurrence and fate of hormone steroids in the environment".

4.6.2.4. Contributing authors for 100 most-cited PiE articles. The authors for the 100 most-cited papers (along with the number of these articles they authored) are shown in Fig. 1. A total of 23 authors each contributed to 3 or more of these articles; six each contributed to at least five articles (Joss, Kuemmerer, Siegrist, Snyder, Sumpter, and Ternes). Of these 23 most-prolific authors of the 100 most-cited papers, 19 did their research in six different European countries (Austria, Denmark, Germany, Italy, Switzerland, and UK) and four in the U.S. (one of whom was also from Korea) and Canada.

4.6.2.5. Country affiliations of the authors for the earliest, most highly cited PiE articles. Of the articles with at least 200 citations, 38 (including one retracted article) were among the earliest works — being published from 1977 to 1999 (listed in Supplementary Table S-2). The countries affiliated with the authors of these 38 articles (with the respective numbers of associated articles in parentheses) were: Canada (1), Denmark (4), Germany (11), Israel (1), Norway (1), Sweden (1), Switzerland (4), The Netherlands (2), UK (10), and US (7).

4.6.2.6. Technical words occurring most often in the abstracts of the 100 most-cited PiE articles. The word cloud in Fig. 2 shows the technical words that each occur at least 20 times in the abstracts of the 100 most-cited articles. It shows a very limited number of chemical classes, therapeutic classes, or specific APIs are frequently featured: antibiotics, carbamazepine, clofibric acid, diclofenac, EDCs, estradiol, ethynylestradiol (EE2), estrogens, estrone, hormones, ibuprofen, and steroids. The prevalence of steroids certainly reaffirms an intersection of PiE with EDCs. Also revealed is a focus on waste treatment, chemical monitoring, and risk.

4.6.2.7. Technical words occurring most often in the titles of the 250 most-cited PiE articles. A similar word cloud (Fig. 3) shows the technical words that each occur at least 5 times in the titles of the 250 most-cited articles. It differs from the abstracts primarily only in the occurrence of four specific APIs or classes: fluoroquinolone, sulfonamides, tetracycline, and triclosan.

4.6.2.8. Articles relevant to PiE with authors employed by the US EPA. With regard to some history behind the U.S. EPA's contributions to the published literature relevant to PiE, the following record was compiled. As of 10 December 2015, a total of 283 articles had been published on PiE-related topics with one or more authors employed by the US EPA. Nearly 91% of these articles are journal articles or book chapters; 24

Fig. 1. Word Cloud of Authors of Top 100 Cited Articles (as of 21 May 15).

are reports or industry guidance documents. These articles date back to 1975 but only nine of them predate 2000. Nine of these EPA-authored articles are among the larger group of 386 most-cited PiE articles. Each of these nine articles (indicated in the on-line listing) had citations counts ranging from 253 to 3064. A complete list of these articles can be accessed on-line here: https://sites.google.com/site/daughton/PPCPs-bibliographic_database.

4.6.2.9. PiE articles that have been retracted or withdrawn. Over the last couple of decades, interest and concern have been growing with respect to ethics in the conduct and publishing of science. The incidence of voluntary and mandated retractions and withdrawals of published papers has been escalating since the 2000s; the first attempt to follow retractions across science began in 2010 with the start of the on-line blog retractionwatch.com. An examination of the PPCPs database indicates that the incidence of retractions for PiE-related articles may be rather low. A total of 11 articles relevant to PiE had been retracted (as of 5 October 2015):

Arnold et al., 1996 "≪RETRACTED≫ Synergistic activation of estrogen receptor with combinations of environmental chemicals".

Blanco et al., 2007 "≪RETRACTED≫ Geographical variation in cloacal microflora and bacterial antibiotic resistance in a threatened avian scavenger in relation to diet and livestock farming practices".

Blanco and Lemus, 2010 "Livestock Drugs and Disease: The Fatal Combination behind Breeding Failure in Endangered Bearded Vultures ≪RETRACTED≫".

Blanco et al., 2009a "≪RETRACTED≫ Microbial pollution in wildlife: Linking agricultural manuring and bacterial antibiotic resistance in red-billed choughs".

Blanco et al., 2009b "≪RETRACTED≫ Ingestion of multiple veterinary drugs and associated impact on vulture health: implications of livestock carcass elimination practices".

Lemus and Blanco, 2009 "≪RETRACTED≫ Cellular and humoral immunodepression in vultures feeding upon medicated livestock carrion".

Lemus et al., 2008 "≪RETRACTED≫ Antibiotics threaten wildlife: circulating quinolone residues and disease in Avian scavengers".

Liu et al., 2012 "≪RETRACTED≫ Degradation of polycyclic musk HHCB in water by O_3, UV, and UV/O_3".

McLachlan, 1997 "≪RETRACTED≫ Synergistic Effect of Environmental Estrogens".

Mohammed et al., 2013 "≪RETRACTED≫ Fate and Transport of EDCs in Soils: Estrone and Its Sulfate Conjugate's Adsorption from Mediator Solutions".

Oropesa et al., 2012 "≪RETRACTED≫ Acute and chronic toxicity of the pharmaceutical levonorgestrel to the freshwater crustacean *Daphnia magna*".

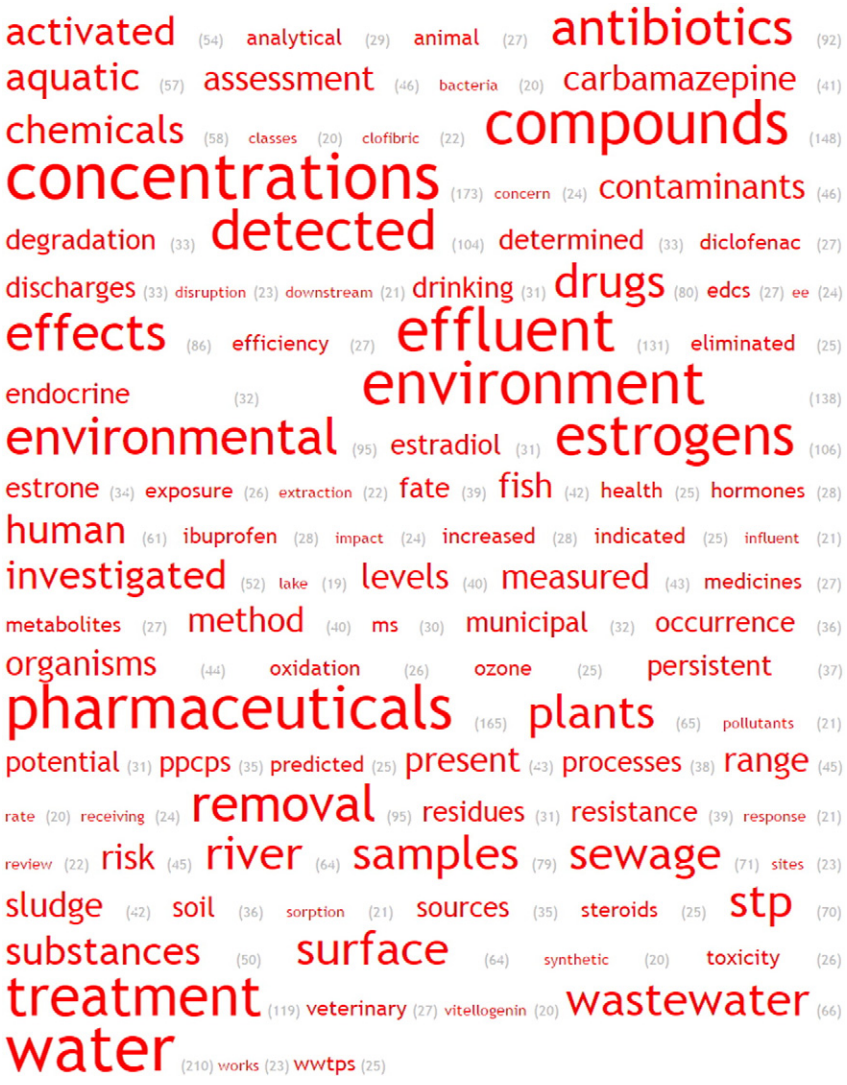

Fig. 2. Word Cloud of Abstracts of Top 100 Cited PiE Articles (as of 20 May 15).

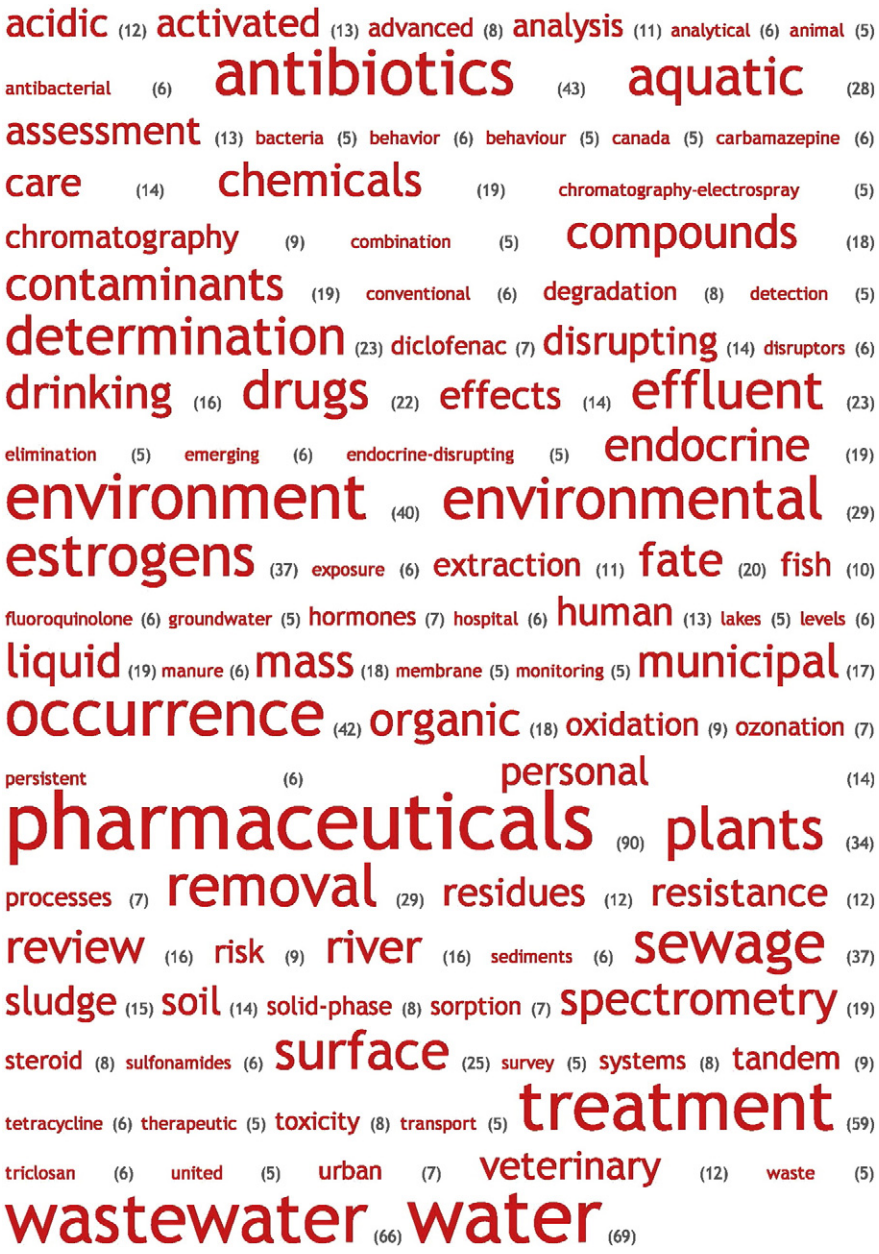

Fig. 3. Word Cloud of Titles of Articles Cited at Least 250 times (as of 14 May 15).

Of these 11 retracted articles, six (among others not related to PiE) have been retracted by the same author (Lemus), whose works have been followed by retractionwatch.com (http://retractionwatch.com/category/jesus-angel-lemus/); another author (McLachlan) had two retracted papers, both published in *Science*. Some of these articles had been cited by others - even years after the retractions. This is because retraction notices can be very time consuming to locate, especially since searches must be conducted on an ongoing basis. There is no standard or accepted practice for how publishers handle the posting of retraction notices. An article by Arnold et al. (1996) has become highly cited (621 citations) and continues to receive citations. This is partly because its retraction became a distracting set-back for the field of EDCs. Other retracted PiE articles have also received citations, sometimes years after retraction: Blanco et al., 2009b (46 citations), Lemus et al., 2008 (69), and McLachlan, 1997 (132).

5. Closing thoughts

A major lesson from this project was the degree of difficulty in compiling comprehensive data on citation frequencies for individual articles and the inordinate time that was required. This was particularly true for un-cited articles, which – surprisingly – are far more difficult to locate than highly cited articles; this difficulty undoubtedly is a factor that contributes to extending the time over which these articles remain un-cited. But it is also surprisingly difficult to locate those articles that composed the top-cited tier, as there are many steps required to ensure comprehensive coverage. These seemingly simple facts lead to the following question. Could ready and free access to meta-data (such as citation frequencies) for all of the published works that comprise PiE (or any other field of research) serve to facilitate the advancement of the field?

Likewise, locating the historical emergence of specialized terms and jargon in the literature is also quite difficult. It is also more difficult to ensure comprehensive scrutiny of the literature. This is the result of major obstacles. First is that the older literature is far more difficult to locate and acquire – especially in full-text form. Second, most of the older articles must be converted to digital formats to permit searching; but optical character recognition can have a high error rate with poor images. This reduces the effectiveness of full-text searching. And third, it is unknown how much of the older literature is simply not accessible on-line. For the topic of PiE, it is likely that a significant number of relevant articles exist in non-English journals, especially German, Dutch, and Danish. This means that the dates provided for the emergence of many of the terms tracked in this paper could be earlier than noted.

PiE is clearly a remarkably interdisciplinary research area. Its expansive scope poses obvious challenges for researchers across numerous disciplines. One obvious challenge rests in the sheer size of the published literature. At the same time, PiE's cross-cutting nature – and its close association with allied topics such as EDCs and emerging contaminants – means that the potential is high for many beneficial collateral outcomes. Resources devoted to PiE can also serve to catalyze advancements for a host of other important topics, not the least of which include: engineered treatment of wastewater and drinking water; water reuse (with an increased imperative imposed by climate change, drought, and aging infrastructures); the toxicological concerns surrounding low-dose exposure and simultaneous/sequential exposure to multiple chemical stressors; the sustainable and prudent use of drugs (especially antibiotics - for both human and veterinary use — and those drugs with high acute toxicity); and environmental stewardship and pollution prevention for reducing API entry to the environment.

The proliferation of papers on the many facets of the PiE topic poses a very important question with respect to the future of how science progresses. As with many fields of investigation, it is clearly not possible for anyone to keep up with its rapidly growing body of published works. It may not even be possible to keep current with single, narrower facets of the larger topic (such as waste treatment or biological effects). Immediate concerns emerge as to the knowledge content and impact of this body of work. In what ways and to what degrees is our understanding of the PiE field being advanced? Does the investment in time and resources that underlie these escalating numbers of articles lead to commensurate benefits to the science community and society? Of course, this presupposes that these impacts can even be identified and measured. Is it possible to identify the most important areas for future research and to guide allocation of resources in these directions? These concerns conflict with the competing importance of quickly identifying previously unrecognized or poorly appreciated (emerging) concerns — the type of research that often requires ignoring what has been previously examined.

As an example relating to impact, it is interesting to examine the PPCPs database for journal articles on PiE that have never been cited or have been very infrequently cited. This includes articles that are 2–3 years old that have never been cited and older articles that have been cited at most 5 times. Among the 15,000 journal articles, these infrequently cited articles currently total over 340, representing over 2% of the database. This prompts the obvious questions as to the possible cause(s) for papers that are rarely cited, including: journal accessibility, perceptions of poor quality by potential citing papers, or the contribution is perceived as redundant with prior published works or as not contributing to advancement of the field. Also possibly at work is the impact of cognitive bias from the Matthew Effect, which serves to perpetuate the citation of articles that have already garnered the most citations while simultaneously fostering continued disinterest in those articles that have yet to the cited (Daughton, 2014c "The Matthew Effect and widely prescribed pharmaceuticals lacking environmental monitoring: Case study of an exposure-assessment vulnerability").

These questions, and many others, relate to the efficiency of science. Does the sheer size of the published literature, regardless of its quality, serve as overwhelming noise that obliterates what would ordinarily be useful? The question at hand is whether the long-establish way in which new knowledge is conveyed – namely, the peer-reviewed journal article – can be radically altered to enhance the way in which useful data and knowledge can be mined. The only aspect of the published literature (which comprises ever-growing numbers of articles as well as journals themselves) that serves to weakly organize or unify it is the practice of cross citation. And the practice of citation can only be examined by means of time-consuming and exhaustive citation analysis, which attempts to reveal the loose networks of citing and cited articles.

The larger question is whether the practice of communicating the findings of research via the conventional published article can be replaced with a more efficient model that serves, in part, to reduce the duplication of effort, minimize research that might add only marginally to a field, and instead help focus on the top priorities. What the priorities might be for PiE – and how they might be established – are themselves challenging questions; the following serve as examples:

Berninger et al., 2015 "Prioritization of pharmaceuticals for potential environmental hazard through leveraging a large scale mammalian pharmacological dataset".

Rudd et al., 2014 "International scientists' priorities for research on pharmaceuticals and personal care products in the environment".

The challenge of a more efficient model for communication is partly being addressed by the rapidly evolving but still rather vague concept of collaborative science, dubbed Science 2.0 (e.g., see: https://en.wikipedia.org/wiki/Science_2.0). Regardless of what that future might look like, a transformation needs to involve a much more efficient way of locating and distilling existing data from the conventional published literature and for formulating new knowledge and insights that can better guide and accelerate the trajectory of a highly complex field of study such as PiE — enhancing its value to society.

EPA notice

The information in this document has been funded wholly by the United States Environmental Protection Agency under. It has been subjected to the Agency's peer and administrative review and has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use. Greatly appreciated were the assistance of MST Scuderi (SEEP, US EPA, Las Vegas) in the maintenance of the EndNote bibliographic database and the technical reviews of this manuscript by Dr. Susan T. Glassmeyer (NERL, ORD, US EPA, Cincinnati, OH) and MST Scuderi.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2016.03.109.

References

ACS. "Special Symposium on 'Pharmaceuticals in the Environment'". 219th National Meeting of the American Chemical Society, Daughton CG and Ternes T (organizers/chairs), San Francisco, CA, 2000 (27 March).

Addison, J.B., 1984. In: Gunther, F.A., Gunther, J.D. (Eds.), Antibiotics in sediments and run-off waters from feedlotsResidue Reviews 92. Springer New York, New York, NY, pp. 1–28 (chapter 1).

Agüera, A., Estrada, L.A.P., Ferrer, I., Thurman, E.M., Malato, S., Fernandez-Alba, A.R., 2005. Application of time-of-flight mass spectrometry to the analysis of phototransformation products of diclofenac in water under natural sunlight. J. Mass Spectrom. 40, 908–915. http://dx.doi.org/10.1002/jms.867.

Aherne, G.W., Briggs, R., 1989. The relevance of the presence of certain synthetic steroids in the aquatic environment. J. Pharm. Pharmacol. 41, 735–736. http://dx.doi.org/10.1111/j.2042-7158.1989.tb06355.x.

Aherne, G.W., English, J., Marks, V., 1985. The role of immunoassay in the analysis of microcontaminants in water samples. Ecotoxicol. Environ. Saf. 9, 79–83. http://dx.doi.org/10.1016/0147-6513(85)90037-5.

Aherne, G.W., Hardcastle, A., Nield, A.H., 1990. Cytotoxic drugs and the aquatic environment: estimation of bleomycin in river and water samples. J. Pharm. Pharmacol. 42, 741–742. http://dx.doi.org/10.1111/j.2042-7158.1990.tb06574.x.

Alameda County, 2012. New County Policy Requires Drug Makers to Pick Up Disposal Costs. p. 1 (Alameda County, CA. Available on: http://www.acgov.org/news/pressreleases/pr201-07-24SafeMed.pdf. (accessed 20 November 2015)).

Allen, H.K., Donato, J., Wang, H.H., Cloud-Hansen, K.A., Davies, J., Handelsman, J., 2010. Call of the wild: antibiotic resistance genes in natural environments. Nat. Rev. Microbiol. 8, 251–259. http://dx.doi.org/10.1038/nrmicro2312.

Altenburger, R., Boedeker, W., Faust, M., Grimme, L.H., 1996. Regulations for combined effects of pollutants: consequences from risk assessment in aquatic toxicology. Food Chem. Toxicol. 34, 1155–1157. http://dx.doi.org/10.1016/S0278-6915(97)00088-4.

Álvarez-Torrellas, S., Rodríguez, A., Ovejero, G., García, J., 2016. Comparative adsorption performance of ibuprofen and tetracycline from aqueous solution by carbonaceous materials. Chem. Eng. J. 283, 936–947. http://dx.doi.org/10.1016/j.cej.2015.08.023.

Anderson, P.D., 2008. Technical Brief: Trace Organic Compounds and Implications for Wastewater Treatment. Water Environment Research Foundation (WERF), Alexandria, VA, p. 114 (CEC3R07, Available on: http://www.iwapublishing.com/books/9781843395249/trace-organic-compounds-and-implications-wastewater-treatment-technical-brief. (accessed 20 November 2015)).

Angeletti, G., Bjørseth, A. (Eds.), 1984. Analysis of Organic Micropollutants in Water: Proceedings of the Third European Symposium held in Oslo, Norway, September 19–21, 1983. Reidel Publishing Company, Dordrecht, The Netherlands http://dx.doi.org/10.1007/978-94-009-6345-0 339 pp.

Anon., 1988. Disposal of pharmaceutical waste. Pharm. J. 241, 712.

Arizona Water Resource, 2000. Endocrine disrupters in water: what are EDs? What risks do they pose? Ariz. Water Resour. 9, 4.

Arnold, S.F., Klotz, D.M., Collins, B.M., Vonier, P.M., Guillette Jr., L.J., McLachlan, J.A., 1996. ≪RETRACTED≫ Synergistic activation of estrogen receptor with combinations of environmental chemicals. Science 272, 1489–1492. http://dx.doi.org/10.1126/science.272.5267.1489.

Associated Press, 2008. An AP Investigation: Pharmaceuticals Found in Drinking Water.

AwwaRF, 2000. Endocrine Disruptors & Pharmaceutically Active Chemicals in Drinking Water Workshop. The University of Iowa, Iowa City, IA (113 pp.; http://www.cheec.uiowa.edu/outreach/endocrine.html; http://www.cheec.uiowa.edu/outreach/endocrine_pharm.pdf, Center for Health Effects of Environmental Contamination (CHEEC), 19–21 April).

Ayscough, N.J., Fawell, J., Franklin, G., Young, W., 2000. Review of human pharmaceuticals in the environment. R&D Report P390. Environment Agency, p. 114 (Available on: (accessed 20 November 2015)).

Backhaus, T., Altenburger, R., Boedeker, W., Faust, M., Scholze, M., Grimme, L.H., 2000a. Predictability of the toxicity of a multiple mixture of dissimilarly acting chemicals to *Vibrio fischeri*. Environ. Toxicol. Chem. 19, 2348–2356. http://dx.doi.org/10.1002/etc.5620190927.

Backhaus, T., Scholze, M., Grime, L.H., 2000b. The single substance and mixture toxicity of quinolones to the bioluminescent bacterium *Vibrio fischeri*. Aquat. Toxicol. 49, 49–61. http://dx.doi.org/10.1016/S0166-445X(99)00069-7.

Baquero, F., Martínez, J.-L., Cantón, R., 2008. Antibiotics and antibiotic resistance in water environments. Curr. Opin. Biotechnol. 19, 260–265. http://dx.doi.org/10.1016/j.copbio.2008.05.006.

Barber, M., 1947. Staphylococcal infection due to penicillin-resistant strains. Br. Med. J. 2, 863–865.

Barceló, D., 2007. Pharmaceutical-residue analysis. TrAC Trends Anal. Chem. 26, 454–455. http://dx.doi.org/10.1016/j.trac.2007.02.008.

Bard, S.M., 2000. Multixenobiotic resistance as a cellular defense mechanism in aquatic organisms. Aquat. Toxicol. 48, 357–389. http://dx.doi.org/10.1016/S0166-445X(00)00088-6.

Baronti, C., Curini, R., D'Ascenzo, G., Di Corcia, A., Gentili, A., Samperi, R., 2000. Monitoring natural and synthetic estrogens at activated sludge sewage treatment plants and in a receiving river water. Environ. Sci. Technol. 34, 5059–5066. http://dx.doi.org/10.1021/es001359q.

Bengtsson, B.-E., Gunnarsson, B., Wall, T., Wennmalm, Å. (Eds.), 2006. Environment and Pharmaceuticals. Apoteket AB (The National Corporation of Swedish Pharmacies), Stockholm County Council, Stockholm University, Stockholm, Sweden (140 pp.; http://www.janusinfo.se/Global/Miljo_och_lakemedel/lakemed_miljo_eng2007.pdf).

Bengtsson, B.-E., Gunnarsson, B., Hagerman, H., Liljelund, K., Wennmalm, Å. (Eds.), 2009. A Healthy Future — Pharmaceuticals in a Sustainable Society. Apoteket AB, MistraPharma, Stockholm County Council, Stockholm, Sweden (201 pp.; http://www.mistrapharma.se/Homepage/Download-File/f/333233/h/557e63b8a520e26d0da9084cc39c526f/Book+MistraPharma+2008+eng).

Bergh, J.J., Breytenbach, J., Du Preez, J.L., 1990. High-performance liquid chromatographic analysis of trimethroprim in the presence of its degradation products. J. Chromatogr. 513, 392–396.

Berninger, J.P., LaLone, C.A., Villeneuve, D.L., Ankley, G.T., 2015. Prioritization of pharmaceuticals for potential environmental hazard through leveraging a large scale mammalian pharmacological dataset. Environ. Toxicol. Chem. http://dx.doi.org/10.1002/etc.2965 (in press).

Bester, K., Huhnerfuss, H., Lange, W., Rimkus, G.G., Theobald, N., 1998. Results of non target screening of lipophilic organic pollutants in the German bight II: polycyclic musk fragrances. Water Res. 32, 1857–1863. http://dx.doi.org/10.1016/S0043-1354(97)00424-7.

Bjørseth, A., Angeletti, G. (Eds.), 1982. Analysis of Organic Micropollutants in Water, first ed. D. Reidel Publishing Company, Dordrecht, Holland http://dx.doi.org/10.1007/978-94-009-7804-1 (376 pp.).

BLAC, 1999. Arzneimittel in der Umwelt: Konzept für ein Untersuchungsprogramm (Pharmaceuticals in the Environment — Plan for a Study Program). Bund/Länderausschuss für Chemikaliensicherheit (BLAC), Hamburg, Germany, p. 43 (Available on: http://www.blac.de/servlet/is/2146/P-2b.pdf. (accessed 20 November 2015)).

Blanco, G., Lemus, J.A., 2010. Livestock drugs and disease: the fatal combination behind breeding failure in endangered bearded vultures ≪RETRACTED≫. PLoS One 5, e14163. http://dx.doi.org/10.1371/journal.pone.0014163.

Blanco, E., Lemus, J.A., Grande, J., Gangoso, B., Frias, O., Hiraldo, F., 2007. ≪RETRACTED≫ Geographical variation in cloacal microflora and bacterial antibiotic resistance in a threatened avian scavenger in relation to diet and livestock farming practices. Environ. Microbiol. 9, 1738–1749. http://dx.doi.org/10.1111/j.1462-2920.2007.01291.x.

Blanco, G., Lemus, J.A., Grande, J., 2009a. ≪RETRACTED≫ Microbial pollution in wildlife: linking agricultural manuring and bacterial antibiotic resistance in red-billed choughs. Environ. Res. 109, 405–412. http://dx.doi.org/10.1016/j.envres.2009.01.007.

Blanco, G., Lemus, J.Á., Martínez, F., Arroyo, B., García-Montijano, M., Grande, J., 2009b. ≪RETRACTED≫ Ingestion of multiple veterinary drugs and associated impact on vulture health: implications of livestock carcass elimination practices. Anim. Conserv. 12, 571–580. http://dx.doi.org/10.1111/j.1469-1795.2009.00283.x.

Bletsou, A.A., Jeon, J., Hollender, J., Archontaki, E., Thomaidis, N.S., 2015. Targeted and non-targeted liquid chromatography-mass spectrometric workflows for identification of transformation products of emerging pollutants in the aquatic environment. TrAC Trends Anal. Chem. 66, 32–44. http://dx.doi.org/10.1016/j.trac.2014.11.009.

Blok, J., Wösten, M.A.D., 2000. Source and Environmental Fate of Natural Oestrogens. Vereniging Rivierwaterbedrijven (RIWA) [Association of River Waterworks (RIWA)], Amsterdam, The Netherlands, p. 51 (Available on: http://trove.nla.gov.au/work/24090359?q&versionId=29122191. (accessed 20 November 2015)).

Bloom, R.A., Matheson III, J.C., 1993. Environmental assessment of avermectins by the US Food and Drug Administration. Vet. Parasitol. 48, 281–294. http://dx.doi.org/10.1016/0304-4017(93)90163-H.

Bortone, S.A., Davis, W.P., 1994. Fish intersexuality as indicator of environmental stress. Bioscience 44.

Bowman, C., 2000. Medicines, chemicals taint water: contaminants pass through sewage plants. Sacramento, CA. Available on: http://www.greenspun.com/bboard/q-and-a-fetch-msg.tcl?msg_id=002rcc (accessed 20 November 2015).

Boxall, A.B.A., Kolpin, D.W., Halling-Sorensen, B., Tolls, J., 2003. Are veterinary medicines causing environmental risks? Environ. Sci. Technol. 37, 286A–294A.

Boyd, G.R., Grimm, D.A., 2001. Occurrence of pharmaceutical contaminants and screening of treatment alternatives for Southeastern Louisiana. Ann. N. Y. Acad. Sci. 948, 80–89. http://dx.doi.org/10.1111/j.1749-6632.2001.tb03989.x.

Bradley, T.J., Williams, W.H., 1975. Evaluation of medicines returned in Manchester DUMP campaign. Pharm. J. 215, 542 (47).

Brain, R.A., Johnson, D.J., Richards, S.M., Hanson, M.L., Sanderson, H., Lam, M.W., et al., 2004. Microcosm evaluation of the effects of an eight pharmaceutical mixture to the aquatic macrophytes *Lemna gibba* and *Myriophyllum sibiricum*. Aquat. Toxicol. 70, 23–40. http://dx.doi.org/10.1016/j.aquatox.2004.06.011.

Brooks, B.W., Foran, C.M., Richards, S.M., Weston, J., Turner, P.K., Stanley, J.K., et al., 2003a. Aquatic ecotoxicology of fluoxetine. Toxicol. Lett. 142, 169–183. http://dx.doi.org/10.1016/S0378-4274(03)00066-3.

Brooks, B.W., Turner, P.K., Stanley, J.K., Weston, J.J., Glidewell, E.A., Foran, C.M., et al., 2003b. Waterborne and sediment toxicity of fluoxetine to select organisms. Chemosphere 52, 135–142. http://dx.doi.org/10.1016/S0045-6535(03)00103-6.

Broom, W.A., Gurd, M.R., Harmer, G.L.M., Randall, S.S., 1961. The stability of hexoestrol in soil and its uptake by plants. J. Endocrinol. 21, 381–385. http://dx.doi.org/10.1677/joe.0.0210381.

Bull, D., Ivie, G., MacConnell, J., Gruber, V., Ku, C., Arison, B., et al., 1984. Fate of avermectin B1a in soil and plants. J. Agric. Food Chem. 32, 94–102. http://dx.doi.org/10.1021/jf00121a025.

Buser, H.R., Poiger, T., Muller, M.D., 1999. Occurrence and environmental behavior of the chiral pharmaceutical drug ibuprofen in surface waters and in wastewater. Environ. Sci. Technol. 33, 2529–2535. http://dx.doi.org/10.1021/es981014w.

Buzby, M.E., 2006. Pharmaceuticals in the environment — a review of PhRMA initiatives. 4th Japan–US Government Conference on Drinking Water Quality Management and Wastewater Control. Merck & Co. Inc. (165-83 pp.; http://www.nilim.go.jp/lab/bcg/siryou/tnn/tnn0402pdf/ks0402021.pdf).

Buzby, M., Meyerhoff, R., 2007. Pharmaceutical research and manufacturers of America: research on pharmaceuticals in the environment. WERF Workshop on Trace Organics: Mapping a Collaborative Research Roadmap, San Francisco, CA, p. 7 (Available on: https://www.werf.org/c/ResearchChallenges/TraceOrganicsCEC/CECWorkshop/SpeakerPresentationsorganizations/PhRMA.aspx. (accessed 20 November 2015)).

Caballa, S.H., Patterson, M., Kapoor, I.P., 1979. In: Khan, M.A.Q., Lech, J.J., Menn, J.J. (Eds.), A terrestrial–aquatic model ecosystem for evaluating the environmental fate of drugs and related residues in animal excretaPesticide and Xenobiotic Metabolism in Aquatic Organisms 99. American Chemical Society, Washington, DC, pp. 183–194 (chapter 12).

Cameron, S., 1996. Study by Alberta pharmacists indicates drug wastage a "mammoth" problem. Can. Med. Assoc. J. 155, 1596–1598.

Caminada, D., Zaja, R., Smital, T., Fent, K., 2008. Human pharmaceuticals modulate P-gp1 (ABCB1) transport activity in the fish cell line PLHC-1. Aquat. Toxicol. 90, 214–222. http://dx.doi.org/10.1016/j.aquatox.2008.08.013.

Campbell, H.V., 2002. Pharmaceuticals in the environment: regulatory and nonregulatory approaches. Environ. Law Report. 32 (ELR:11200–11).

Carballa, M., Omil, F., Lema, J.M., Llompart, M., Garcia-Jares, C., Rodriguez, I., et al., 2004. Behavior of pharmaceuticals, cosmetics and hormones in a sewage treatment plant. Water Res. 38, 2918–2926. http://dx.doi.org/10.1016/j.watres.2004.03.029.

Carpenter, D.O., Arcaro, K., Spink, D.C., 2002. Understanding the human health effects of chemical mixtures. Environ. Health Perspect. 110, 25–42.

Carr, M., 2000. Flush with Drugs: Waterways Examined for Potential Risks Posed by Medicines Released Down Drains. The Dallas Morning News, Dallas, TX (accessed 20 November 2015).

Chen, Z., Pavelic, P., Dillon, P., Naidu, R., 2002. Determination of caffeine as a tracer of sewage effluent in natural waters by on-line solid-phase extraction and liquid chromatography with diode-array detection. Water Res. 36, 4830–4838. http://dx.doi.org/10.1016/S0043-1354(02)00221-X.

Chiu, C., Westerhoff, P.K., 2010. Trace organics in Arizona surface and wastewaters. In: Halden, R.U. (Ed.), Contaminants of Emerging Concern in the Environment: Ecological and Human Health Considerations. American Chemical Society, Washington, DC, pp. 81–117 (chapter 4).

Christensen, F.M., 1998. Pharmaceuticals in the environment—a human risk? Regul. Toxicol. Pharmacol. 28, 212–221. http://dx.doi.org/10.1006/rtph.1998.1253.

Chui, G., 2000. Tainted Waters: Trace Amounts of Medicine, Lotions and Household Products are Showing Up in Waterways. San Jose Mecury News, San Jose, CA (accessed 20 November 2015).

Cleuvers, M., 2002. Aquatische Ökotoxikologie ausgewählter arzneimittel - algentest und akuter daphnientest [Aquatic Ecotoxicology of Selected Pharmaceutical Agents - Algal and Acute Daphnia Tests]. Umweltwiss. Schadst. Forsch. 14, 85–89. http://dx.doi.org/10.1065/uwsf2002.04.025.

Cleuvers, M., 2003. Aquatic ecotoxicity of pharmaceuticals including the assessment of combination effects. Toxicol. Lett. 142, 185–194. http://dx.doi.org/10.1016/S0378-4274(03)00068-7.

Coats, J.R., Metcalf, R.L., Lu, P.Y., Brown, D.D., Williams, J.F., Hansen, L.G., 1976. Model ecosystem evaluation of the environmental impacts of the veterinary drugs phenothiazine, sulfamethazine, clopidol, and diethylstilbestrol. Environ. Health Perspect. 18, 167–179.

Colborn, T., vom Saal, F.S., Soto, A.M., 1993. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ. Health Perspect. 101, 378–384.

Committee on Hormonally Active Agents in the Environment, Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council, 1999t. Hormonally Active Agents in the Environment. The National Academies Press, Washington, DC (452 pp.; http://books.nap.edu/books/0309064198/html).

Committee on Toxicants and Pathogens in Biosolids Applied to Land, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies, National Research Council, 2002t. Biosolids Applied to Land: Advancing Standards and Practices. The National Academies Press, Washington, DC (368 pp.; http://www.nap.edu/books/0309084865/html).

Crisp, T.M., Clegg, E.D., Cooper, R.L., Wood, W.P., Anderson, D.G., Baetcke, K.P., et al., 1998. Environmental endocrine disruption: an effects assessment and analysis. Environ. Health Perspect. 106, 11–56.

Crook, J., Mosher, J.J., Casteline, J.M., 2005. Status and Role of Water Reuse: An International View. Global Water Research Coalition, London, UK, p. 137 (Available on: http://www.waterrf.org/resources/Lists/SpecialReports/Attachments/2/WaterReuse.pdf. (accessed 20 November 2015)).

Crowdy, S.H., Jones, D.R., 1956. The translocation of sulphonamides in higher plants: I. Uptake and translocation in broad beans. J. Exp. Bot. 7, 335–346. http://dx.doi.org/10.1093/jxb/7.3.335.

Crowdy, S.H., Grovem, J.F., Hemming, H.G., Robinson, K.C., 1956. The translocation of antibiotics in higher plants: II. The movement of griseofulvin in broad bean and tomato. J. Exp. Bot. 7, 42–64. http://dx.doi.org/10.1093/jxb/7.1.42.

CSTEE, 2001. Opinion on: draft CPMP discussion paper on environmental risk assessment of medicinal products for human use [non-genetically modified organism (non-GMO) containing]. C2/JCD/csteeop/CPMPpaperRAssessHumPharm12062001/D(01), Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE), European Commission Directorate-General Health and Consumer Protection, 24th CSTEE Plenary Meeting, Brussels, Belgium, p. 22 (Available on: http://ec.europa.eu/food/fs/sc/sct/out111_en.pdf. (accessed 20 November 2015)).

Damstra, T., Barlow, S., Bergman, A., Kavlock, R., Van Der Kraak, G. (Eds.), 2002. Global Assessment of the State-of-the-science of Endocrine Disruptors. World Health Organization, WHO, Geneva, Switzerland (Volume WHO/PCS/EDC/02/2, 180 pp.; http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/).

Daughton, C.G., 2001a. Emerging pollutants, and communicating the science of environmental chemistry and mass spectrometry: pharmaceuticals in the environment. J. Am. Soc. Mass Spectrom. 12, 1067–1076. http://dx.doi.org/10.1016/S1044-0305(01)00287-2.

Daughton, C.G., 2001b. Illicit drugs in municipal sewage: proposed new non-intrusive tool to heighten public awareness of societal use of illicit/abused drugs and their potential for ecological consequence. In: Daughton, C.G., Jones-Lepp, T. (Eds.), Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues. American Chemical Society, Washington, DC, pp. 348–364 (chapter 20).

Daughton, C.G., 2001c. Pharmaceuticals and personal care products in the environment: overarching issues and overview. In: Daughton, C.G., Jones-Lepp, T.L. (Eds.), Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues. American Chemical Society, Washington, DC, pp. 2–38 (chapter 1).

Daughton, C.G., 2002. Environmental stewardship and drugs as pollutants. Lancet 360, 1035–1036. http://dx.doi.org/10.1016/S0140-6736(02)11176-7.

Daughton, C.G., 2003a. Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. I. Rationale for and avenues toward a green pharmacy. Environ. Health Perspect. 111, 757–774. http://dx.doi.org/10.1289/ehp.5947.

Daughton, C.G., 2003b. Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. II. Drug disposal, waste reduction, and future directions. Environ. Health Perspect. 111, 775–785. http://dx.doi.org/10.1289/ehp.5948.

Daughton, C.G., 2005. Emerging chemicals as pollutants in the environment: a 21st century perspective. Renew. Resour. J. 23, 6–23.

Daughton, C.G., 2006. Emerging pollutants — questions, challenges, and the future. Inaugural Issue, Network of Reference Laboratories for Monitoring of Emerging Environmental Pollutants, EU, Stresa, Italy, p. 15 (Available on: http://www.norman-network.net/sites/default/files/files/bulletins/newsletter_norman_1.pdf. (accessed 20 November 2015), June).

Daughton, C.G., 2007. Pharmaceuticals in the environment: sources and their management. In: Petrović, M., Barceló, D. (Eds.), Analysis, Fate and Removal of Pharmaceuticals in the Water Cycle 50. Elsevier Science, Amsterdam, The Netherlands, pp. 1–58 (chapter 1).

Daughton, C.G., 2008. Pharmaceuticals as environmental pollutants: the ramifications for human exposure. In: Heggenhougen, K., Quah, S. (Eds.), International Encyclopedia of Public Health 5. Academic Press, Oxford, England, pp. 66–102.

Daughton, C.G., 2010a. Drugs and the Environment: Stewardship & Sustainability. National Exposure Research Laboratory, Environmental Sciences Division, US EPA, Las Vegas, NV, p. 196 NERL-LV-ESD 10/081, EPA/600/*R*-10/106. (Available on: https://drive.google.com/file/d/0B2H7EPtvem2-b3dWeVZzRmdsTmc/view. (accessed 20 November 2015)).

Daughton, C.G., 2010b. Pharmaceutical ingredients in drinking water: overview of occurrence and significance of human exposure. In: Halden, R.U. (Ed.), Contaminants of Emerging Concern in the Environment: Ecological and Human Health Considerations. American Chemical Society, Washington, DC, pp. 9–68 (chapter 2).

Daughton, C.G., 2011. Illicit drugs: contaminants in the environment and utility in forensic epidemiology. Rev. Environ. Contam. Toxicol. 210, 59–110. http://dx.doi.org/10.1007/978-1-4419-7615-4_3.

Daughton, C.G., 2012. Using biomarkers in sewage to monitor community-wide human health: isoprostanes as conceptual prototype. Sci. Total Environ. 424, 16–38. http://dx.doi.org/10.1016/j.scitotenv.2012.02.038.

Daughton, C.G., 2013. Pharmaceuticals in the environment: sources and their management. In: Petrovic, M., Perez, S., Barcelo, D. (Eds.), Analysis, Removal, Effects and Risk of Pharmaceuticals in the Water Cycle — Occurrence and Transformation in the Environment 62. Elsevier, pp. 37–69 (chapter 2).

Daughton, C.G., 2014a. In: Daughton, C.G. (Ed.), Drug Disposal & Stewardship: Ramifications for the Environment and Human Health. US Environmental Protection Agency, Las Vegas, NV (Available on: https://drive.google.com/file/d/0B2H7EPtvem2-UHZwRWxEY2FLY2s/view. (accessed 20 November 2015)).

Daughton, C.G., 2014b. Eco-directed sustainable prescribing: feasibility for reducing water contamination by drugs. Sci. Total Environ. 493, 392–404. http://dx.doi.org/10.1016/j.scitotenv.2014.06.013.

Daughton, C.G., 2014c. The Matthew effect and widely prescribed pharmaceuticals lacking environmental monitoring: case study of an exposure-assessment vulnerability. Sci. Total Environ. 466–467, 315–325. http://dx.doi.org/10.1016/j.scitotenv.2013.06.111.

Daughton, C.G., Brooks, B.W., 2011. Active pharmaceutical ingredients and aquatic organisms. In: Beyer, W.N., Meador, J.P. (Eds.), Environmental Contaminants in Biota: Interpreting Tissue Concentrations. CRC Press, Taylor and Francis, Boca Raton, FL, pp. 287–347 (chapter 8).

Daughton, C.G., Jones-Lepp, T. (Eds.), 2001. Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues. American Chemical Society, Washington, DC http://dx.doi.org/10.1021/bk-2001-0791 396 pp.

Daughton, C.G., Ruhoy, I.S., 2007. Pharmaceuticals in the Environment — Why Should Anyone Care? KNAPPE Newsletter. http://www.micropollutants.org/Docs/577.pdf.

Daughton, C.G., Ruhoy, I.S., 2008. The afterlife of drugs and the role of pharmEcovigilance. Drug Saf. 31, 1069–1082. http://dx.doi.org/10.2165/0002018-200831120-00004.

Daughton, C.G., Ruhoy, I.S., 2009. Environmental footprint of pharmaceuticals: the significance of factors beyond direct excretion to sewers. Environ. Toxicol. Chem. 28, 2495–2521. http://dx.doi.org/10.1897/08-382.1.

Daughton, C.G., Ruhoy, I.S., 2010. Pharmaceuticals in the environment — why should we care? In: Roig, B. (Ed.), Pharmaceuticals in the Environment: Current Knowledge and Need Assessment to Reduce Presence and Impact. IWA Publishing, London, UK, pp. xiii–xvii (chapter Foreword)

Daughton, C.G., Scuderi, M.S.T., 2016a. Drug Disposal and Environmental Stewardship: Relevant Literature. U.S. Environmental Protection Agency, Las Vegas, Nevada ((a comprehensive bibliographic database of literature references compiled and maintained by CG Daughton and MST Scuderi; first implemented 20 May 2010), pp Available on: see the "Drug Disposal" file at: https://sites.google.com/site/daughton/PPCPs-bibliographic_database. (accessed 20 November 2015)).

Daughton, C.G., Scuderi, M.S.T., 2016b. Pharmaceuticals and Personal Care Products (PPCPs): Relevant Literature. U.S. Environmental Protection Agency, Las Vegas, NV ((a comprehensive bibliographic database of literature references; first implemented 19 February 2008), pp Available on: see the "PPCPs Literature" file at: https://sites.google.com/site/daughton/PPCPs-bibliographic_database. (accessed 20 November 2015)).

Daughton, C.G., Ternes, T.A., 1999. Pharmaceuticals and personal care products in the environment: agents of subtle change? Environ. Health Perspect. 107, 907–938. http://dx.doi.org/10.2307/3434573.

Davis, J.E., 2007. Are one or two dangerous? Methyl salicylate exposure in toddlers. J. Emerg. Med. 32, 63–69. http://dx.doi.org/10.1016/j.jemermed.2006.08.009.

Davis, T.R.A., Burg, A.W., Neumeyer, J.L., Butters, K.M., Wadler, B.D., 1970. Organic Chemical Pollution of Freshwater. Water Quality Criteria Data Book Volume I, Prepared for the Environmental Protection Agency, Water Quality Office by Arthur D. Little, Inc., Life Sciences Division, Cambridge, MA, p. 379 (Available on: http://catalog.hathitrust.org/Record/100719624. (accessed 20 November 2015)).

DEA, 2010. Press release: DEA Heads First-ever Nationwide Prescription Drug Take-back Day. US Department of Justice, Drug Enforcement Administration (DEA), Springfield, VA (Available on: http://www.justice.gov/dea/pubs/pressrel/pr081910.html. (accessed 20 November 2015)).

DEA, 2014. Disposal of controlled substances 21 CFR parts 1300, 1301, 1304, 1305, 1307, and 1317. Fed. Regist. 79, 53520–53570.

Demerec, M., 1945. Production of *Staphylococcus* strains resistant to various concentrations of penicillin. Proc. Natl. Acad. Sci. U. S. A. 31, 16–24.

Dershewitz, R.A., Williamson, J.W., 1977. Prevention of childhood household injuries: a controlled clinical trial. Am. J. Public Health 67, 1148–1153. http://dx.doi.org/10.2105/ajph.67.12.1148.

Desbrow, C., Routledge, E.J., Brighty, G.C., Sumpter, J.P., Waldock, M., 1998. Identification of estrogenic chemicals in STW effluent. 1. Chemical fractionation and in vitro biological screening. Environ. Sci. Technol. 32, 1549–1558. http://dx.doi.org/10.1021/es9707973.

Diaz, R., Ibanez, M., Sancho, J.V., Hernandez, F., 2012. Target and non-target screening strategies for organic contaminants, residues and illicit substances in food, environmental and human biological samples by UHPLC-QTOF-MS. Anal. Methods 4, 196–209. http://dx.doi.org/10.1039/C1AY05385J.

Dielman, R.W., 1978. A report on hospital effluent problems with low level radionuclides. Environ. Int. 1, 51–53. http://dx.doi.org/10.1016/S0160-4120(78)80076-2.

Dietrich, D.R., Webb, S.F., Petry, T., 2002a. Hot spot pollutants: pharmaceuticals in the environment. Toxicol. Lett. Spec. Issue 131, 1–146. http://dx.doi.org/10.1016/S0378-4274(02)00096-6.

Dietrich, D.R., Webb, S.F., Petry, T., 2002b. Hot spot pollutants: pharmaceuticals in the environment. Toxicol. Lett. 131, 1–3. http://dx.doi.org/10.1016/S0378-4274(02)00062-0.

Dobson, R., 2000. Anti-depressants get into water system. Britain. (Available on: http://www.mail-archive.com/ctrl@listserv.aol.com/msg41565.html. (accessed 20 November 2015)).

Dodds, E.C., Goldberg, L., Lawson, W., Robinson, R., 1938. Oestrogenic activity of certain synthetic compounds. Nature 141, 247–248. http://dx.doi.org/10.1038/141247b0.

Donaldson, W.T., 1977. Trace organics in water. Environ. Sci. Technol. 11, 348–351. http://dx.doi.org/10.1021/es60127a012.

Donn, J., Mendoza, M., Pritchard, J., 2008. Pharmaceuticals Found in Drinking Water, Affecting Wildlife and Maybe Humans. (Available on: http://hosted.ap.org/specials/interactives/pharmawater_site/day1_01.html. (accessed 20 November 2015)).

Drewes, J.E., Fox, P., Jekel, M., 2001. Occurrence of iodinated X-ray contrast media in domestic effluents and their fate during indirect potable reuse. J. Environ. Sci. Health A A36, 1633–1645.

Dsikowitzky, L., Schwarzbauer, J., Littke, R., 2002. Distribution of polycyclic musks in water and particulate matter of the Lippe River (Germany). Org. Geochem. 33, 1747–1758. http://dx.doi.org/10.1016/S0146-6380(02)00115-8.

Dunne, M., 9 July 2000. Pharmaceutical Pollution: Traces of Medicines Found in N.O.-Area Water. The Advocate, Baton Rouge, LA (accessed 20 November 2015).

Eckerman, I., Martineus, J.-C., 1997. Medicines and the Environment — What Do We Know Today? Swedish Association of Physicians for the Environment, Stockholm, Sweden, p. 26 (Available on: http://www.researchgate.net/publication/242131124_MEDICINES_AND_THE_ENVIRONMENT_What_Do_We_Know_Today. (accessed 20 November 2015))

EIFAC, 1987. Working Party on Water Quality Criteria for European Freshwater Fish, Water Quality Criteria for European Freshwater Fish. Revised report on combined effects on freshwater fish and other aquatic life of mixtures of toxicants in water. European Inland Fisheries Advisory Commission (EIFAC), Food and Agriculture Organization of the United Nations, Rome, Italy, p. 75 EIFAC/T37Rev.1. (Available on: http://www.fao.org/docrep/017/s8880e/s8880e.pdf. (accessed 20 November 2015)).

Emke, E., Evans, S., Kasprzyk-Hordern, B., de Voogt, P., 2014. Enantiomer profiling of high loads of amphetamine and MDMA in communal sewage: a Dutch perspective. Sci. Total Environ. 487, 666–672. http://dx.doi.org/10.1016/j.scitotenv.2013.11.043.

Epel, D., 1998. Use of multidrug transporters as first lines of defense against toxins in aquatic organisms. Comp. Biochem. Physiol. A 120, 23–28. http://dx.doi.org/10.1016/S1095-6433(98)10005-3.

Epel, D., Smital, T., 2001. Multidrug — multixenobiotic transporters and their significance with respect to environmental levels of pharmaceuticals and personal care products. In: Daughton, C.G., Jones-Lepp, T.L. (Eds.), Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues. American Chemical Society, Washington, DC, pp. 244–263 (chapter 14).

Escher, B.I., Fenner, K., 2011. Recent advances in environmental risk assessment of transformation products. Environ. Sci. Technol. 45, 3835–3847. http://dx.doi.org/10.1021/es1030799.

Escher, B.I., Hermens, J.L.M., 2002. Modes of action in ecotoxicology: their role in body burdens, species sensitivity, QSARs, and mixture effects. Environ. Sci. Technol. 36, 4201–4217. http://dx.doi.org/10.1021/es015848h.

Eschke, H.D., Traud, J., Dibowski, H.J., 1994. Untersuchungen zum Vorkommen polycyclischer Moschus-Duftstoffe in verschiedenen Umweltkompartimenten – Nachweis und Analytik mit GC/MS in Oberflässern und Fischen (1. Mitteilung) (Studies on the occurrence of polycyclic musk flavors in different environmental compartments - 1st communication: detection and analysis by GC/MS in surface and sewage waters and fish). Umweltwiss. Schadst. Forsch. 6, 183–189. http://dx.doi.org/10.1007/BF03166352.

Espín, S., García-Fernández, A.J., Herzke, D., Shore, R.F., Hattum, B., Martínez-López, E., et al., 2016. Tracking pan-continental trends in environmental contamination using sentinel raptors—what types of samples should we use? Ecotoxicology 1–25 http://dx.doi.org/10.1007/s10646-016-1636-8.

Evgenidou, E.N., Konstantinou, I.K., Lambropoulou, D.A., 2015. Occurrence and removal of transformation products of PPCPs and illicit drugs in wastewaters: a review. Sci. Total Environ. 505, 905–926. http://dx.doi.org/10.1016/j.scitotenv.2014.10.021.

Farré, Ml, Pérez, S., Kantiani, L., Barceló, D., 2008. Fate and toxicity of emerging pollutants, their metabolites and transformation products in the aquatic environment. TrAC Trends Anal. Chem. 27, 991–1007. http://dx.doi.org/10.1016/j.trac.2008.09.010.

Fent, K., Weston, A.A., Caminada, D., 2006. Ecotoxicology of human pharmaceuticals. Aquat. Toxicol. 76, 122–159. http://dx.doi.org/10.1016/j.aquatox.2005.09.009.

Ferguson, R.W., 2014. Keeping Families Safe Around Medicine. Safe Kids Worldwide, Washington, D.C., p. 24 (Available on: http://www.safekids.org/sites/default/files/research_reports/medicine_safety_study_2014.pdf. (accessed 20 November 2015)).

Ferrer, I., Thurman, E.M., 2003a. Analysis of Emerging Contaminants. In: Ferrer, I., Thurman, E.M. (Eds.), ACS Symposium #850: Liquid Chromatography/Mass Spectrometry, MS/MS and Time of Flight MS: Analysis of Emerging Contaminants. American Chemical Society, Washington, DC, pp. 2–13 (chapter 1).

Ferrer, I., Thurman, E.M., 2003b. Liquid chromatography/time-of-flight/mass spectrometry (LC/TOF/MS) for the analysis of emerging contaminants. TrAC Trends Anal. Chem. 22, 750–756. http://dx.doi.org/10.1016/S0165-9936(03)01013-6.

Fielding, M., Gibson, T.M., James, H.A., Mcloughlin, K., Steel, C.P., 1981. Organic micropollutants in drinking water. Technical Report TR159. Water Research Centre, Marlow, UK (Available on: http://www.osti.gov/energycitations/product.biblio.jsp?osti_id=6457017. (accessed 20 November 2015)).

Fitzgerald, K.T., Bronstein, A.C., Flood, A.A., 2006. "Over-the-counter" drug toxicities in companion animals. Clin. Tech. Small Anim. Pract. 21, 215–226. http://dx.doi.org/10.1053/j.ctsap.2006.10.006.

Fong, P.P. (Ed.), 1998. Zebra mussel spawning is induced in low concentrations of putative serotonin reuptake inhibitorsBiol. Bull. 194, 143–149.

Fong, P.P., 2001. Antidepressants in aquatic organisms: a wide range. In: Daughton, C.G., Jones-Lepp, T.L. (Eds.), Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues. American Chemical Society, Washington, DC (364-281, chapter 15).

Fono, L.J., Sedlak, D.L., 2005. Use of the chiral pharmaceutical propranolol to identify sewage discharges into surface waters. Environ. Sci. Technol. 39, 9244–9252. http://dx.doi.org/10.1021/es047965t.

Fono, L.J., Sedlak, D.L., 2007. A simple method for the measurement of organic iodine in wastewater and surface water. Water Res. 41, 1580–1586. http://dx.doi.org/10.1016/j.watres.2006.12.032.

Franke, S., Hildebrandt, S., Schwarzbauer, J., Link, M., Francke, W., 1995. Organic compounds as contaminants of the Elbe River and its tributaries. Part II: GC/MS screening for contaminants of the Elbe water. Fresenius J. Anal. Chem. 353, 39–49. http://dx.doi.org/10.1007/BF00322888.

Frost, N., Griffiths, P., 2008. Introduction to sewage epidemiology and the wastewater system. Assessing Illicit Drugs in Wastewater: Potential and Limitations of a New Monitoring Approach. Insights Series No. 9. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Lisbon, Portugal, pp. 9–20 (chapter 1).

Fu, H.-Z., Wang, M.-H., Ho, Y.-S., 2013. Mapping of drinking water research: a bibliometric analysis of research output during 1992–2011. Sci. Total Environ. 443, 757–765. http://dx.doi.org/10.1016/j.scitotenv.2012.11.061.

Garrison, A.W., 1977. Analysis of organic compounds in water to support health effects studies. Ann. N. Y. Acad. Sci. 298, 2–19. http://dx.doi.org/10.1111/j.1749-6632.1977.tb19251.x.

Garrison, A.W., Pope, J.D., Allen, F.R., 1976. GC/MS analysis of organic compounds in domestic wastewaters. In: Keith, L.H. (Ed.), Identification and Analysis of Organic Pollutants in Water. Ann Arbor Science Publishers, Ann Arbor, MI, pp. 517–556 (chapter 30).

Gesell, T.F., Prichard, H.M., Davis, E.M., Pirtle, O.L., DiPietro, W., 1975. Nuclear Medicine Environmental Discharge Measurement. Final Report. International Atomic Energy Agency (IAEA), International Nuclear Information System (INIS), Vienna, Austria, p. 93 8325568. (Available on: https://inis.iaea.org/search/search.aspx?orig_q=RN:8325568. (accessed 20 November 2015)).

Gilbertson, T.J., Hornish, R.E., Jaglan, P.S., Koshy, K.T., Nappier, J.L., Stahl, G.L., et al., 1990. Environmental fate of ceftiofur sodium, a cephalosporin antibiotic. Role of animal excreta in its decomposition. J. Agric. Food Chem. 38, 890–894. http://dx.doi.org/10.1021/jf00093a064.

Glassmeyer, S.T., Furlong, E.T., Kolpin, D.W., Cahill, J.D., Zaugg, S.D., Werner, S.L., et al., 2005. Transport of chemical and microbial compounds from known wastewater discharges: potential for use as indicators of human fecal contamination. Environ. Sci. Technol. 39, 5157–5169. http://dx.doi.org/10.1021/es048120k.

Glassmeyer, S.T., Hinchey, E.K., Boehme, S.E., Daughton, C.G., Ruhoy, I.S., Conerly, O., et al., 2009. Disposal practices for unwanted residential medications in the United States. Environ. Int. 35, 566–572. http://dx.doi.org/10.1016/j.envint.2008.10.007.

Gledhill, W.E., 1975. Biodegradation of 3,4,4′-trichlorocarbanilide, TCC®, in sewage and activated sludge. Water Res. 9, 649–654. http://dx.doi.org/10.1016/0043-1354(75)90171-2.

Goldhammer, A., 2008. Pharmaceuticals in the nation's drinking water: assessing potential risks and actions to address the issue. Statement at the Senate Environment and Public Works Committee, Subcommittee on Transportation Safety, Infrastructure Security, and Water Quality, p. 7 (Available on: http://c.ymcdn.com/sites/www.news/resource/resmgr/imported/goldhammer_testimony-(4-15-2008).pdf. (accessed 20 November 2015)).

Grayling, T., 1999. Guidelines for safe disposal of unwanted pharmaceuticals in and after emergencies. World Health Organization, WHO Office for Humanitarian Assistance in Bosnia and Herzegovina, p. 31 WHO/HTP/EDM/99.2. (Available on: http://www.who.int/water_sanitation_health/medicalwaste/unwantpharm.pdf. (accessed 20 November 2015)).

Green, R.E., Newton, I., Shultz, S., 2004. Diclofenac poisoning as a cause of vulture population declines across the Indian subcontinent. J. Appl. Ecol. 41, 793–800. http://dx.doi.org/10.1111/j.0021-8901.2004.00954.x.

Greene, L.A., 2000. Controversy swirls around toilet-to-tap project. Environ. Health Perspect. 108, A447.

Gregers-Hansen, B., 1964a. Decomposition of diethylstilboestrol in soil. Plant Soil 20, 50–58. http://dx.doi.org/10.1007/BF01378097.

Gregers-Hansen, B., 1964b. The uptake by plants of diethylstilboestrol and of its glucuronide. Plant Soil 20, 215–220. http://dx.doi.org/10.1007/BF01376450.

Grob, K., 1973. Organic substances in potable water and in its precursor: part I. Methods for their determination by gas–liquid chromatography. J. Chromatogr. A 84, 255–273. http://dx.doi.org/10.1016/S0021-9673(01)91705-4.

Gruber, V., Halley, B.A., Hwang, S.H.U.C., Ku, C.C., 1990. Mobility of avermectin B_{1a} in soil. J. Agric. Food Chem. 38, 886–890. http://dx.doi.org/10.1021/jf00093a063.

Gunn, J.C., Lishman, J., 1967. Letters to editor regarding "problem of unused drugs". Br. Med. J. 3, 863. http://dx.doi.org/10.1136/bmj.3.5569.863-a.
Hagan, J.R., 1996. An examination of acute environmental toxicity of pharmaceutical compounds using quantitative structure–activity relationships (*Daphnia magna*) Doctoral dissertation Drexel University (pp Available on: https://books.google.com/books/about/An_Examination_of_Acute_Environmental_To.html?id=CveGuAAACAAJ. (accessed 20 November 2015)).
Halden, R.U., 2015. Epistemology of contaminants of emerging concern and literature meta-analysis. J. Hazard. Mater. 282, 2–9. http://dx.doi.org/10.1016/j.jhazmat.2014.08.074.
Haley, C.J., Matheson III, J.C., Eirkson III, C.E., 1993. Requirements of the FDA for the environmental assessment of animal health products. J. Hazard. Mater. 35, 217–228. http://dx.doi.org/10.1016/0304-3894(93)80007-3.
Halford, B., 2008a. Don't flush: what to do with your unused pharmaceuticals. Chem. Eng. News 86, 16.
Halford, B., 2008b. Side effects: pharmaceuticals have been finding their way into our environment for a long time, but just what are they doing there? Chem. Eng. News 86, 13–17.
Hall, C.T., 2000. Makeup, Medication May Pollute Waterways. Hearst Communications Inc., San Francisco, CA (Available on: http://www.sfgate.com/green/article/Makeup-Medication-May-Pollute-Waterways-2766984.php. (accessed 20 November 2015)).
Halley, B.A., VandenHeuvell, W.J.A., Wislocki, P.G., Herd, R., Wardhaugh, K., 1993. Environmental effects of the usage of avermectin in livestock. Vet. Parasitol. 48, 109–125.
Halling-Sorensen, B., Nors Nielsen, S., Lanzky, P.F., Ingerslev, F., Holten Lutzhoft, H.C., Jorgensen, S.E., 1998. Occurrence, fate and effects of pharmaceutical substances in the environment — a review. Chemosphere 36, 357–393. http://dx.doi.org/10.1016/S0045-6535(97)00354-8.
Harries, J.E., Sheahan, D.A., Jobling, S., Matthiessen, P., Neall, P., Routledge, E.J., et al., 1996. A survey of estrogenic activity in United Kingdom inland waters. Environ. Toxicol. Chem. 15, 1993–2002. http://dx.doi.org/10.1002/etc.5620151118.
Harris, D.W., Karandikar, D.S., Spencer, M.G., Leach, R.H., Bower, A.C., Mander, G.A., 1979. Returned-medicines campaign in Birmingham. Lancet 313, 599–601. http://dx.doi.org/10.1016/S0140-6736(79)91020-1.
Hart, R.J., Marshall, F.S.V., 1976. Wastage of pharmaceuticals. Lancet 308, 1239–1240. http://dx.doi.org/10.1016/S0140-6736(76)91159-4.
Hartmann, A., 1998. Drug Load of Hospital Wastewater and Its Ecotoxicological Relevance Doctoral dissertation Eidgenöessische Technische Hochschule Zuerich, Zürich, Switzerland, p. 123 (Available on: 10.3929/ethz-a-002003722; http://e-collection.library.ethz.ch/eserv/eth:22747/eth-22747-01.pdf. (accessed 20 November 2015)).
Harzing, A.-W., 2014. A longitudinal study of Google Scholar coverage between 2012 and 2013. Scientometrics 98, 565–575. http://dx.doi.org/10.1007/s11192-013-0975-y.
Heberer, T., 2002a. Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. Toxicol. Lett. 131, 5–17. http://dx.doi.org/10.1016/S0378-4274(02)00041-3.
Heberer, T., 2002b. Tracking persistent pharmaceutical residues from municipal sewage to drinking water. J. Hydrol. 266, 175–189. http://dx.doi.org/10.1016/S0022-1694(02)00165-8.
Heberer, T., Feldmann, D., Reddersen, K., Altmann, H.-J., Zimmermann, T., 2001a. Removal of pharmaceutical residues and other persistent organics from municipal sewage and surface waters applying membrane filtration. J. Contemp. Water Res. Educ. 120, 18–29.
Heberer, T., Verstraeten, I.M., Meyer, M.T., Mechlinski, A., Reddersen, K., 2001b. Occurrence and fate of pharmaceuticals during bank filtration – preliminary results from investigations in Germany and the United States. J. Contemp. Water Res. Educ. 120, 4–17.
Heim, S., Schwarzbauer, J., Littke, R., 2004. Monitoring of waste deposit derived groundwater contamination with organic tracers. Environ. Chem. Lett. 2, 21–25. http://dx.doi.org/10.1007/s10311-003-0054-3.
Heisterkamp, I., Gandrass, J., Ruck, W., 2004. Bioassay-directed chemical analysis utilizing LC–MS: a tool for identifying estrogenic compounds in water samples? Anal. Bioanal. Chem. 378, 709–715. http://dx.doi.org/10.1007/s00216-003-2380-5.
Heller, S.R., McGuire, J.M., Budde, W.L., 1975. Trace organics by GC/MS. Environ. Sci. Technol. 9, 210–213. http://dx.doi.org/10.1021/es60101a012.
Hendriks, A.J., Maas-Diepeveen, J.L., Noordsij, A., Van der Gaag, M.A., 1994. Monitoring response of XAD-concentrated water in the Rhine delta: a major part of the toxic compounds remains unidentified. Water Res. 28, 581–598. http://dx.doi.org/10.1016/0043-1354(94)90009-4.
Herd, R., Wardhaugh, K., 1993. Environmental impact of avermectin usage in livestock. Vet. Parasitol. Spec. Issue 48, 1–344.
Hermens, J., Leeuwangh, P., 1982. Joint toxicity of mixtures of 8 and 24 chemicals to the guppy (*Poecilia reticulata*). Ecotoxicol. Environ. Saf. 6, 302–310. http://dx.doi.org/10.1016/0147-6513(82)90020-3.
Herrera-Lopez, S., Hernando, M.D., García-Calvo, E., Fernández-Alba, A.R., Ulaszewska, M.M., 2014. Simultaneous screening of targeted and non-targeted contaminants using an LC-QTOF-MS system and automated MS/MS library searching. J. Mass Spectrom. 49, 878–893. http://dx.doi.org/10.1002/jms.3428.
Hignite, C., Azarnoff, D.L., 1977. Drugs and drug metabolites as environmental contaminants: chlorophenoxyisobutyrate and salicylic acid in sewage water effluent. Life Sci. 20, 337–341.
Hirsch, R., Ternes, T.A., Haberer, K., Mehlich, A., Ballwanz, F., Kratz, K.-L., 1998. Determination of antibiotics in different water compartments via liquid chromatography-electrospray tandem mass spectrometry. J. Chromatogr. A 815, 213–223. http://dx.doi.org/10.1016/S0021-9673(98)00335-5.
Hirsch, R., Ternes, T., Haberer, K., Kratz, K.-L., 1999. Occurrence of antibiotics in the aquatic environment. Sci. Total Environ. 225, 109–118. http://dx.doi.org/10.1016/S0048-9697(98)00337-4.
Hites, R.A., Lopez-Avila, V., 1979. Identification of organic compounds in an industrial waste water. Anal. Chem. 51, 1452A–1456A. http://dx.doi.org/10.1021/ac50050a002.
Hogenboom, A.C., van Leerdam, J.A., de Voogt, P., 2009. Accurate mass screening and identification of emerging contaminants in environmental samples by liquid chromatography-hybrid linear ion trap orbitrap mass spectrometry. J. Chromatogr. A 1216, 510–519. http://dx.doi.org/10.1016/j.chroma.2008.08.053.
Holbrook, R.D., Novak, J.T., Grizzard, T.J., Love, N.G., 2002. Estrogen receptor agonist fate during wastewater and biosolids treatment processes: a mass balance analysis. Environ. Sci. Technol. 36, 4533–4539. http://dx.doi.org/10.1021/es020577b.
Holten Lützhöft, H.-C., 2000. Environmental Risk Assessment of Antimicrobials Doctoral dissertation Royal Danish School of Pharmacy, Copenhagen, Denmark, p. 133 (accessed 20 November 2015).
Hoppe-Jones, C., Oldham, G., Drewes, J.E., 2010. Attenuation of total organic carbon and unregulated trace organic chemicals in U.S. riverbank filtration systems. Water Res. 44, 4643–4659. http://dx.doi.org/10.1016/j.watres.2010.06.022.
Hotchkiss, A.K., Rider, C.V., Blystone, C.R., Wilson, V.S., Hartig, P.C., Ankley, G.T., et al., 2008. Fifteen years after "wingspread"–environmental endocrine disrupters and human and wildlife health: where we are today and where we need to go. Toxicol. Sci. 105, 235–259. http://dx.doi.org/10.1093/toxsci/kfn030.
Huber, W.G., 1971. In: Pitts, J.N., Metcalf, R.L. (Eds.), Antibacterial drugs as environmental contaminantsAdvances in Environmental Science and Technology 2. Wiley & Sons, New York, NY, pp. 289–320.
Hübner, U., Miehe, U., Jekel, M., 2012. Optimized removal of dissolved organic carbon and trace organic contaminants during combined ozonation and artificial groundwater recharge. Water Res. 46, 6059–6068. http://dx.doi.org/10.1016/j.watres.2012.09.001.
Hübner, U., von Gunten, U., Jekel, M., 2015. Evaluation of the persistence of transformation products from ozonation of trace organic compounds — a critical review. Water Res. 68, 150–170. http://dx.doi.org/10.1016/j.watres.2014.09.051.
Hug, C., Ulrich, N., Schulze, T., Brack, W., Krauss, M., 2014. Identification of novel micropollutants in wastewater by a combination of suspect and nontarget screening. Environ. Pollut. 184, 25–32. http://dx.doi.org/10.1016/j.envpol.2013.07.048.
Ibáñez, M., Sancho, J.V., Hernández, F., McMillan, D., Rao, R., 2008. Rapid non-target screening of organic pollutants in water by ultraperformance liquid chromatography coupled to time-of-light mass spectrometry. TrAC Trends Anal. Chem. 27, 481–489. http://dx.doi.org/10.1016/j.trac.2008.03.007.
International Society of Doctors for the Environment (ISDE), 2010E. Strategic Approach to International Chemicals Management: Nomination of emerging policy issues for consideration by the International Conference on Chemicals Management at its third session. Strategic Approach to International Chemicals Management (SAICM), Geneva, Switzerland, p. 8 (Available on: http://www.cec.org/Storage/101/10036_f-56-10-6231012_C3sOdJuh_SAICM_ICCM_Emerging_issuesd_proposal_Int._Doctors.pdf. (accessed 20 November 2015)).
Isomaa, B., Lilius, H., 1995. The urgent need for in vitro tests in ecotoxicology. Toxicol. in Vitro 9, 821–825. http://dx.doi.org/10.1016/0887-2333(95)00085-2.
Jelić, A., Petrović, M., Barceló, D., 2012. Pharmaceuticals in drinking water. In: Barceló, D. (Ed.), Emerging Organic Contaminants and Human Health. 20.Springer-Verlag, Berlin/Heidelberg, Germany, pp. 47–70
Jeong, T.-Y., Kim, H.Y., Kim, S.D., 2015. Multi-generational effects of propranolol on *Daphnia magna* at different environmental concentrations. Environ. Pollut. 206, 188–194. http://dx.doi.org/10.1016/j.envpol.2015.07.003.
Jiménez-González, C., 2000. Life Cycle Assessment in Pharmaceutical Applications Doctoral dissertation North Carolina State University, Raleigh, NC, p. 278 (Available on: http://catalog.lib.ncsu.edu/record/NCSU1521043. (accessed 20 November 2015)).
Jjemba, P.K., 2002. The potential impact of veterinary and human therapeutic agents in manure and biosolids on plants grown on arable land: a review. Agric. Ecosyst. Environ. 93, 267–278. http://dx.doi.org/10.1016/S0167-8809(01)00350-4.
Johnson, A.C., Sumpter, J.P., 2001. Removal of endocrine-disrupting chemicals in activated sludge treatment works. Environ. Sci. Technol. 35, 4697–4703. http://dx.doi.org/10.1021/es010171j.
Jørgensen, S.E., Halling-Sørensen, B., 2000. Drugs in the environment. Chemosphere 40, 691–699. http://dx.doi.org/10.1016/S0045-6535(99)00438-5.
Joss, A., Carballa, M., Kreuzinger, N., Aiegrist, H., Zabczynski, S., 2006. Wastewater treatment. In: Ternes, T.A., Joss, A. (Eds.), Human Pharmaceuticals, Hormones and Fragrances: The Challenge of Micropollutants in Urban Water Management. IWA Publishing, London, UK, pp. 243–292 (chapter 6).
Jungclaus, G., Avila, V., Hites, R., 1978. Organic compounds in an industrial wastewater: a case study of their environmental impact. Environ. Sci. Technol. 12, 88–96. http://dx.doi.org/10.1021/es60137a015.
Kampa, E., 2008. Proceedings of the expert workshop on the design of instruments to limit pollution from PPs. Deliverable number D3.2, KNAPPE: Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters, p. 44 (Available on: http://www.ecologic.de/download/projekte/1850-1899/1878/knappe_d32_proceedings_york_instruments.pdf. (accessed 20 November 2015)).
Karst, K.R., 2015. U.S. Supreme Court is Asked to Review First-in-the-Nation Safe Drug Disposal Ordinance. FDA Law Blog. http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2015/01/us-supreme-court-is-asked-to-review-first-in-the-nation-safe-drug-disposal-ordinance.html.
Kasprzyk-Hordern, B., Baker, D.R., 2012. Estimation of community-wide drugs use via stereoselective profiling of sewage. Sci. Total Environ. 423, 142–150. http://dx.doi.org/10.1016/j.scitotenv.2012.02.019.
Kasprzyk-Hordern, B., Kondakal, V.V.R., Baker, D.R., 2010. Enantiomeric analysis of drugs of abuse in wastewater by chiral liquid chromatography coupled with tandem mass spectrometry. J. Chromatogr. A 1217, 4575–4586. http://dx.doi.org/10.1016/j.chroma.2010.04.073.
Katz, B., Griffin, D., 2007. Using chemical and microbiological indicators to track the impacts from the land application of treated municipal wastewater and other sources

on groundwater quality in a karstic springs basin. Environ. Geol. 55, 801–821. http://dx.doi.org/10.1007/s00254-007-1033-y.
Keck, G., 2006. Teaching environmental toxicology for veterinary students and veterinarians: some new trends. J. Vet. Pharmacol. Ther. 29, 15–16. http://dx.doi.org/10.1111/j.1365-2885.2006.00771_5.x.
Keith, L.H. (Ed.), 1976a. Identification and Analysis of Organic Pollutants in Water. Ann Arbor Science Publishers, Inc., Ann Arbor, MI (718 pp.; https://books.google.com/books?id=YBJSAAAAMAAJ).
Keith, L.H., 1976b. Recent advances in the identification and analysis of organic pollutants in water. Life Sci. 19, 1631–1635. http://dx.doi.org/10.1016/0024-3205(76)90067-9.
Kemper, N., 2008. Veterinary antibiotics in the aquatic and terrestrial environment. Ecol. Indic. 8, 1–13. http://dx.doi.org/10.1016/j.ecolind.2007.06.002.
Khan, S.J., 2002. Occurrence, behaviour and fate of pharmaceutical residues in sewage treatment Doctoral dissertation University of New South Wales, New South Wales, Australia, p. 383 (accessed 20 November 2015).
Khan, S.J., Ongerth, J.E., 2002. Estimation of pharmaceutical residues in primary and secondary sewage sludge based on quantities of use and fugacity modelling. Water Sci. Technol. 46, 105–113.
Khetan, S.K., Collins, T.J., 2007. Human pharmaceuticals in the aquatic environment: a challenge to green chemistry. Chem. Rev. 107, 2319–2364. http://dx.doi.org/10.1021/cr020441w.
Kidd, K.A., Blanchfield, P.J., Mills, K.H., Palace, V.P., Evans, R.E., Lazorchak, J.M., et al., 2007. Collapse of a fish population after exposure to a synthetic estrogen. Proc. Natl. Acad. Sci. U. S. A. 104, 8897–8901. http://dx.doi.org/10.1073/pnas.0609568104.
Kinch, M.S., Haynesworth, A., Kinch, S.L., Hoyer, D., 2014. An overview of FDA-approved new molecular entities: 1827–2013. Drug Discov. Today 19, 1033–1039. http://dx.doi.org/10.1016/j.drudis.2014.03.018.
Kirchner, M., Holsen, H., Norpoth, K., 1973. Fluoreszenzspektroskopische Bestimmung ovulationshemmender Steroide aus Wasser und Abwassern auf der DC-Platte (Fluorescence spectroscopic determination of anti-ovulatory steroids in water and waste water on thin layer chromatography plate). Zentralblatt fur Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene Erste Abteilung Originale Reihe B: Hygiene, praventive Medizin 157 pp. 44–52.
Klavarioti, M., Mantzavinos, D., Kassinos, D., 2009. Removal of residual pharmaceuticals from aqueous systems by advanced oxidation processes. Environ. Int. 35, 402–417. http://dx.doi.org/10.1016/j.envint.2008.07.009.
Kleopfer, R.D., Fairless, B.J., 1972. Characterization of organic components in a municipal water supply. Environ. Sci. Technol. 6, 1036–1037. http://dx.doi.org/10.1021/es60071a006.
Kleywegt, S., Smyth, S.-A., Parrott, J., Schaefer, K., Lagacé, E., Payne, M., et al., 2007. Pharmaceuticals and personal care products in the Canadian environment: research and policy directions. NWRI Scientific Assessment Report Series No 8, Niagara-on-the-Lake, Ontario, Canada, p. 53 (Available on: http://www.ec.gc.ca/INRE-NWRI/default.asp?lang=En&n=C00A589F-1; https://www.ec.gc.ca/inre-nwri/default.asp?lang=En&n=C00A589F-1&offset=1&toc=show. (accessed 20 November 2015)).
Klupinski, T.P., Strozier, E.D., Friedenberg, D.A., Brinkman, M.C., Gordon, S., Clark, P., 2015. Identification of new and distinctive exposures from little cigars. Chem. Res. Toxicol. http://dx.doi.org/10.1021/acs.chemrestox.5b00371.
Knight, W.M., 1980. Estrogens administered to food producing animals: environmental considerations. In: McLachlan, J.A. (Ed.), Estrogens in the Environment; Proceedings of the Symposium on Estrogens in the Environment, Raleigh, North Carolina, U.S.A., September 10–12, 1979. 5. Elsevier/North-Holland, New York, Amsterdam, Oxford, pp. 391–402.
Kolpin, D.W., Furlong, E.T., Meyer, M.T., Thurman, E.M., Zaugg, S.D., Barber, L.B., et al., 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999–2000: a national reconnaissance. Environ. Sci. Technol. 36, 1202–1211. http://dx.doi.org/10.1021/es011055j.
Konemann, H., 1981. Fish toxicity tests with mixtures of more than two chemicals: a proposal for a quantitative approach and experimental results. Toxicology 19, 229–238.
Koren, G., 1993. Medications which can kill a toddler with one tablet or teaspoonful. Clin. Toxicol. 31, 407–413. http://dx.doi.org/10.3109/15563659309000409.
Kortenkamp, A., Altenburger, R., 1998. Synergisms with mixtures of xenoestrogens: a re-evaluation using the method of isoboles. Sci. Total Environ. 221, 59–73. http://dx.doi.org/10.1016/S0048-9697(98)00261-7.
Kortenkamp, A., Altenburger, R., 1999. Approaches to assessing combination effects of oestrogenic environmental pollutants. Sci. Total Environ. 233, 131–140. http://dx.doi.org/10.1016/S0048-9697(99)00228-4.
Kosjek, T., Heath, E., 2008. Applications of mass spectrometry to identifying pharmaceutical-transformation products in water treatment. TrAC Trends Anal. Chem. 27, 807–820. http://dx.doi.org/10.1016/j.trac.2008.08.014.
Kosjek, T., Heath, E., Petrovic, M., Barceló, D., 2007. Mass spectrometry for identifying pharmaceutical biotransformation products in the environment. TrAC Trends Anal. Chem. 26, 1076–1085. http://dx.doi.org/10.1016/j.trac.2007.10.005.
Kratz, W., Abbas, B., Linke, I., 2000. Arzneimittelwirkstoffe in der Umwelt (Medication Active Ingredients in the Environment). Umweltwiss. Schadst. Forsch. 12, 343–349. http://dx.doi.org/10.1065/uwsf2000.11.034.
Kronimus, A., Schwarzbauer, J., Dsikowitzky, L., Heim, S., Littke, R., 2004. Anthropogenic organic contaminants in sediments of the Lippe river, Germany. Water Res. 38, 3473–3484. http://dx.doi.org/10.1016/j.watres.2004.04.054.
Kümmerer, K., 2001a. Drugs in the environment: emission of drugs, diagnostic aids and disinfectants into wastewater by hospitals in relation to other sources — a review. Chemosphere 45, 957–969. http://dx.doi.org/10.1016/S0045-6535(01)00144-8.
Kümmerer, K. (Ed.), 2001b. Pharmaceuticals in the Environment - Sources, Fate, Effects and Risks, first ed. Springer-Verlag, Berlin, Germany http://dx.doi.org/10.1007/978-3-662-04634-0 265 pp.
Kümmerer, K. (Ed.), 2004a. Pharmaceuticals in the Environment - Sources, Fate, Effects, and Risks, second ed. Springer, Berlin, Germany http://dx.doi.org/10.1007/978-3-662-09259-0 (527 pp.).
Kümmerer, K., 2004b. Resistance in the environment. J. Antimicrob. Chemother. 54, 311–320. http://dx.doi.org/10.1093/jac/dkh325.
Kümmerer, K., 2007. Sustainable from the very beginning: rational design of molecules by life cycle engineering as an important approach for green pharmacy and green chemistry. Green Chem. 9, 899–907. http://dx.doi.org/10.1039/b618298b.
Kümmerer, K. (Ed.), 2008. Pharmaceuticals in the Environment - Sources, Fate, Effects, and Risks, third ed. Springer, Berlin, Germany (522 pp; http://www.springer.com/us/book/9783540746638).
Kümmerer, K., 2009a. Antibiotics in the aquatic environment — a review — part I. Chemosphere 75, 417–434. http://dx.doi.org/10.1016/j.chemosphere.2008.11.086.
Kümmerer, K., 2009b. Antibiotics in the aquatic environment — a review — part II. Chemosphere 75, 435–441. http://dx.doi.org/10.1016/j.chemosphere.2008.12.006.
Kurelec, B., 1992. The multixenobiotic resistance mechanism in aquatic organisms. Crit. Rev. Toxicol. 22, 23–43. http://dx.doi.org/10.3109/10408449209145320.
Kurelec, B., 1995. Inhibition of multixenobiotic resistance mechanism in aquatic organisms: ecotoxic consequences. Sci. Total Environ. 171, 197–204. http://dx.doi.org/10.1016/0048-9697(95)04689-4.
Kurelec, B., 1997. A new type of hazardous chemical: the chemosensitizers of multixenobiotic resistance. Environ. Health Perspect. 105, 855–860.
Landesumweltamt Brandenburg (LUA), 1999. Humanarzneimittel in der Umwelt: Erhebung von Humanarzneimittelmengen im Land Brandenburg 1999 (Human pharmaceuticals in the environment: collection of human medicinal amounts in the state of Brandenburg in 1999). Landesumweltamt Brandenburg, Brandenburg, Germany, p. 32 (Available on: http://www.lugv.brandenburg.de/cms/media.php/lbm1.a.3310.de/lua_bd25.pdf. (accessed 20 November 2015)).
Langelier, K.M., 1993. Barbiturate poisoning in twenty-nine bald eagles. In: Redig, P.T., Cooper, J.E., Remple, J.D., Hunter, D.B. (Eds.), Raptor Biomedicine. University of Minnesota Press, Minneapolis, MN, pp. 231–232 (chapter 39).
Layton, A.C., Gregory, B.W., Seward, J.R., Schultz, T.W., Sayler, G.S., 2000. Mineralization of steroidal hormones by biosolids in wastewater treatment systems in Tennessee USA. Environ. Sci. Technol. 34, 3925–3931. http://dx.doi.org/10.1021/es9914487.
Leach, R.H., White, P.L., 1978. Use and wastage of prescribed medicines in the home. J. R. Coll. Gen. Pract. 28, 32–36.
Lemus, J.A., Blanco, G., 2009. ≪RETRACTED≫ Cellular and humoral immunodepression in vultures feeding upon medicated livestock carrion. Proc. R. Soc. B Biol. Sci. 276, 2307–2313. http://dx.doi.org/10.1098/rspb.2009.0071.
Lemus, J.A., Blanco, G., Grande, J., Arroyo, B., Garcia-Montijano, M., Martinez, F., 2008. ≪RETRACTED≫ Antibiotics threaten wildlife: circulating quinolone residues and disease in Avian scavengers. PLoS Med. 16, e1444. http://dx.doi.org/10.1371/journal.pone.0001444.
Lewis, E.T., Cucciare, M.A., Trafton, J.A., 2014. What do patients do with unused opioid medications? Clin. J. Pain 30, 654–662. http://dx.doi.org/10.1097/01.ajp.0000435447.96642.f4.
Li, G., Nie, X., Gao, Y., An, T., 2016. Can environmental pharmaceuticals be photocatalytically degraded and completely mineralized in water using g-C_3N_4/TiO_2 under visible light irradiation?—Implications of persistent toxic intermediates. Appl. Catal. B Environ. 180, 726–732. http://dx.doi.org/10.1016/j.apcatb.2015.07.014.
Liebelt, E.L., Shannon, M.W., 1993. Small doses, big problems: a selected review of highly toxic common medications. Pediatr. Emerg. Care 9, 292–297.
Liu, X., Chen, Z., Wang, L., Wu, Y., Garoma, T., 2012. ≪RETRACTED≫ Degradation of polycyclic musk HHCB in water by O_3, UV, and UV/O_3. J. Photochem. Photobiol. A Chem. 230, 1–9. http://dx.doi.org/10.1016/j.jphotochem.2011.12.017.
Loffler, D., Rombke, J., Meller, M., Ternes, T.A., 2005. Environmental fate of pharmaceuticals in water/sediment systems. Environ. Sci. Technol. 39, 5209–5218. http://dx.doi.org/10.1021/es0484146.
Lopez-Avila, V., Hites, R.A., 1980. Organic compounds in an industrial wastewater. Their transport into sediments. Environ. Sci. Technol. 14, 1382–1390. http://dx.doi.org/10.1021/es60171a007.
Lovegrove, M.C., Mathew, J., Hampp, C., Governale, L., Wysowski, D.K., Budnitz, D.S., 2014. Emergency hospitalizations for unsupervised prescription medication ingestions by young children. Pediatrics 134, 1009–1016. http://dx.doi.org/10.1542/peds.2014-0840.
Luckenbach, T., Epel, D., 2008. ABCB- and ABCC-type transporters confer multixenobiotic resistance and form an environment-tissue barrier in bivalve gills. Am. J. Physiol. Regul. Integr. Comp. Physiol. 294. http://dx.doi.org/10.1152/ajpregu.00563.2007 (R1919-R29).
Mackay, D., Hughes, D.M., Romano, M.L., Bonnell, M., 2014. The role of persistence in chemical evaluations. Integr. Environ. Assess. Manag. 10, 588–594. http://dx.doi.org/10.1002/ieam.1545.
Manning, M., 2000. Traces of Drugs Found in LV Wash. Las Vegas Sun, Las Vegas, NV (Available on: http://www.lasvegassun.com/news/2000/oct/16/traces-of-drugs-found-in-lv-wash/. (accessed 20 November 2015)).
Mansur, M., Martellaro, J., 2000. Rivers Face New Threat: Medicines (accessed 20 November 2015).
Martínez Bueno, M.J., Aguera, A., Gomez, M.J., Hernando, M.D., Garcia-Reyes, J.F., Fernandez-Alba, A.R., 2007. Application of liquid chromatography/quadrupole-linear ion trap mass spectrometry and time-of-flight mass spectrometry to the determination of pharmaceuticals and related contaminants in wastewater. Anal. Chem. 79, 9372–9384. http://dx.doi.org/10.1021/ac0715672.
Masters, R.W., 2001. Pharmaceuticals and endocrine disruptors in rivers and on tap. J. Contemp. Water Res. Educ. 120, 1–3.
Mastrocco, F., 2005. Pharmaceuticals in the Environment (PIE): Assessing Risk to Human Health.

Mastroianni, N., Lopez de Alda, M., Barcelo, D., 2014. Analysis of ethyl sulfate in raw wastewater for estimation of alcohol consumption and its correlation with drugs of abuse in the city of Barcelona. J. Chromatogr. A 1360, 93–99. http://dx.doi.org/10.1016/j.chroma.2014.07.051.

Matheson III, John C., 1988. The nuts and bolts of preparing an environmental assessment. Food Drug Cosmet. Law J. 43, 831–841.

McClellan OB, Castorani, SJ. "Continuous (flexible) sewage monitoring machine for sampling building effluent to measure for certain controlled substances." Patent No: US 4,941,360. Issue Date: 17 July 1990; 4 pp. Available on: http://www.freepatentsonline.com/4941360.html. (accessed 20 November 2015).

McLachlan, J.A., 1997. ≪RETRACTED≫ Synergistic effect of environmental estrogens. Science 277, 459–463. http://dx.doi.org/10.1126/science.277.5325.459d.

Mehendale, H.M., 1994. Amplified interactive toxicity of chemicals at nontoxic levels: mechanistic considerations and implications to public health. Environ. Health Perspect. 102, 139–149.

Menicucci, M.M., Coon, C.L., 1993-1994. Environmental regulation of health care facilities: a prescription for compliance. SMU Law Rev. 47, 537–577.

Meyer, M.T., Bumgarner, J.E., Varns, J.L., Daughtridge, J.V., Thurman, E.M., Hostetler, K.A., 2000. Use of radioimmunoassay as a screen for antibiotics in confined animal feeding operations and confirmation by liquid chromatography/mass spectrometry. Sci. Total Environ. 248, 181–187. http://dx.doi.org/10.1016/S0048-9697(99)00541-0.

Miller, C.P., 1948. Bacterial resistance to antibiotics. Ann. Intern. Med. 29, 765–774.

Miyazaki, T., Yamagishi, T., Matsumoto, M., 1984. Residues of 4-chloro-1-(2,4-dichlorophenoxy)-2-methoxybenzene(triclosan methyl) in aquatic biota. Bull. Environ. Contam. Toxicol. 32, 227–232. http://dx.doi.org/10.1007/BF01607490.

Mohammed, A., Yang, Y.S., Du, X.Q., Musa, A., 2013. ≪RETRACTED≫ Fate and transport of EDCs in soils: estrone and its sulfate conjugate's adsorption from mediator solutions. Water Air Soil Pollut. 224, 1–11. http://dx.doi.org/10.1007/s11270-012-1432-x.

Möhle, E., Kempter, C., Kern, A., Metzger, J.W., 1999. Untersuchungen zum abbau von pharmaka in kommunalen Kläranlagen mit HPLC-electrospray-massenspektrometrie [Examination of the degradation of drugs in municipal sewage plants using liquid chromatography-electrospray mass spectrometry]. Acta Hydrochim. Hydrobiol. 27, 430–436.

Möller, P., Dulski, P., Bau, M., Knappe, A., Pekdeger, A., Sommer-von, Jarmersted C., 2000. Anthropogenic gadolinium as a conservative tracer in hydrology. J. Geochem. Explor. 69–70, 409–414. http://dx.doi.org/10.1016/S0375-6742(00)00083-2.

Montague, P., 1998. Drugs in the Water. Rachel's Environmental Health Weekly.

Montague, P., 2000. Pay Dirt from the Human Genome. Rachel's Environmental Health Weekly.

Müller, W.E.G., Steffen, R., Rinkevich, B., Matranga, V., Kurelec, B., 1996. The multixenobiotic resistance mechanism in the marine sponge *Suberites domuncula*: its potential applicability for the evaluation of environmental pollution by toxic compounds. Mar. Biol. 125, 165–170. http://dx.doi.org/10.1007/BF00350770.

Murphy, M.J., 1994. Toxin exposures in dogs and cats: drugs and household products. J. Am. Vet. Med. Assoc. 205, 557–560.

Nessel, R.J., Wallace, D.H., Wehner, T.A., Tait, W.E., Gomez, L., 1989. Environmental fate of ivermectin in a cattle feedlot. Chemosphere 18, 1531–1541. http://dx.doi.org/10.1016/0045-6535(89)90044-1.

NGWA, 2000. Emerging issues conference - pharmaceuticals - endocrine disrupting chemicals - pesticides - arsenic and radon. Emerging Issues Conference, Minneapolis, Minnesota, National Ground Water Association, 7–8 June (7–8 June).

Nicholson, W.A., 1967. Collection of unwanted drugs from private homes. Br. Med. J. 3, 730–731.

Norpoth, K., Nehrkorn, A., Kirchner, M., Holsen, H., Teipel, H., 1973. Untersuchingen zur ovulationshemmender Steroide Frage des Loslichkeit und Stabilitat in Wasser, Abwassern und Belebtschlamm (Studies on the problem of solubility and stability of steroid ovulation inhibitors in water, waste water, and activated sludge). Zentralblatt Fuer Bakteriologie Parasitenkunde Infektionskrankheiten Und Hygiene Erste Abteilung Originale Reihe B Hygiene Krankenhaushygiene Betriebshygiene Praeventive Medizin 156 pp. 500–511.

NRC (Ed.), 1999. Identifying Future Drinking Water Contaminants. National Research Council, The National Academies Press, Washington, DC (260 pp; http://books.nap.edu/catalog/9595.html).

Nunes, B., 2015. How to answer the question — are drugs real threats to biological systems or overrated innocuous chemicals? In: Andreazza, A.C., Scola, G. (Eds.), Toxicology Studies - Cells, Drugs and Environment. InTech Europe, Rijeka, Croatia, pp. 129–152 (chapter 6)

Oaks, J.L., Gilbert, M., Virani, M.Z., Watson, R.T., Meteyer, C.U., Rideout, B.A., et al., 2004. Diclofenac residues as the cause of vulture population decline in Pakistan. Nature 427, 630–633. http://dx.doi.org/10.1038/nature02317.

Office of the Press Secretary, 2015. Weekly Address: Dispose of Your Expired and Unwanted Prescription Drugs. The White House, Washington, DC, p. 4 (Available on: https://www.whitehouse.gov/the-press-office/2015/09/26/weekly-address-dispose-your-expired-and-unwanted-prescription-drugs. (accessed 20 November 2015)).

Oppel, J., Broll, G., Loffler, D., Meller, M., Rombke, J., Ternes, T., 2004. Leaching behaviour of pharmaceuticals in soil-testing-systems: a part of an environmental risk assessment for groundwater protection. Sci. Total Environ. 328, 265–273. http://dx.doi.org/10.1016/j.scitotenv.2004.02.004.

Oropesa, A., Guimarães, L., Martins, A., Soler, F., Guilhermino, L., 2012. ≪RETRACTED≫ Acute and chronic toxicity of the pharmaceutical levonorgestrel to the freshwater crustacean *Daphnia magna*. Ecotoxicology 21, 1582. http://dx.doi.org/10.1007/s10646-011-0824-9.

Oros, D.R., Jarman, W.M., Lowe, T., David, N., Lowe, S., Davis, J.A., 2003. Surveillance for previously unmonitored organic contaminants in the San Francisco Estuary. Mar. Pollut. Bull. 46, 1102–1110. http://dx.doi.org/10.1016/S0025-326X(03)00248-0.

Osemwengie, L.I., Steinberg, S., 2001. On-site solid-phase extraction and laboratory analysis of ultra-trace synthetic musks in municipal sewage effluent using gas chromatography-mass spectrometry in the full-scan mode. J. Chromatogr. A 932, 107–118. http://dx.doi.org/10.1016/S0021-9673(01)01216-X.

Panter, G.H., Thompson, R.S., Beresford, N., Sumpter, J.P., 1999. Transformation of a non-oestrogenic steroid metabolite to an oestrogenically active substance by minimal bacterial activity. Chemosphere 38, 3579–3596. http://dx.doi.org/10.1016/S0045-6535(98)00572-4.

Park, J., 2005. Pharmaceuticals in the Environment and Management Approaches in Korea. Korea Environment Institute (KEI), Seoul, Korea, p. 139 RE - 12. (Available on: http://webbook.me.go.kr/DLi-File/007/150647.pdf. (accessed 20 November 2015)).

Patiño, Y., Díaz, E., Ordóñez, S., 2016. Pre-concentration of nalidixic acid through adsorption–desorption cycles: adsorbent selection and modelling. Chem. Eng. J. 283, 486–494. http://dx.doi.org/10.1016/j.cej.2015.07.084.

Patterson, D.B., Brumley, W.C., Kelliher, V., Ferguson, P.L., 2002. Application of U.S. EPA methods to the analysis of pharmaceuticals and personal care products in the environment: determination of clofibric acid in sewage effluent by GC–MS. Am. Lab. 34, 20–28.

Paxéus, N., 1996. Organic pollutants in the effluents of large wastewater treatment plants in Sweden. Water Res. 30, 1115–1122. http://dx.doi.org/10.1016/0043-1354(95)00278-2.

Peck, H.M., 1977. The environmental impact of drugs. Toxicol. Pathol. 5, 9–11. http://dx.doi.org/10.1177/019262337700500103.

Pedersen, J.A., Yeager, M.A., Suffet, I.H., 2003. Xenobiotic organic compounds in runoff from fields irrigated with treated wastewater. J. Agric. Food Chem. 51, 1360–1372. http://dx.doi.org/10.1021/jf025953q.

Pedersen, J.A., Soliman, M., Suffet, I.H., 2005. Human pharmaceuticals, hormones, and personal care product ingredients in runoff from agricultural fields irrigated with treated wastewater. J. Agric. Food Chem. 53, 1625–1632. http://dx.doi.org/10.1021/jf049228m.

Penning, W., Aina, G., Helm, B., 1986. Integration and use of the list of organic micropollutants in the aquatic environment in the ECDIN data bank. In: Bjørseth, A., Angeletti, G. (Eds.), Organic Micropollutants in the Aquatic Environment. Springer Netherlands, pp. 484–490 (chapter 52).

Petrasek, A.C., Kugelman, I.J., Austern, B.M., Pressley, T.A., Winslow, L.A., Wise, R.H., 1983. Fate of toxic organic compounds in wastewater treatment plants. J. Water Pollut. Control Fed. 55, 1286–1296.

Petrie, B., Barden, R., Kasprzyk-Hordern, B., 2015. A review on emerging contaminants in wastewaters and the environment: current knowledge, understudied areas and recommendations for future monitoring. Water Res. 72, 3–27. http://dx.doi.org/10.1016/j.watres.2014.08.053.

Petrie, B., Youdan, J., Barden, R., Kasprzyk-Hordern, B., 14 March 2016. A new framework to diagnose the direct disposal of prescribed drugs in wastewater — a case study of the antidepressant fluoxetine. Environ. Sci. Technol. http://dx.doi.org/10.1021/acs.est.6b00291.

Petrovic, M., Eljarrat, E., Lopez de Alda, M.J., Barcelo, D., 2004. Endocrine disrupting compounds and other emerging contaminants in the environment: a survey on new monitoring strategies and occurrence data. Anal. Bioanal. Chem. 378, 549–562. http://dx.doi.org/10.1007/s00216-003-2184-7.

Poiger, T., Buser, H.R., Muller, M.D., Balmer, M.E., Buerge, I.J., 2003. Occurrence and fate of organic micropollutants in the environment: regional mass balances and source apportioning in surface waters based on laboratory incubation studies in soil and water, monitoring, and computer modeling. Chimia 57, 492–498.

Potera, C., 2000. Drugged drinking water. Environ. Health Perspect. 108, A446.

Pramer, D., 1953. Observations of the uptake and translocation of five actinomycete antibiotics by cucumber seedlings. Ann. Appl. Biol. 40, 617–622. http://dx.doi.org/10.1111/j.1744-7348.1953.tb01100.x.

Purdom, C.E., Hardiman, P.A., Bye, V.V.J., Eno, N.C., Tyler, C.R., Sumpter, J.P., 1994. Estrogenic effects of effluents from sewage treatment works. Chem. Ecol. 8, 275–285. http://dx.doi.org/10.1080/02757549408038554.

Purvis, A., 1996. The goodwill pill mess. Time (April 29).

Qian, F., He, M., Song, Y., Tysklind, M., Wu, J., 2015. A bibliometric analysis of global research progress on pharmaceutical wastewater treatment during 1994–2013. Environ. Earth Sci. 73, 4995–5005. http://dx.doi.org/10.1007/s12665-015-4183-3.

Rahman, S.Z., 2015. Do we really need multiple terms for a single concept in the field of environmental pharmacovigilance? Int. Arch. BioMed. Clin. Res. 21, 1–2.

Rahman, S., Khan, R., Gupta, V., Uddin, M., 2007. Pharmacoenvironmentology — a component of pharmacovigilance. Environ. Health 6, 20. http://dx.doi.org/10.1186/1476-069X-6-20.

Rajapakse, N., Ong, D., Kortenkamp, A., 2001. Defining the impact of weakly estrogenic chemicals on the action of steroidal estrogens. Toxicol. Sci. 60, 296–304. http://dx.doi.org/10.1093/toxsci/60.2.296.

Raloff, J., 1998. Drugged waters — does it matter that pharmaceuticals are turning up in water supplies. Sci. News 153, 187–189.

Raloff, J., 1999. Medicinal waters: where ibuprofen goes — the finding of clofibric acid and diclofenac in the water of Swiss lakes, leads to the question of why ibuprofen was not being found. Sci. News 156, 126.

Raloff, J., 2000a. Excreted drugs: something looks fishy. Sci. News 157, 388.

Raloff, J., 2000b. More waters test positive for drugs. Sci. News 157, 212.

Rao, Y., Xue, D., Pan, H., Feng, J., Li, Y., 2016. Degradation of ibuprofen by a synergistic UV/Fe(III)/Oxone process. Chem. Eng. J. 283, 65–75. http://dx.doi.org/10.1016/j.cej.2015.07.057.

Rastogi, T., Leder, C., Kummerer, K., 2015. A sustainable chemistry solution to the presence of pharmaceuticals and chemicals in the aquatic environment — the example of re-

designing β-blocker atenolol. RSC Adv. 5, 27–32. http://dx.doi.org/10.1039/C4RA10294K.
Rauch-Williams, T., Hoppe-Jones, C., Drewes, J.E., 2010. The role of organic matter in the removal of emerging trace organic chemicals during managed aquifer recharge. Water Res. 44, 449–460. http://dx.doi.org/10.1016/j.watres.2009.08.027.
Reid, M.J., Langford, K.H., Mørland, J., Thomas, K.V., 2011. Analysis and interpretation of specific ethanol metabolites, ethyl sulfate, and ethyl glucuronide in sewage effluent for the quantitative measurement of regional alcohol consumption. Alcohol. Clin. Exp. Res. 35, 1–7. http://dx.doi.org/10.1111/j.1530-0277.2011.01505.x.
Reungoat, J., Escher, B.I., Macova, M., Argaud, F.X., Gernjak, W., Keller, J., 2012. Ozonation and biological activated carbon filtration of wastewater treatment plant effluents. Water Res. 46, 863–872. http://dx.doi.org/10.1016/j.watres.2011.11.064.
Reuters, 1998. Researchers find estrogen-like chemicals in toiletries. (8 October). Available on http://www.boston.com/globe (accessed 20 November 2015).
Richards, S.M., Wilson, C.J., Johnson, D.J., Castle, D.M., Lam, M., Mabury, S.A., et al., 2004. Effects of pharmaceutical mixtures in aquatic microcosms. Environ. Toxicol. Chem. 23, 1035–1042. http://dx.doi.org/10.1897/02-616.
Richardson, M.L., Bowron, J.M., 1985. The fate of pharmaceutical chemicals in the aquatic environment. J. Pharm. Pharmacol. 37, 1–12. http://dx.doi.org/10.1111/j.2042-7158.1985.tb04922.x.
Ricking, M., Schwarzbauer, J., Franke, S., 2003. Molecular markers of anthropogenic activity in sediments of the Havel and Spree Rivers (Germany). Water Res. 37, 2607–2617. http://dx.doi.org/10.1016/S0043-1354(03)00078-2.
Rimkus, G.G., Rimkus, B., Wolf, M., 1994. Nitro musks in human adipose-tissue and breast-milk. Chemosphere 28, 421–432. http://dx.doi.org/10.1016/0045-6535(94)90138-4.
Robinson, I., Junqua, G., Van Coillie, R., Thomas, O., 2007. Trends in the detection of pharmaceutical products, and their impact and mitigation in water and wastewater in North America. Anal. Bioanal. Chem. 387, 1143–1151. http://dx.doi.org/10.1007/s00216-006-0951-y.
Rodríguez-Álvarez, T., Rodil, R., Rico, M., Cela, R., Quintana, J.B., 2014. Assessment of local tobacco consumption by liquid chromatography-tandem mass spectrometry sewage analysis of nicotine and its metabolites, cotinine and *trans*-3′-hydroxycotinine, after enzymatic deconjugation. Anal. Chem. 86, 10274–10281. http://dx.doi.org/10.1021/ac503330c.
Rogers, H.R., 1996. Sources, behaviour and fate of organic contaminants during sewage treatment and in sewage sludges. Sci. Total Environ. 185, 3–26. http://dx.doi.org/10.1016/0048-9697(96)05039-5.
Rouhi, A.M., 2008. Drug pollution. Chem. Eng. News 86, 3.
Routledge, E.J., Sheahan, D., Desbrow, C., Brighty, G.C., Waldock, M., Sumpter, J.P., 1998. Identification of estrogenic chemicals in STW effluent. 2. In vivo responses in trout and roach. Environ. Sci. Technol. 32, 1559–1565.
Rudd, M., Ankley, G., Boxall, A., Brooks, B., 2014. International scientists' priorities for research on pharmaceuticals and personal care products in the environment. Integr. Environ. Assess. Manag. 10, 576–587. http://dx.doi.org/10.1002/ieam.1551.
Rurainski, R.D., Theiss, H.J., Zimmermann, W., 1977. Über das vorkommen von natürlichen und synthetischen oestrogenen im trinkwasser (Concerning the occurrence of natural and synthetic estrogens in drinking water). GWF-Wasser Abwasser 118, 288–291.
Russo, D., Spasiano, D., Vaccaro, M., Andreozzi, R., Puma, G.L., Reis, N.M., et al., 2016. Direct photolysis of benzoylecgonine under UV irradiation at 254 nm in a continuous flow microcapillary array photoreactor. Chem. Eng. J. 283, 243–250. http://dx.doi.org/10.1016/j.cej.2015.07.061.
Ryu, Y., Reid, M.J., Thomas, K.V., 2015. Liquid chromatography–high resolution mass spectrometry with immunoaffinity clean-up for the determination of the oxidative stress biomarker 8-iso-prostaglandin F2alpha in wastewater. J. Chromatogr. A 1409, 146–151. http://dx.doi.org/10.1016/j.chroma.2015.07.060.
Sager, N.B., Williams, R.L., 1994. Environmental assessment and finding of no significant impact for TOPAMAX® (Topiramate). US Food and Drug Administration, Center for Drug Evaluation and Research, Division of Neuropharmacological Drug Products (HFD-120), p. 46 (Available on: http://www.accessdata.fda.gov/drugsatfda_docs/nda/96/020505_000_environmental_rvw.pdf. (accessed 20 November 2015)).
Samuelsen, O., Solheim, E., Lunestad, B., 1991. Fate and microbiological effects of furazolidone in a marine aquaculture sediment. Sci. Total Environ. 108, 275–283. http://dx.doi.org/10.1016/0048-9697(91)90364-K.
Santos, L.H.M.L.M., Araújo, A.N., Fachini, A., Pena, A., Delerue-Matos, C., Montenegro, M.C.B.S.M., 2010. Ecotoxicological aspects related to the presence of pharmaceuticals in the aquatic environment. J. Hazard. Mater. 175, 45–95. http://dx.doi.org/10.1016/j.jhazmat.2009.10.100.
Sarmah, A.K., Meyer, M.T., Boxall, A.B.A., 2006. A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment. Chemosphere 65, 725–759. http://dx.doi.org/10.1016/j.chemosphere.2006.03.026.
Sattelberger, R., 1999. Arzneimittelrückstände in der Umwelt – Bestandsaufnahme und Problemdarstellung (Pharmaceutical residues in the environment - an inventory and problem representation). Umweltbundesamt GmbH Österreich [Federal Environment Agency – Austria], Vienna, Austria, p. 121 *R*-162. (Available on: http://www.umweltbundesamt.at/fileadmin/site/publikationen/r162.pdf. (accessed 20 November 2015)).
Schecker, J., Al-Ahmad, A., Bauer, M., Zellmann, H., Kümmerer, K., 1998. Arzneimittel in der umwelt: elimination des zytostatikums ifosfamid während der simulierten zersetzung von Hausmüll im Labormaßstab [Pharmaceuticals in the environment: elimination of the antineoplastic agent ifosfamide in a laboratory-scale waste bioreactor]. Umweltwiss. Schadst. Forsch. 10, 339–344. http://dx.doi.org/10.1007/BF03037676.
Schueler, F.W., 1946. Sex hormonal action and chemical constitution. Science 103, 221–223. http://dx.doi.org/10.1126/science.103.2669.221.
Schwarzbauer, J., Ricking, M., 2010. Non-target screening analysis of river water as compound-related base for monitoring measures. Environ. Sci. Pollut. Res. 17, 934–947. http://dx.doi.org/10.1007/s11356-009-0269-3.
Schwarzenbach, R.P., Escher, B.I., Fenner, K., Hofstetter, T.B., Johnson, C.A., von Gunten, U., et al., 2006. The challenge of micropollutants in aquatic systems. Science 313, 1072–1077. http://dx.doi.org/10.1126/science.1127291.
Schymanski, E.L., Singer, H.P., Slobodnik, J., Ipolyi, I.M., Oswald, P., Krauss, M., et al., 2015. Non-target screening with high-resolution mass spectrometry: critical review using a collaborative trial on water analysis. Anal. Bioanal. Chem. 407, 6237–6255. http://dx.doi.org/10.1007/s00216-015-8681-7.
Sedlak, D.L., 1998. Transport and Transformation of Antibiotics and Hormones in the Aquatic Environment. Project: HRA 699-518-97. University of California, Berkeley, Berkeley, CA, p. 32 (Available on: http://www.nwri-usa.org/pdfs/NWRITransportandTransformationOfAntibioticsandHormonesInTheAquaticEnvironment.pdf. (accessed 20 November 2015)).
Sedlak, D.L., Pinkston, K.E., 2001. Factors affecting the concentrations of pharmaceuticals released to the aquatic environment. J. Contemp. Water Res. Educ. 120, 56–64.
Sedlak, D.L., Gray, J.L., Pinkston, K.E., 2000. Understanding microcontaminants in recycled water. Environ. Sci. Technol. 34, 508A–515A. http://dx.doi.org/10.1021/es003513e.
Seiler, R.L., Zaugg, S.D., Thomas, J.M., Howcroft, D.L., 1999. Caffeine and pharmaceuticals as indicators of waste water contamination in wells. Ground Water 37, 405–410.
Senate and House of Representatives of the United States of America in Congress, 2010o. Secure and Responsible Drug Disposal Act of 2010. 124 Stat. 2858. Public Law 111–273, p. 4.
SETAC, 2000. Veterinary and human pharmaceuticals — fate and effects. Third SETAC World Congress, Session 3C (and various others), Brighton, United Kingdom (21–25 May).
Sharma, V.K., 2008. Oxidative transformations of environmental pharmaceuticals by Cl_2, ClO_2, O_3, and Fe(VI): kinetics assessment. Chemosphere 73, 1379–1386. http://dx.doi.org/10.1016/j.chemosphere.2008.08.033.
Shirreff, W.T., Pearlman, L.N., 1940. Oil of wintergreen poisoning: (report of two additional fatal cases). Can. Med. Assoc. J. 43, 264–268.
Shultz, S., Baral, H.S., Charman, S., Cunningham, A.A., Das, D., Ghalsasi, G.R., et al., 2004. Diclofenac poisoning is widespread in declining vulture populations across the Indian subcontinent. Proc. R. Soc. B Biol. Sci. 271, 458–460. http://dx.doi.org/10.1098/rsbl.2004.0223.
Sievers, R.E., Barkley, R.M., Eiceman, G.A., Shapiro, R.H., Walton, H.F., Kolonko, K.J., et al., 1977. Environmental trace analysis of organics in water by glass capillary column chromatography and ancillary techniques: products of ozonolysis. J. Chromatogr. 142, 745–754. http://dx.doi.org/10.1016/S0021-9673(01)92082-5.
Silva, E., Rajapakse, N., Kortenkamp, A., 2002. Something from "nothing" — eight weak estrogenic chemicals combined at concentrations below NOECs produce significant mixture effects. Environ. Sci. Technol. 36, 1751–1756. http://dx.doi.org/10.1021/es0101227.
Singh, S.P., 2006. Assessing the Sources, Quantities, and Trends on Human Waste Contamination along Protected South Florida Ecosystem: A Chemical Tracer Based Study Doctoral dissertation Florida International University, Miami, Florida, p. 256 (Available on: http://wwwlib.umi.com/dissertations/fullcit/3235619. (accessed 20 November 2015)).
Sixsmith, D.G., Smail, G.A., 1978. Evaluation of medicines returned in Glasgow DUMP campaign. Health Bull. 36, 88–90.
Smital, T., Kurelec, B., 1997. Inhibitors of the multixenobiotic resistance mechanism in natural waters: in vivo demonstration of their effects. Environ. Toxicol. Chem. 16, 2164–2170. http://dx.doi.org/10.1002/etc.5620161025.
Smital, T., Kurelec, B., 1998. The chemosensitizers of multixenobiotic resistance mechanism in aquatic invertebrates: a new class of pollutants. Mutat. Res. Fundam. Mol. Mech. Mutagen. 399, 43–53. http://dx.doi.org/10.1016/S0027-5107(97)00265-0.
Smith, C.A., 2002. Managing pharmaceutical waste: what pharmacists should know. J. Pharm. Soc. Wis. (Nov/Dec:17–22).
Snyder, S.A., Westerhoff, P., Yoon, Y., Sedlak, D.L., 2003. Pharmaceuticals, personal care products, and endocrine disruptors in water: implications for the water industry. Environ. Eng. Sci. 20, 449–469. http://dx.doi.org/10.1089/109287503768335931.
Sodd, V.J., Velten, R.J., Saenger, E.L., 1975. Concentrations of the medically useful radionuclides, technetium-99m and iodine-131 at a large metropolitan waste water treatment plant. Health Phys. 28, 355–359.
Soliman, M.A., Pedersen, J.A., Suffet, I.H., 2004. Rapid gas chromatography–mass spectrometry screening method for human pharmaceuticals, hormones, antioxidants and plasticizers in water. J. Chromatogr. A 1029, 223–237. http://dx.doi.org/10.1016/j.chroma.2003.11.098.
Sørensen, B.H., 2008. Veterinary medicines. In: Jorgensen, S.E. (Ed.), Encyclopedia of Ecology. Academic Press, Oxford, UK, pp. 3679–3684.
Stahlschmidt-Allner, P., Allner, B., Römbke, J., Knacker, T., 1997. Endocrine disrupters in the aquatic environment. Environ. Sci. Pollut. Res. 4, 155–162. http://dx.doi.org/10.1007/BF02986325.
Stob, M., 1956. Fecal elimination of hormones in sheep and cattle treated with synthetic estrogens. J. Anim. Sci. 15, 990–996.
Stokes, A., 1954. Uptake and translocation of griseofulvin by wheat seedlings. Plant Soil 5, 132–142. http://dx.doi.org/10.1007/BF01343846.
Straub, J.O., 2016. Aquatic environmental risk assessment for human use of the old antibiotic sulfamethoxazole in Europe. Environ. Toxicol. Chem. 35 (4), 767–779.
Struzeski, E.J., 1975. Waste treatment and disposal methods for the pharmaceutical industry. EPA 330/1-75-001. US Environmental Protection Agency, National Field Investigations Center, Denver, CO, p. 161 (Available on: http://cfpub.epa.gov/ols/catalog/advanced_brief_record.cfm?&FIELD1=SUBJECT&INPUT1=Criteria&TYPE1=EXACT&LOGIC1=

AND&COLL=&SORT_TYPE=MTIC&item_count=3306; http://nepis.epa.gov/Exe/ZyPDF.cgi?Dockey=9101OJJ3.PDF. (accessed 20 November 2015)).
Stumm-Zollinger, E., Fair, G.M., 1965. Biodegradation of steroid hormones. J. Water Pollut. Control Fed. 37, 1506–1510.
Sumpter, J.P., Jobling, S., 1995. Vitellogenesis as a biomarker for estrogenic contamination of the aquatic environment. Environ. Health Perspect. 103, 173–178.
Tabak, H.H., Bunch, R.L., 1970. Steroid hormones as water pollutants I. Metabolism of natural and synthetic ovulation-inhibiting hormones by microorganisms of activated sludge and primary settled sewage. In: Corum, C.J. (Ed.), Developments in Industrial Microbiology, Society for Industrial Microbiology, American Institute of Biological SciencesProceedings of the Twenty-Sixth General Meeting of the Society for Industrial Microbiology Held in Burlington, Vermont, August 17–22, 1969. Garamond/Pridemark Press, Baltimore, MD, pp. 367–376 (chapter 35).
Tabak, H.H., Bloomhuff, R.N., Bunch, R.L., 1981. Steroid hormones as water pollutants II. Studies on the persistence and stability of natural urinary and synthetic ovulation-inhibiting hormones in treated and treated wastewaters. In: Underkofler, L.A. (Ed.), Developments in Industrial Microbiology, Society for Industrial Microbiology, American Institute of Biological SciencesProceedings of the Thirty-Seventh General Meeting of the Society for Industrial Microbiology Held in Flagstaff, Arixona, Austust 9–15, 1980. Grayson & Biedenbach Associates, Washington, DC, pp. 497–519 (chapter 43).
Taylor, R.J., 1978. Towards better prescribing. J. R. Coll. Gen. Pract. 28, 263–270.
ter Laak, T.L., Kooij, P.J.F., Tolkamp, H., Hofman, J., 2014. Different compositions of pharmaceuticals in Dutch and Belgian rivers explained by consumption patterns and treatment efficiency. Environ. Sci. Pollut. Res. 21, 12843–12855. http://dx.doi.org/10.1007/s11356-014-3233-9.
Ternes, T.A., 1998. Occurrence of drugs in German sewage treatment plants and rivers. Water Res. 32, 3245–3260. http://dx.doi.org/10.1016/S0043-1354(98)00099-2.
Ternes, T.A., 1999. Drugs and hormones as pollutants of the aquatic environment: determination and ecotoxicological impacts. Sci. Total Environ. 225, 1–2. http://dx.doi.org/10.1016/S0048-9697(98)00327-1.
Ternes, T.A., Hirsch, R., Mueller, J., Haberer, K., 1998. Methods for the determination of neutral drugs as well as betablockers and β_2-sympathomimetics in aqueous matrices using GC/MS and LC/MS/MS. Fresenius J. Anal. Chem. 362, 329–340. http://dx.doi.org/10.1007/s002160051083.
Ternes, T.A., Kreckel, P., Mueller, J., 1999a. Behaviour and occurrence of estrogens in municipal sewage treatment plants — II. Aerobic batch experiments with activated sludge. Sci. Total Environ. 225, 91–99. http://dx.doi.org/10.1016/S0048-9697(98)00335-0.
Ternes, T.A., Stumpf, M., Mueller, J., Haberer, K., Wilken, R.-D., Servos, M., 1999b. Behaviour and occurrence of estrogens in municipal sewage treatment plants – I. Investigations in Germany, Canada and Brazil. Sci. Total Environ. 225, 81–90. http://dx.doi.org/10.1016/S0048-9697(98)00334-9.
Thiele-Bruhn, S., 2003. Pharmaceutical antibiotic compounds in soils - a review. J. Plant Nutr. Soil Sci. (Zeitschrift Fur Pflanzenernahrung und Bodenkunde) 166, 145–167. http://dx.doi.org/10.1002/jpln.200390023.
Tolls, J., 2001. Sorption of veterinary pharmaceuticals in soils: a review. Environ. Sci. Technol. 35, 3397–3406. http://dx.doi.org/10.1021/es0003021.
Toomey, B.H., Epel, D., 1993. Multixenobiotic resistance in *Urechis caupo* embryos: protection from environmental toxins. Biol. Bull. 185, 355–364.
Troll, M.M., Menten, M.L., 1945. Salicylate poisoning: report of four cases. Am. J. Dis. Child. 69, 37–43.
Tscharke, B.J., White, J.M., Gerber, J.P., 22 Jul 2015. Estimates of tobacco use by wastewater analysis of anabasine and anatabine. Drug Test. Anal. http://dx.doi.org/10.1002/dta.1842.
Tyler, C.R., Routledge, E.J., 1998. Natural and anthropogenic environmental oestrogens: the scientific basis for risk assessment; oestrogenic effects in fish in English rivers with evidence of their causation. Pure Appl. Chem. 70, 1795–1804.
Tyler, C.R., Jobling, S., Sumpter, J.P., 1998. Endocrine disruption in wildlife: a critical review of the evidence. Crit. Rev. Toxicol. 28, 319–361. http://dx.doi.org/10.1080/10408449891344236.
USEPA, 1994. Guides to Pollution Prevention. Selected Hospital Waste Streams. US Environmental Protection Agency, Cincinnati, OH, p. 51 EPA /625/7–90/009. (Available on: http://www.istc.illinois.edu/info/library_docs/other_pubs/p2_guide_hospital_waste_streams.pdf. (accessed 20 November 2015)).
USEPA, 2005. Session on environmental stewardship for pharmaceuticals in the environment. Workshop on Pharmaceuticals in the Environment. US Environmental Protection Agency, National Center for Environmental Research and Office of Research and Development (National Exposure Research Laboratory), Las Vegas, NV (23–25 August (23–25 August), http://archive.epa.gov/ncer/publications/web/pdf/finalsummarypharma1.pdf).
USEPA, 2007. EPA Method 1698: Steroids and Hormones in Water, Soil, Sediment, and Biosolids by HRGC/HRMS. US Environmental Protection Agency, Washington, DC, p. 69 EPA-821-*R*-08-003. (Available on: http://water.epa.gov/scitech/methods/cwa/bioindicators/upload/2008_01_03_methods_method_1698.pdf. (accessed 20 November 2015)).
USFDA, 1998. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application. US Food and Drug Administration, Rockville, MD (July, Rev 1):39. CDER/CBER CMC 6, Available on: http://www.fda.gov/cber/guidelines.htm. (accessed 20 November 2015)).
USFWS, 2003. Pentobarbital Poisoning of Eagles. U.S. Fish and Wildlife Service, pp. 9–10 (Available on: http://digitalcommons.unl.edu/cgi/viewcontent.cgi?article=1010&context=secwdspubs. (accessed 20 November 2015)).
USGAO, 2011. Environmental health: action needed to sustain agencies' collaboration on pharmaceuticals in drinking water. U.S. Government Accountability Office (USGAO), Washington, DC, p. 52 GAO-11-346. (Available on: http://www.gao.gov/Products/GAO-11-346. (accessed 20 November 2015)).
Vaarkamp, H., 1991. De veterinaire praktijk en het milieu: wat te doen en wat te laten (Veterinary practice and the environment: what to do and what to omit). Tijdschr. Diergeneeskd. (Netherlands Journal of Veterinary Science) 116, 73–77.
Velagaleti, R., 1997. Behavior of pharmaceutical drugs (human and animal health) in the environment. Drug Inf. J. 31, 715–722.
Verlicchi, P., Galletti, A., Masotti, L., 2010. Management of hospital wastewaters: the case of the effluent of a large hospital situated in a small town. Water Sci. Technol. 61, 2507–2519. http://dx.doi.org/10.2166/wst.2010.138.
Vincent, P.G., 1993. Environmental assessment: U.S. requirements in new drug applications. J. Hazard. Mater. 35, 211–216. http://dx.doi.org/10.1016/0304-3894(93)80006-2.
von Rathner, M., Sonneborn, M., 1979. Biologisch wirksame Östrogene in trink- und abwasse (Biologically active oestrogens in portable water and effluents). Forum Städte-Hyg. 30, 45–49.
Vouk, V.B., Butler, G.C., Upton, A.C., Parke, D.V., Asher, S.C. (Eds.), 1987. Methods for assessing the effects of mixtures of chemicals. John Wiley & Sons, Chichester, UK (894 pp; http://globalecology.stanford.edu/SCOPE/SCOPE_30/SCOPE_30.html).
Waggott, A., 1981. In: Cooper, W.J. (Ed.), Trace organic substances in the River LeeChemistry in Water Reuse 2. Ann Arbor Science, Ann Arbor, Michigan, pp. 55–99 (chapter 4).
Wall, R., Strong, L., 1987. Environmental consequences of treating cattle with the antiparasitic drug ivermectin. Nature 327, 418–421.
Warman, P.R., Thomas, R.L., 1981. Chlortetracycline in soil amended with poultry manure. Can. J. Soil Sci. 61, 161–163. http://dx.doi.org/10.4141/cjss81-017.
Water Research Centre, 1974. A comprehensive list of polluting substances which have been identified in various fresh waters, effluent discharges, aquatic animals and plants, and bottom sediments. COST project 64b: Analysis of Organic Micropollutants in Water. Stevenage Laboratory, Hertfordshire, England, p. 99 (EUCO/MDU/40/74 XII/825/74, Available on: http://aei.pitt.edu/38763/; http://aei.pitt.edu/38763/1/A3723.pdf. (accessed 20 November 2015)).
Watts, C.D., Craythrone, M., Fielding, M., Steel, C.P., 1984. Identification of non volatile organics in water using field desorption mass spectrometry and high performance liquid chromatography. In: Angeletti, G., Bjørseth, A. (Eds.), Analysis of Organic Micropollutants in Water. 1983.Reidel Publishing Company, Dordrecht, The Netherlands, pp. 120–131
WEF, 2007. Effects of Wastewater Treatment on Microconstituents. Water Environment Federation, p. 17 (Order No: P07014E, Available on: http://www.mi-wea.org/docs/EffectsOfWWTrmtOnMicroconsituents.pdf. (accessed 20 November 2015)).
Wegener, G., Persin, J., Karrenbrock, F., Rörden, O., Hübner, I., 1999. Vorkommen und verhalten von natürlichen und synthetischen Östrogenen und deren Konjugate in der aquatischen Umwelt (Presence and behaviour of natural and synthetic estrogens and their conjugates in the aquatic environment). Vom Wasser 92, 347–360.
Weigel, S., Bester, K., Hühnerfuss, H., 2001. New method for rapid solid-phase extraction of large-volume water samples and its application to non-target screening of North Sea water for organic contaminants by gas chromatography-mass spectrometry. J. Chromatogr. A 912, 151–161. http://dx.doi.org/10.1016/S0021-9673(01)00529-5.
WERF, 2010. Workshop Proceedings: Diagnostic Tools to Evaluate Impacts of Trace Organic Compounds on Aquatic Populations and Communities. Water Environmental Research Foundation, Alexandria, VA (12–13 January 125 pp.).
Weyer, P., Riley, D., 2001. Endocrine Disruptors and Pharmaceuticals in Drinking Water. AWWA Research Foundation, American Water Works Association, Denver, CO (116 pp.; https://books.google.com/books/about/Endocrine_Disruptors_and_Pharmaceuticals.html?id=IlpjSAzsbiMC).
Whalen, S., 2015. U.S. Supreme Court Decides Not to Hear Pharmaceutical Industry Case Against Drug Disposal Law. http://www.productstewardship.us/news/233389/U.S.-Supreme-Court-Decides-Not-to-Hear-Pharmaceutical-Industry-Case-Against-Drug-Disposal-Law.htm.
Wick, C., 2014. Comment: mandatory drug take-back programs: will they survive the dormant commerce clause challenge? Tulane Environ. Law J. 27, 371.
Wilken, R.D., Ternes, T.A., Heberer, T., 2000. Pharmaceuticals in sewage, surface and drinking water in Germany. In: Deininger, R.A., Literathy, P., Bartram, J. (Eds.), Security of Public Water Supplies. 66. Kluwer Academic Publishers, Dordrecht, The Netherlands, pp. 227–240.
Williams, R.T. (Ed.), 2005. Human Pharmaceuticals: Assessing the Impacts on Aquatic Ecosystems. SETAC Press, Pensacola, FL (368 pp; https://www.setac.org/store/ViewProduct.aspx?id=1034154; https://books.google.com/books?isbn=1880611821).
Wilson, I., 1976. Steroids as water pollutants: a literature survey of synthetic and and natural hormonal steroids and the analytical methods for their determinationn <as cited by others>. Technical Memorandum 115. Water Research Centre, Stevenege, Hertforshire, UK, p. 64 (Available on: http://trove.nla.gov.au/work/27278736?selectedversion=NBD2511446. (accessed 20 November 2015)).
Wilson, I., 1978. Contraceptive steroids in water supplies Masters dissertation Chelsea College of Science Technology, London, UK (pp Available on: http://www.worldcat.org/title/contraceptive-steroids-in-water-supplies/oclc/731238454. (accessed 20 November 2015)).
Wilson, J., 1991. Forum: Too Much of a Good Thing - John Wilson Wonders How Many People Even Start Taking the Tablets. New Scientist.
Wilson, S.C., Duarte-Davidson, R., Jones, K.C., 1996. Screening the environmental fate of organic contaminants in sewage sludges applied to agricultural soils: 1. The potential for downward movement to groundwaters. Sci. Total Environ. 185, 45–57. http://dx.doi.org/10.1016/0048-9697(95)05041-8.
Wode, F., van Baar, P., Dünnbier, U., Hecht, F., Taute, T., Jekel, M., et al., 2015. Search for over 2000 current and legacy micropollutants on a wastewater infiltration site with a UPLC-high resolution MS target screening method. Water Res. 69, 274–283. http://dx.doi.org/10.1016/j.watres.2014.11.034.

Woods, M., 2000. Researchers Warn of Drug Pollution: Drug, Chemical Residue Found in Waterways. The Toledo Blade, Toledo, OH (Available on: http://news.google.com/newspapers?nid=1350&dat=20000328&id=lEVRAAAAIBAJ&sjid=AwQEAAAAIBAJ&pg=6675,4243696. (accessed 20 November 2015)).

Yamagishi, T., Miyazaki, T., Horii, S., Kaneko, S., 1981. Identification of musk xylene and musk ketone in freshwater fish collected from the Tama River, Tokyo. Bull. Environ. Contam. Toxicol. 26, 656–662. http://dx.doi.org/10.1007/BF01622152.

Yamagishi, T., Miyazaki, T., Horii, S., Akiyama, K., 1983. Synthetic musk residues in biota and water from Tama River and Tokyo Bay (Japan). Arch. Environ. Contam. Toxicol. 12, 83–89. http://dx.doi.org/10.1007/BF01055006.

Ying, G.-G., Kookana, R.S., Ru, Y.-J., 2002. Occurrence and fate of hormone steroids in the environment. Environ. Int. 28, 545–551. http://dx.doi.org/10.1016/S0160-4120(02)00075-2.

Zedda, M., Zwiener, C., 2012. Is nontarget screening of emerging contaminants by LC-HRMS successful? A plea for compound libraries and computer tools. Anal. Bioanal. Chem. 403, 2493–2502. http://dx.doi.org/10.1007/s00216-012-5893-y.

Zuccato, E., Chiabrando, C., Castiglioni, S., Calamari, D., Bagnati, R., Schiarea, S., et al., 2005. Cocaine in surface waters: a new evidence-based tool to monitor community drug abuse. Environ. Health J. Global Access Sci. Source 4. http://dx.doi.org/10.1186/1476-069X-4-14.

Zuccato, E., Chiabrando, C., Castiglioni, S., Bagnati, R., Fanelli, R., 2008. Estimating community drug abuse by wastewater analysis. Environ. Health Perspect. 116, 1027–1032. http://dx.doi.org/10.1289/ehp.11022.

Zuer, P.S., 2000. Drugs down the drain: surprisingly little research exists on the potential environmental effects of pharmaceuticals and personal care products. Chem. Eng. News 78, 51–53. http://dx.doi.org/10.1021/cen-v078n015.p051.