Chapter 16

Pharmaceuticals and Personal Care Products: Risks, Challenges, and Solutions

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Additional information is available at the end of the chapter

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Abstract

Pharmaceuticals and personal care products (PPCPs) encompass a large class of chemical contaminants that can originate from human usage and excretions and veterinary applications. These pollutants have captured the attention of scientists, governments, and the public as several studies across the globe reveal their widespread occurrence in low-level concentrations in wastewater and the aquatic environment. Most of the research on PPCPs has been generated from efforts in highly developed countries, primarily North America and Europe, although investigations and reports are emerging from Southeast Asia and China. With the increased concern of potential threats triggered by the occurrence of these chemicals in the environment, environmental risk assessment (ERA) strategies for such compounds have considerably evolved over the past decade. Regulations are in effect or planned in several western nations, however, there is no global standard for conducting ERAs. As the scope of the problem evolves, substantial research will be imperative to address these contaminants and their occurrence in the environment. This chapter will discuss the evolution of the risk associated with the occurrence of PPCPs in the environment, the challenges faced by their existence here, and the colloquy about solutions to address this escalating issue.

Keywords: pharmaceuticals and personal care products (PPCPs), pharmaceuticals, contaminants of emerging concern (CECs), environmental risk assessment (ERA), aquatic environment

1. Introduction

Anthropogenic pollutants enter surface and ground waters via a multitude of processes. Commercial activities such as manufacturing emissions, waste disposal, and accidental releases are a few examples [1]. Other practices include deliberate introduction such as

sewage sludge application to land, groundwater recharge, and consumer activity which involves both the excretion and purposeful disposal of a wide range of naturally occurring and anthropogenic chemicals [1, 2]. During the last few decades, the impact of chemical pollution in the water has focused almost exclusively on the conventional "priority pollutants" [3]. Priority pollutants are a group of chemicals regulated under legislation such as the Clean Water Act (CWA) of 1972 by the United States Environmental Protection Agency (US EPA) and the Water Framework Directive (2000/60/EC) (WFD), an updated version of Council Directive 76/464/EEC, by the Environment Directorate General of the European Commission (DG Environment) for the European Union (EU) [4, 5]. These pollutants are chemicals that have specific effects on organisms, comprised mainly of agricultural and industrial chemicals and their synthesis by-products [4–6]. The prioritized lists of 126 pollutants and 33 substances in the US and EU, respectively, currently include chemicals that were selected primarily because of their toxicity, persistence, and degradability, among other factors [4, 7, 8]. Chemical production rates and the frequency of occurrence in waters was also considered [4, 5].

Pharmaceuticals and personal care products (PPCPs) are among a group of chemicals termed "contaminants of emerging concern" (CECs). CECs are not necessarily new pollutants as they may have been present in the environment for several years, but their presence and significance are only now being evaluated [3]. Due to their medical properties, PPCPs have an inherent biological effect; furthermore, they behave as persistent pollutants because of their continual infusion into the aquatic ecosystem [9–11].

2. Risks

Considering scientific literature dating as far back as the early 1900s, more than 130 million organic and inorganic substances had been indexed by the American Chemical Society in the Chemical Abstracts Service (CAS) Registry, which is updated daily with about 15 thousand new substances [12]. Over eight million chemicals are commercially available, but only 350 thousand are inventoried and/or regulated globally [4, 8, 12–14].

Figure 1 shows that the majority of chemicals in commerce are "industrial" chemicals, a significant percentage of these chemicals fall into the categories of "cosmetics ingredients" and "pharmaceuticals". Collectively, these two categories contain several compounds that are potentially persistent and bioaccumulative [14]. Caffeine, nicotine, and aspirin are a few of the pharmaceutically active compounds that have been known for years to enter the environment [3]. Only more recently has it become evident that drugs and personal care products from a wide spectrum of therapeutic and consumer-use classes exist in the environment in low concentrations [15, 16]. Over 50 million pounds of antibiotics are produced annually in the United States, with approximately 60% for human use and 40% for animal agriculture, therefore, veterinary medicines contribute considerably to PPCP occurrence [17]. In addition to pharmaceuticals, compounds such as synthetic fragrances, detergents, disinfectants, and insect repellents are among the man-made chemicals that are now beginning to accumulate in the natural environment [18].

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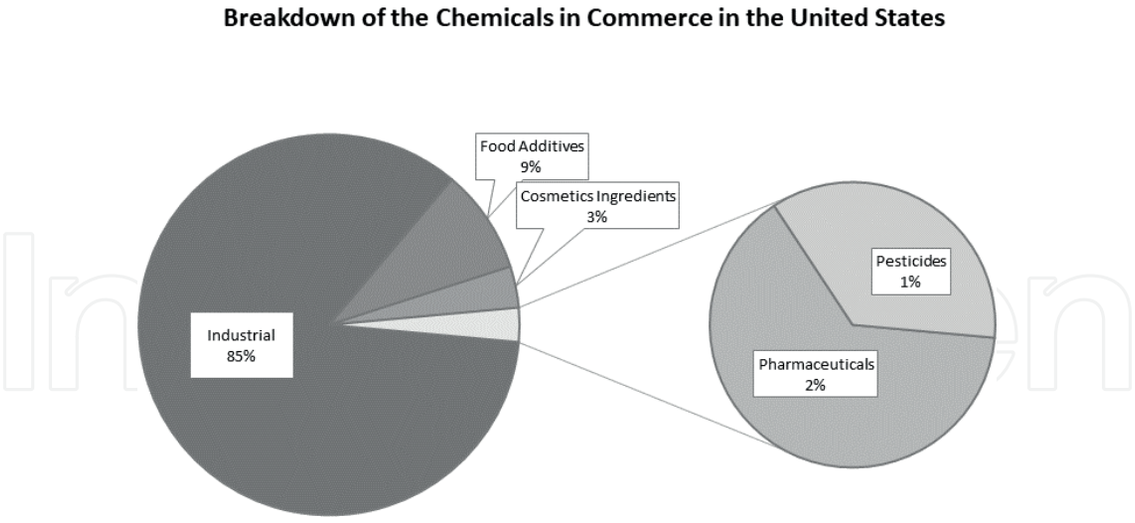

Figure 1. Estimated number and categories of chemicals in commerce registered for use in the United States over the past 30 years. Not all chemicals may be in current use. Similar proportions would be anticipated in other countries. Adapted with permission from [14]. Copyright 2006 American Chemical Society.

Increasing introduction to the marketplace of new pharmaceuticals is adding to the already large array of poorly understood chemical classes that each have distinct modes of biochemical action [1]. In the United States, legislation exists that requires an assessment of potential risk to the environment by new pharmaceutical products. Under this policy, the Food and Drug Administration (US FDA) is required to consider the environmental impacts of manufacture, use, and distribution of human drugs as well as investigational use and approvals of veterinary drugs [19, 20]. The European Commission recently published a Roadmap that acknowledges the Commission's effort toward developing a similar strategy that will address the manufacture, use and disposal of active pharmaceutical ingredients [21].

Figure 2 illustrates the numerous pathways by which antibiotics and other PPCPs are introduced into the environment which can be both point and non-point sources [22, 23]. Municipal sewage, both treated and untreated, is the most likely route for human use drugs to enter the environment. Wastewater treatment processes achieve variable and often incomplete removal of antibiotics [24, 25]. Human pharmaceuticals are excreted from the body in urine and feces as unchanged parent compounds, metabolites or conjugated substances; furthermore, because of their polarity, water solubility and persistence some of these compounds may not be completely eliminated or transformed during sewage treatment [26, 27]. Therefore, residential and commercial healthcare facilities, specifically hospitals, are known contributors of antibiotics to municipal wastewater [2, 19, 28–30]. Additionally, the incorrect disposal of expired or unwanted medicines in the sink, toilet, or in household solid waste that is then taken to landfills contribute to the occurrence of pharmaceuticals in wastewater [31–33]. Another possible pathway begins with the disposal of unwanted illicit drugs, synthesis byproducts, raw products and intermediates into domestic sewage systems by clandestine drug operations [3, 32, 34]. Other probable entries include leakage from pipelines, tanks, waste ponds or landfills, and atmospheric deposition [35].

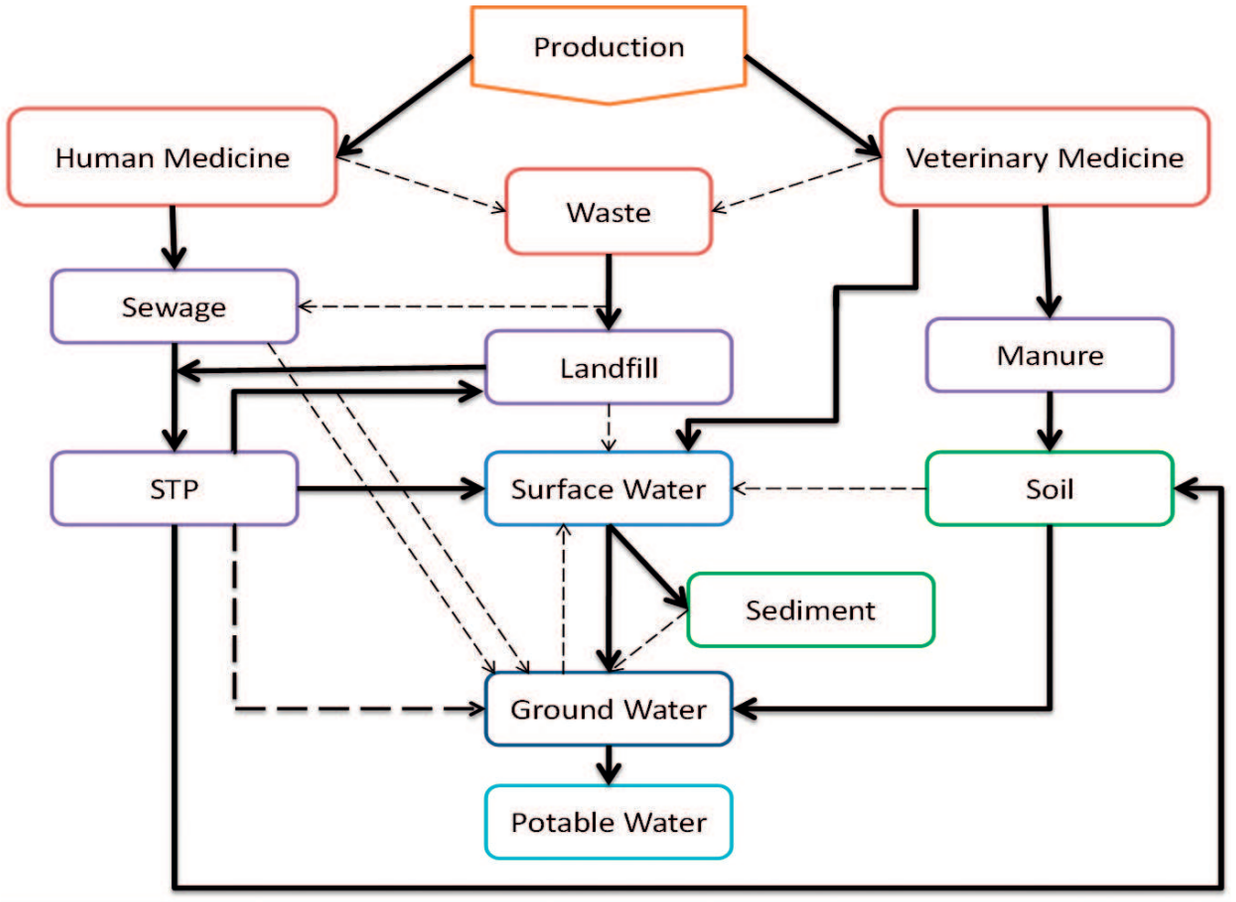

Figure 2. Source, fate, and distribution of PPCPs in the environment.

Veterinary medicines may enter the environment through a number of pathways, with terrestrial runoff from concentrated animal feeding operations (CAFOs) and wind-borne drift of agriculturally-applied antimicrobials to crops being the primary sources [32, 34, 36]. After administration, the substances may be metabolized in the animal which changes their physical, chemical and eco-toxicological properties, but even metabolites may be reconverted to their parent compounds after excretion [37, 38]. Accidental leakage or leaching from animal waste storage can also be a source. Still another major channel by which veterinary antibiotics are released into the environment is through application of manure or slurry to agricultural fields as fertilizer [34, 36, 39].

Dependent upon the chemical properties and structures of PPCPs, several processes can affect the fate and transport of these compounds in the environment. These include, but are not limited to, sorption, biotic transformation, and abiotic transformation [7, 24, 27]. Most PPCPs are water soluble and have a low volatility, although there are few that may strongly adsorb to soils and are somewhat persistent. These characteristics allow them to be easily transported and omnipresent in various aquatic environments [7, 19]. Because PPCPs can be introduced on a continual basis to the aquatic environment, they are ubiquitously present in waters; their removal or transformation by biodegradation, hydrolysis, photolysis, and other processes is continually countered by their replenishment [3].

With concentrations typically ranging from the low parts per trillion (ppt) and parts per billion (ppb) levels, several individual PPCPs or their metabolites from a variety of therapeutic classes (**Table 1**) have been detected in environmental samples from all over the world [3]. More than 80 pharmaceuticals and their metabolites have been detected in almost

Therapeutic class	Examples of generic names	Examples of brand names
Analgesics/non-steroidal anti-inflammatories (NSAIDs)	Acetaminophen (analgesic) Diclofenac Ibuprofen Ketoprofen Naproxen	Tylenol Voltaren Advil Oruvail Naprosyn
Antimicrobials/antibiotics	e.g., sulfonamides, fluoroquinolones	Many
Antiepileptics	Carbamazepine	Tegretal
Antihypertensives (betablockers, beta-adrenergic receptor inhibitors)	Bisoprolol Metoprolol	Concor Lopressor
Antineoplastic	Cyclophosphamide Ifosfamide	Cycloblastin Holoxan
Antiseptics	Triclosan	Irgasan DP 300
Contraceptives	β-Estradiol 17a-Ethinyl estradiol	Diogyn Oradiol
Hormonally active agents Androgens Anti-acne agents adrenocorticosteroids inhalable Steroids Estrogen antagonists	Fluoxymesterone Isotretinoin Tretinoin Prednisone Triamcinolone Fluticasone Tamoxifen	Accutane Retin-A Flovent Nolvadex
β_2-Sympathomimetics (bronchodilators)	Albuterol	Ventolin
Lipid regulators (anti-lipidemics; cholesterol-reducing agents; and their bioactive metabolites)	Clofibrate (active metabolite: clofibric acid) Gemfibrozil	Atromid-S Lopoid
Musks (synthetic)	Nitromusks Polycyclic musks Reduced metabolites of nitromusks	Musk xylene Celestolide Substituted amino nitrobenzenes
Anti-anxiety/hypnotic agents	Diazepam	Valium
Sun screen agents	Methylbenzylidene camphor avobenzene Octyl methoxycinnamate	Eusolex 6300 Parsol A Parsol MOX
X-ray contrast agents	Diatrizoate	Hypaque

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Table 1. Chemical classes (and members) of PPCPs detected in environmental samples.

Chemical class	Location	Concentration range (ng/L)	References
Multiple pharmaceuticals	North America *U.S.*	ND – 72	[51]
	East Asia *China* *Japan* *Korea*	ND – 5911	[52–57]
	Europe *Finland* *Norway* *Portugal* *U.K.*	ND – 126,000	[58–61]
Antimicrobials/antibiotics	North America *U.S.*	90–320	[24, 62]
	East Asia *China* *Korea*	ND – 21,278	[52, 63–72]
	Europe *Finland* *Sweden* *U.K.*	ND – 3052	[61, 73, 74]
Hormonally active agents	North America *Canada*	0.2–96	[75]
	East Asia *China* *Japan* *Korea*	ND – 253.8	[52, 53, 76–83]
	Europe *Portugal*	ND – 25	[60]
Antiepileptics	East Asia *China*	230–1110	[84]
Antiseptics	Europe *Norway*	160–480	[59]
Musks (synthetic)	North America *U.S.*	495–3730	[85]
	East Asia *China* *Japan*	<4–2050	[86–89]
	Europe *Portugal*	1–889	[60]
Sun screen agents	East Asia *China*	21–1287	[90]
	Europe *U.K.*	<2–6325	[61]

ND: not detected.

Table 2. Representation of the global occurrence of PPCPs in WWTP effluents.

every aquatic environment in North America and Europe surface waters [33, 40–44]. A national reconnaissance study on the occurrence of pharmaceuticals, hormones, and other organic wastewater contaminants (OWCs) in United States streams found that one or more OWCs were found in 80% of the stream samples, with 82 compounds of the 95 analyzed for detected during the study [40]. In another project, source water, finished drinking water, and distribution system (tap) water from 19 United States drinking-water treatment (DWT) plants was analyzed for 51 pharmaceuticals and pharmaceutical metabolites. Targeted compounds were detected most frequently in source water with at least one compound being detected in all 19 source waters; they were also found in approximately 89% of finished drinking waters and 87% of distribution systems [45]. In yet another study conducted by the United States Geological Survey (USGS) and the Centers for Disease Control and Prevention (CDC), several compounds that were frequently detected in samples of stream water and raw-water supplies were also detected in samples collected throughout the DWT facility, indicating that these compounds resist removal through conventional water-treatment processes [46].

PPCPS have been reported in hospital wastewaters, wastewater treatment plant (WWTP) effluents, WWTP biosolids, soil, surface waters, groundwaters, sediments, biota, and drinking water [33, 40, 47–50]. Since WWTPs are considered a major source of these pollutants, several investigations of environmental loads of PPCPs examine WWTP effluents (**Table 2**) [28]. There is less documented research of PPCP occurrence in coastal or marine ecosystems. A wide distribution of clofibric acid, caffeine, and DEET in concentrations up to 19, 16, and 1.1 ng/L, respectively, was measured throughout the North Sea and along European coasts [91]. Sulfamethoxazole, carbamazepine, tamoxifen, and indomethacin were discovered in China in the Yangtze River Estuary at levels ranging from 4.2 to 159 ng/L [92]. In the United States, sulfamethoxazole was detected in at least four bays ranging in concentrations from 4.8 to 65 ng/L, while trimethoprim was found at a maximum concentration of 72.2 ng/L in Jamaica Bay, New York and 2.1 ng/L off the coast of California [93–95].

3. Challenges

An ecological or environmental risk assessment (ERA) is defined as the means of evaluating the probabilities and magnitudes of adverse effects to human health or ecological receptors, directly or indirectly, as a result of exposure to pollutants and other anthropogenic activities [96]. ERAs are employed to estimate any potential harm that could emerge from environmental contaminants, with a known degree of certainty, using scientific methodologies. The innovation of ERAs has become necessary as improved research reveals chemicals in the environment at levels that are potentially toxic to humans and/or our valuable natural resources [11]. The specific methodology for carrying out an ERA may vary depending on the chemical being assessed, but the core principles and the key stages of the process are fundamentally the same in each case (**Figure 3**).

ERAs can be used to predict the likelihood of future adverse effects, prospective, or to evaluate the likelihood that effects are caused by past exposure to stressors, retrospective [97].

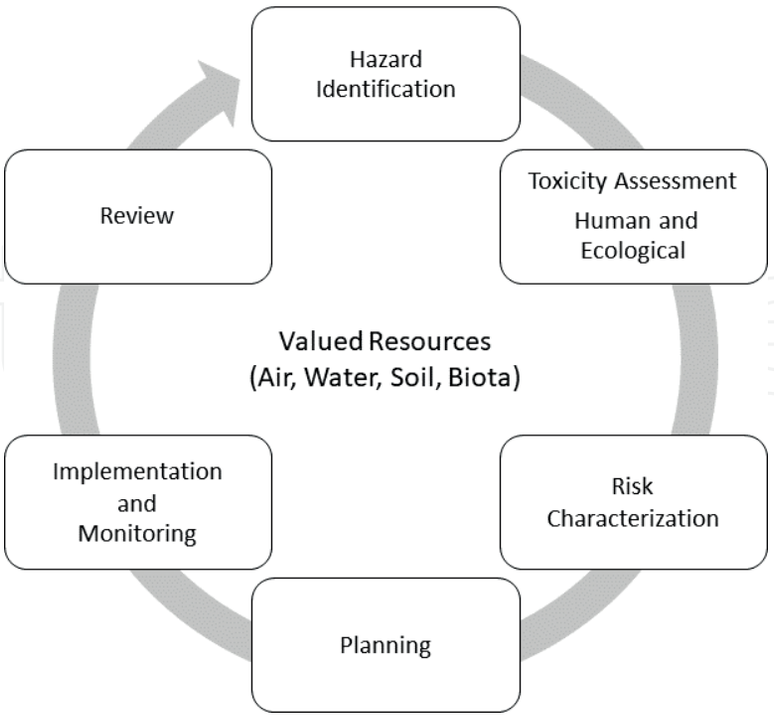

Figure 3. Flow chart for a general ERA process.

Examples of prospective uses include establishing drinking water goals or wastewater discharge limits. Federal and state regulatory programs also utilize prospective ERAs to reduce toxic tort liabilities and improved public relations. The government may use retrospective ERAs as a decision making tool, for example, when determining Comprehensive Environmental Response, Compensation, and Liability Act – CERCLA or Superfund – projects [11, 98, 99]. In many cases, both approaches are included in a single risk assessment. Combined retrospective and prospective risk assessments tend to be beneficial in situations where ecosystems have a history of previous impacts and/or the potential for future effects from multiple chemical, physical, or biological stressors [97].

Although the concentrations of these PPCPs generally range from the low ppt- to ppb-levels, there is increasing evidence that PPCPs may have significant impacts on natural biotic communities. There are two major concerns with the presence of low-level concentrations of pharmaceuticals in the aquatic environment: the potential toxicity of these compounds to aquatic organisms and the exposure to humans through drinking water [23, 31, 100]. Some PPCPs, such as antidepressants, birth control drugs, and other medications have been detected in fish tissue and were identified as the cause of neurological, biochemical, and physiological changes [100, 101]. Because pharmaceuticals are designed to target specific metabolic and molecular pathways in humans and animals, it is assumed that they may affect the same pathways in animals with identical or similar target organs, tissues, cells or biomolecules. Certain receptors in lower vertebrates resemble those in humans, while others are different or lacking; in these cases, dissimilar modes of actions may occur in the lower animals [102, 103].

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Acute toxicity studies typically show that the concentrations of PPCPs to produce effects such as death in half of the exposed organisms (EC_{50}) range of 25 to ≥500 mg/L; one particular example found that the chronic toxicity or median lethal dose (LC_{50}) of furazolidone, which is largely used in medicated fish feed, at 40 mg/kg in the mosquito larvae, *Culex pipiens* [31]. In a study that tested the effects of tylosin and oxytetracycline on three species of soil fauna, neither of the substances had any effect at environmentally relevant concentrations; however, as soil ecosystems are built up by complex and linked food webs, the study concluded that it is not yet possible to exclude that indirect effects on soil fauna driven by changes in the microbial community and alteration of the decomposer system may occur [38].

Since antibiotics are specifically designed to control bacteria in plants and animals of economic interest, this obviously makes them hazardous to bacteria and other micro-organisms in the environment. There is growing concern that low level concentrations of antibiotics in the environment contribute to the emergence of strains of disease-causing bacteria that are resistant to even high doses of these drugs [23]. Current evidence supports that feeding low doses of antibiotics to livestock in an attempt to improve production efficiency has produced resistant strains of certain microorganisms. Bacterial strains evolve and become resistant to multiple antibiotics if they are continually exposed to low doses of antibiotics in the environment since the three mechanisms of gene transfer – conjugation, transduction, and transformation – all occur in the aquatic environment [104].

Streams and rivers that receive low levels of chronic antibiotic exposure can be viewed as a source and a reservoir of resistant genes as well as a means for their dispersion. In addition, if non-target organisms, such as cyanobacteria, are over-exposed to antibiotics, they may be negatively affected, which will disturb the aquatic food chain [6]. Increased bacterial resistance has been seen in waste effluent from hospitals and pharmaceutical plants indicating that the ultimate disposal of antibiotics may be a serious public health issue [23, 29]. Furthermore, individual compounds may interact synergistically or antagonistically with other chemicals present in the environment [6, 15, 16].

4. Solutions

The production and usage of most pharmaceutical and personal care products will either stabilize or increase. It is probable that the environmental load of these chemicals will follow the same trend. Although remedying this issue seems unfeasible, it cannot be regarded as a terminal quandary. Instead, tactics should be implemented to minimize their impact on the environment.

There are four major factors that determine the concentrations of drug residues reported in environmental samples: (1) frequency of use, (2) excretion of un-metabolized drugs, (3) persistence on biodegradation, and (4) the analytical method used [105]. Due to the consequential concern resulting from the detection of PPCPs in the aquatic environment, sensitive analytical techniques have been developed to investigate this new class of environmental pollutants; techniques that will have to continue to evolve in order to improve method accuracy and sensitivity [105]. Likewise, methodology must be designed to analyze compounds in combination [93].

Perhaps reform should begin with production of PPCPs, specifically pharmaceuticals. Medicinal drugs are intended to be metabolized by organisms, yet, approximately 20% or more of these compounds are excreted in their parent form or as metabolites [26, 105]. After excretion, these compounds could possibly mix with other chemicals already present in the environment or biodegradation and transformation may occur: circumstances which could produce other metabolites or by-products, conceivably leading to a substance that may be far more toxic than the parent compounds [105]. Production of pharmaceuticals that are fully absorbed or completely metabolized by the organism would be ideal; this, however, may be impractical. The responsibility then shifts from the pharmaceutical industry to the medical industry. By purposefully managing prescriptions with deep scrutiny, doctors may begin to begin to alleviate the issue through reduction of input [26].

Effective regulation of PPCPs is implausible without a global colloquy giving great consideration to the creation and installation of a well-developed, universal ERA procedure for these contaminants. Existing protocols must be expanded to adapt to the gravity of the potential impacts of these unique compounds in the environment. Implementation of a retrospective aspect to the protocol may also be necessary in the near future [93].

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