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

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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

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## 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].

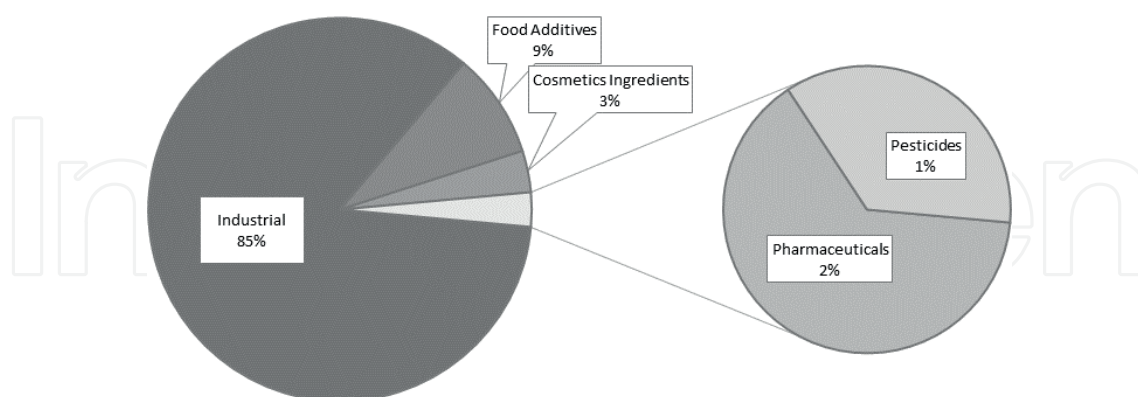
Pharmaceuticals and personal care products (PPCPs) are among a group of chemicals termed “contaminants of emerging concern” (CECs). CECs are not necessarily new pollutants as they may have been present in the environment for several years, but their presence and significance are only now being evaluated [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].

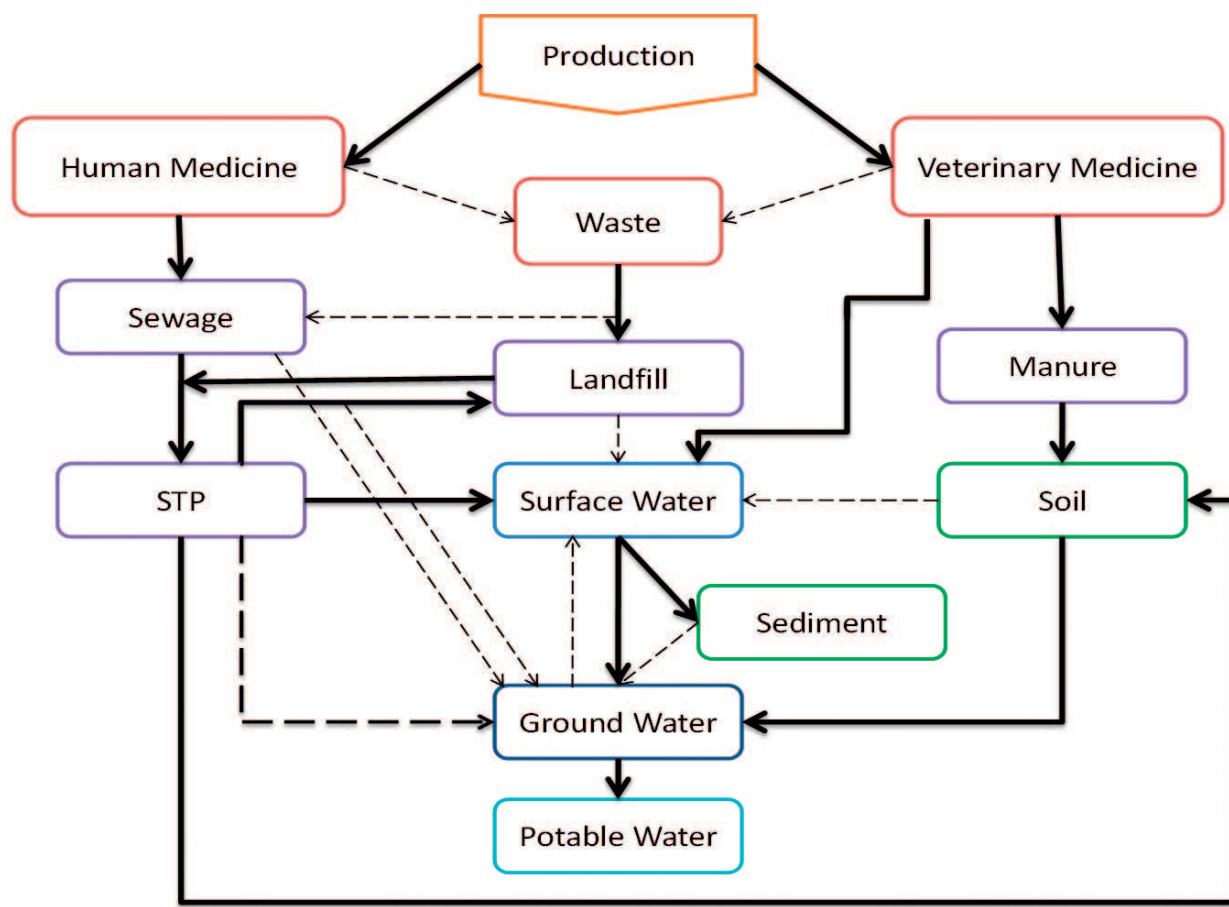
### Breakdown of the Chemicals in Commerce in the United States



**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	$\beta$ -Estradiol 17 $\alpha$ -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
$\beta_2$ -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

Adapted with permission from [3]. Copyright 2001 American Chemical Society.

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



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

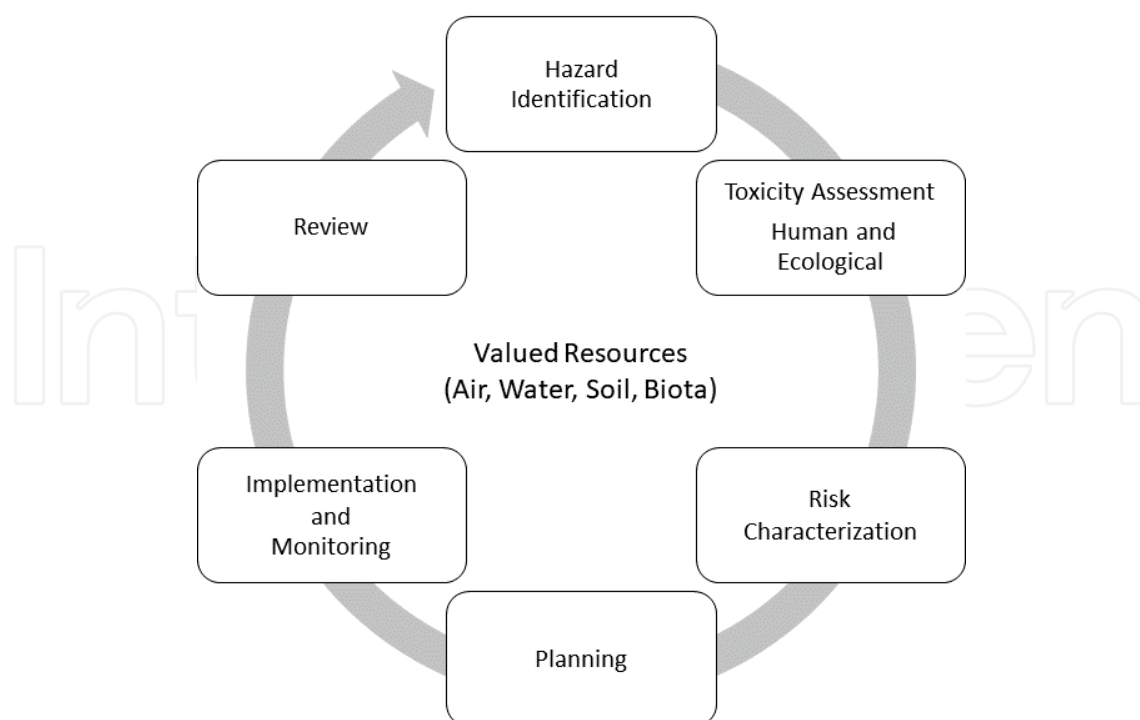
PPCPS have been reported in hospital wastewaters, wastewater treatment plant (WWTP) effluents, WWTP biosolids, soil, surface waters, groundwaters, sediments, biota, and drinking water [33, 40, 47–50]. Since WWTPs are considered a major source of these pollutants, several investigations of environmental 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].

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  $\geq 500$  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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## References

- [1] Daughton CG. Pharmaceuticals and personal care products (PPCPs) as environmental pollutants: Pollution from personal actions. In: California Bay-Delta Authority Contaminant Stressor Workshop; Sacramento, CA; 2004
- [2] Daughton CG. Chemicals from the practice of healthcare: Challenges and unknowns posed by residues in the environment. *Environmental Toxicology and Chemistry*. 2009;28(12):2490-2494
- [3] Daughton CG. Pharmaceuticals and personal care products in the environment: Overarching issues and overview. In: *Pharmaceuticals and Care Products in the Environment*. Washington, DC: American Chemical Society; 2001. p. 2-38
- [4] Clean Water Act of 1972. 33 U.S.C. § 1251 et seq. 2002
- [5] European Union. EUR-Lex [Internet]. [Updated: 2017]. Available from: <http://eur-lex.europa.eu/oj/direct-access.html> [Accessed: 19 July 2017]

- [6] Jones OAH, Voulvoulis N, Lester JN. Potential impact of pharmaceuticals on environmental health. *Bulletin of the World Health Organization*. 2003;**81**(10):768-769
- [7] Ellis JB. Pharmaceutical and personal care products (PPCPs) in urban waters. *Environmental Pollution*. 2006;**144**:184-189
- [8] Lee GF, Jones-Lee A. Unrecognized environmental pollutants. In: *Water Encyclopedia: Surface and Agricultural Water*. Hoboken, NJ: Wiley; 2005. p. 371-373
- [9] Harada A, Komori K, Nakada N, Kitamura K, Suzuki Y. Biological effects of PPCPs on aquatic lives and evaluation of river waters affected by different wastewater treatment levels. *Water Science and Technology*. 2008;**58**(8):1541-1546
- [10] Ferrari B, Mons R, Vollat B, Frayssé B, Paxéaus N, Giudice RL, et al. Environmental risk assessment of six human pharmaceuticals: Are the current environmental risk assessment procedures sufficient for the protection of the aquatic environment? *Environmental Toxicology and Chemistry*. 2004;**23**(5):1344-1354
- [11] Van der Oost R, Beyer J, Vermeulen NPE. Fish bioaccumulation and biomarkers in environmental risk assessment: A review. *Environmental Toxicology and Pharmacology*. 2003;**13**(2):57-149
- [12] Chemical Abstracts Service. CAS Content. Retrieved from CAS | A Division of the American Chemical Society; 2017, July 17. <http://www.cas.org/content>
- [13] Hooper K. Lessons from the PBDEs—The value of monitoring community body burdens using breast milk. In: 6th Biennial State of the Estuary Conference; Oakland, CA; 2003
- [14] Muir DCG, Howard PH. Are there other persistent organic pollutants? A challenge for environmental chemists. *Environmental Science & Technology*. 2006;**40**(23):7157-7166
- [15] Jones OAH, Voulvoulis N, Lester JN. Human pharmaceuticals in the aquatic environment a review. *Environmental Technology*. 2001;**22**(12):1383-1394
- [16] Hansen H, De Rosa CT, Pohl H, Fay M, Mumtaz MM. Public health challenges posed by chemical mixtures. *Environmental Health Perspectives*. 1998;**106**(Suppl 6):1271-1280
- [17] Levy SB. The challenge of antibiotic resistance. *Scientific American*. 1998;**278**(3):32-39
- [18] Nilsen EB, Rosenbauer RR, Furlong ET, Burkhardt MR, Werner SL, Greaser L, et al. Pharmaceuticals, Personal Care Products and Anthropogenic Waste Indicators Detected in Streambed Sediments of the Lower Columbia River and Selected Tributaries. National Ground Water Association. 2007; Paper 4483, p. 15
- [19] Breton R, Boxall A. Pharmaceuticals and personal care products in the environment: Regulatory drivers and research needs. *QSAR & Combinatorial Science*. 2003;**22**(3): 399-409
- [20] National Environmental Policy Act of 1969. 42 U.S.C. § 4332 et seq. 1994
- [21] European Commission (EC), Evaluation Road map, available at: [http://ec.europa.eu/smart-regulation/roadmaps/docs/2016\\_move\\_059\\_ev\\_accident\\_investigation\\_en.pdf](http://ec.europa.eu/smart-regulation/roadmaps/docs/2016_move_059_ev_accident_investigation_en.pdf)

- [22] Díaz-Cruz MS. Environmental behavior and analysis of veterinary and human drugs in soils, sediments and sludge. *TrAC Trends in Analytical Chemistry*. 2003;**22**(6):340-351
- [23] Yang S, Carlson K. Routine monitoring of antibiotics in water and wastewater with a radioimmunoassay technique. *Water Research*. 2004;**38**(14-15):3155-3166
- [24] Brown KD, Kulis J, Thomson B, Chapman TH, Mawhinney DB. Occurrence of antibiotics in hospital, residential, and dairy effluent, municipal wastewater, and the Rio Grande in New Mexico. *Science of the Total Environment*. 2006;**366**(2-3):772-783
- [25] Deblonde T, Cossu-Leguille C, Hartemann P. Emerging pollutants in wastewater: A review of the literature. *International Journal of Hygiene and Environmental Health*. 2001;**214**:442-448
- [26] Kümmerer K, Al-Ahmad A. Estimation of the cancer risk in humans resulting from the presence of cyclophosphamide and ifosfamide in surface water. *Environmental Science and Pollution Research*. 2010;**17**:486-496
- [27] Monteiro SC, Boxall ABA. Occurrence and fate of human pharmaceuticals in the environment. In: *Reviews of Environmental Contamination and Toxicology*. New York, NY: Springer New York; 2010
- [28] Liu J, Wong M. Pharmaceuticals and personal care products (PPCPs): A review on environmental contamination in China. *Environment International*. 2013;**59**:208-224
- [29] Guardabassi L, Petersen A, Olsen JE, Dalsgaard A. Antibiotic resistance in *Acinetobacter* spp. isolated from sewers receiving waste effluent from a hospital and a pharmaceutical plant. *Applied and Environmental Microbiology*. 1998;**64**(9):3499-3502
- [30] Hartmann A, Alder AC, Koller T, Widmer RM. Identification of fluoroquinolone antibiotics as the main source of umuC genotoxicity in native hospital wastewater. *Environmental Toxicology and Chemistry*. 1998;**17**(3):377-382
- [31] Halling-Sørensen B, Nielsen SN, Lanzky PF, Ingerslev F, Lützhøft HCH, Jørgensen SE. Occurrence, fate and effects of pharmaceutical substances in the environment—A review. *Chemosphere*. 1998;**36**(2):357-393
- [32] Hirsch R, Ternes T, Haberer K, Kratz KL. Occurrence of antibiotics in the aquatic environment. *The Science of the Total Environment*. 1999;**225**(1-2):109-118
- [33] Bound JP, Voulvoulis N. Household disposal of pharmaceuticals as a pathway for aquatic contamination in the United Kingdom. *Environmental Health Perspectives*. 2005;**113**(12):1705
- [34] Campagnolo ER, Johnson KR, Karpatis A, Rubin CS, Kolpin DW, Meyer MT, et al. Antimicrobial residues in animal waste and water resources proximal to large-scale swine and poultry feeding operations. *The Science of the Total Environment*. 2002;**299**(1-3): 89-95
- [35] Pepper IL, Gerba CP, Brusseau ML, editors. *Pollution Science*. San Diego, CA: Academic Press; 1996



- [36] Howard P, Muir DCG. Identifying new persistent and bioaccumulative organics among chemicals in commerce II: Pharmaceuticals. *Environmental Science & Technology*. 2011;**45**:6938-6946
- [37] Gibson GG, Skett P. *Introduction to Drug Metabolism*. Cheltenham, Great Britain: Nelson Thornes; 2001
- [38] Baguer AJ, Jensen J, Krogh PH. Effects of the antibiotics oxytetracycline and tylosin on soil fauna. *Chemosphere*. 2000;**40**(7):751-757
- [39] Kim SC, Davis JG, Truman CC, Ascough JC II, Carlson K. Simulated rainfall study for transport of veterinary antibiotics-mass balance analysis. *Journal of Hazardous Materials*. 2010;**175**(1-3):836-843
- [40] Kolpin DW, Furlong ET, Meyer MT, Thurman EM, Zaugg SD, Barber LB, et al. Pharmaceuticals, hormones, and other organic wastewater contaminants in US streams, 1999-2000: A national reconnaissance. *Environmental Science & Technology*. 2002;**36**(6):1202-1211
- [41] Ternes TA. Occurrence of drugs in German sewage treatment plants and rivers. *Water Research*. 1998;**32**(11):3245-3260
- [42] Wiegel S, Aulinger A, Brockmeyer R, Harms H, Löffler J, Reincke H, et al. Pharmaceuticals in the river Elbe and its tributaries. *Chemosphere*. 2004;**57**(2):107-126
- [43] Sacher F, Lange FT, Brauch H-J, Blankenhorn I. Pharmaceuticals in groundwaters: Analytical methods and results of a monitoring program in Baden-Württemberg, Germany. *Journal of Chromatography A*. 2001;**938**(1-2):199-210
- [44] Brown AFM, Dortch Q, Van Dolah FM, Leighfield TA, Morrison W, Thessen AE, et al. Effect of salinity on the distribution, growth, and toxicity of *Karenia* spp. *Harmful Algae*. 2006;**5**(2):199-212
- [45] Benotti MJ, Trenholm RA, Vanderford BJ, Holady JC, Stanford BD, Snyder SA. Pharmaceuticals and endocrine disrupting compounds in U.S. drinking water. *Environmental Science & Technology*. 2008;**43**(3):597-603
- [46] Stackelberg PE, Furlong ET, Meyer MT, Zaugg SD, Henderson AK, Reissman DB. Persistence of pharmaceutical compounds and other organic wastewater contaminants in a conventional drinking-water-treatment plant. *Science of the Total Environment*. 2004;**329**(1-3):99-113
- [47] Watkinson AJ, Murby EJ, Kolpin DW, Costanzo SD. The occurrence of antibiotics in an urban watershed: From wastewater to drinking water. *Science of the Total Environment*. 2009;**407**(8):2711-2723
- [48] Kümmerer K, Henninger A. Promoting resistance by the emission of antibiotics from hospitals and households into effluent. *Clinical Microbiology and Infection*. 2003;**9**(12):1203-1214
- [49] Costanzo SD, Murby J, Bates J. Ecosystem response to antibiotics entering the aquatic environment. *Marine Pollution Bulletin*. 2005;**51**(1-4):218-223



- [50] Kim SC, Carlson K. Quantification of human and veterinary antibiotics in water and sediment using SPE/LC/MS/MS. *Analytical and Bioanalytical Chemistry*. 2007;**387**(4): 1301-1315
- [51] Thomas PM, Foster GD. Tracking acidic pharmaceuticals, caffeine, and triclosan through the wastewater treatment process. *Environmental Toxicology and Chemistry*. 2005;**24**(1):25-30
- [52] Behera SK, Kim HW, Oh JE, Park HS. Occurrence and removal of antibiotics, hormones and several other pharmaceuticals in wastewater treatment plants of the largest industrial city of Korea. *Science of the Total Environment*. 2011;**409**(20):4351-4360
- [53] Nakada N, Tanishima T, Shinohara H, Kiri K, Takadaet H. Pharmaceutical chemicals and endocrine disrupters in municipal wastewater in Tokyo and their removal during activated sludge treatment. *Water Research*. 2006;**40**(17):3297-3303
- [54] Zhao JL, Ying GG, Liu YS, Chen F, Yang JF, Wang L, et al. Occurrence and a screening-level risk assessment of human pharmaceuticals in the Pearl River system, South China. *Environmental Toxicology and Chemistry*. 2010;**29**(6):1377-1384
- [55] Zhou HD, Wu CY, Huang X, Gao MJ, Wen XH, Tsuno H, et al. Occurrence of selected pharmaceuticals and caffeine in sewage treatment plants and receiving rivers in Beijing, China. *Water Environment Research*. 2010;**82**(11):2239-2248
- [56] Sui Q, Huang J, Deng SB, Yu G, Fan Q. Occurrence and removal of pharmaceuticals, caffeine and DEET in wastewater treatment plants of Beijing, China. *Water Research*. 2010;**44**(2):417-426
- [57] Sui Q, Huang J, Deng SB, Chen WW, Yu G. Seasonal variation in the occurrence and removal of pharmaceuticals and personal care products in different biological wastewater treatment processes. *Environmental Science & Technology*. 2011;**45**(8):3341-3348
- [58] Vieno NM, Tuhkanen T, Kronberg L. Analysis of neutral and basic pharmaceuticals in sewage treatment plants and in recipient rivers using solid phase extraction and liquid chromatography-tandem mass spectrometry detection. *Journal of Chromatography A*. 2006;**1134**(1-2):101-111
- [59] Weigel S, Berger U, Jensen E, Kallenborn R, Thoresen H, Hühnerfuss H. Determination of selected pharmaceuticals and caffeine in sewage and seawater from Tromsø/Norway with emphasis on ibuprofen and its metabolites. *Chemosphere*. 2004;**56**(6):583-592
- [60] Salgado R, Noronha JP, Oehmen A, Carvalho G, Reis MAM. Analysis of 65 pharmaceuticals and personal care products in 5 wastewater treatment plants in Portugal using a simplified analytical methodology. *Water Science & Technology*. 2010;**62**(12): 2862-2871
- [61] Kasprzyk-Hordern B, Dinsdale RM, Guwy AJ. The removal of pharmaceuticals, personal care products, endocrine disruptors and illicit drugs during wastewater treatment and its impact on the quality of receiving waters. *Water Research*. 2009;**43**(2):363-380

- [62] Yang SW, Carlson K. Evolution of antibiotic occurrence in a river through pristine, urban and agricultural landscapes. *Water Research*. 2003;**37**(19):4645-4656
- [63] Peng XZ, Wang ZD, Kuang WX, Tan JH, Li K. A preliminary study on the occurrence and behavior of sulfonamides, ofloxacin and chloramphenicol antimicrobials in wastewaters of two sewage treatment plants in Guangzhou, China. *Science of the Total Environment*. 2006;**371**(1-3):314-322
- [64] Peng XZ, Tan JH, Tang CM, Yu YY, Wang ZD. Multiresidue determination of fluoroquinolone, sulfonamide, trimethoprim, and chloramphenicol antibiotics in urban waters in China. *Environmental Toxicology and Chemistry*. 2008;**27**(1):73-79
- [65] Minh TB, Leung HW, Loi IH, Chan WH, So MK, Mao JQ, et al. Antibiotics in the Hong Kong metropolitan area: Ubiquitous distribution and fate in Victoria Harbour. *Marine Pollution Bulletin*. 2009;**58**(7):1052-1062
- [66] Li B, Zhang T. Mass flows and removal of antibiotics in two municipal wastewater treatment plants. *Chemosphere*. 2001;**83**(9):1284-1289
- [67] Gulkowska A, Leung HW, So MK, Taniyasu S, Yamashita N, Yeung WYL, et al. Removal of antibiotics from wastewater by sewage treatment facilities in Hong Kong and Shenzhen, China. *Water Research*. 2008;**42**(1-2):395-403
- [68] Tong CL, Zhuo XJ, Guo Y. Occurrence and risk assessment of four typical fluoroquinolone antibiotics in raw and treated sewage and in receiving waters in Hangzhou, China. *Journal of Agricultural and Food Chemistry*. 2001;**59**(13):7303-7309
- [69] Gao LH, Shi YL, Li WH, Niu HY, Liu JM, Cai YQ. Occurrence of antibiotics in eight sewage treatment plants in Beijing, China. *Chemosphere*. 2012;**86**(6):665-671
- [70] Chang H, Hu JY, Wang LZ, Shao B. Occurrence of sulfonamide antibiotics in sewage treatment plants. *Chinese Science Bulletin*. 2008;**53**(4):514-520
- [71] Xiao Y, Chang H, Jia A, Hu JY. Trace analysis of quinolone and fluoroquinolone antibiotics from wastewaters by liquid chromatography-electrospray tandem mass spectrometry. *Journal of Chromatography A*. 2008;**1214**(1-2):100-108
- [72] Zhao JL, Ying GG, Liu YS, Chen F, Yang JF, Wang L. Occurrence and risks of triclosan and triclocarban in the Pearl River system, South China: From source to the receiving environment. *Journal of Hazardous Materials*. 2010;**179**(1-3):215-222
- [73] Vieno NM, Tuhkanen T, Kronberg L. Elimination of pharmaceuticals in sewage treatment plants in Finland. *Water Research*. 2007;**41**(5):1001-1012
- [74] Lindberg RH, Wennberg P, Johansson MI, Tysklind M, Andersson BAV. Screening of human antibiotic substances and determination of weekly mass flows in five sewage treatment plants in Sweden. *Environmental Science & Technology*. 2005;**39**(10):3421-3429
- [75] Servos MR, Bennie DT, Burnison BK, Jurkovic A, McInnis R, Neheli T, et al. Distribution of estrogens, 17 $\beta$ -estradiol and estrone in Canadian municipal wastewater treatment plants. *Science of the Total Environment*. 2005;**336**(1-3):155-170

- [76] Liu S, Ying GG, Zhao JL, Zhou LJ, Yang B, Chen ZF, et al. Occurrence and fate of androgens, estrogens, glucocorticoids and progestagens in two different types of municipal wastewater treatment plants. *Journal of Environmental Monitoring*. 2012;**14**(2):482-491
- [77] Liu S, Ying GG, Zhao JL, Chen F, Yang B, Zhou LJ, et al. Trace analysis of 28 steroids in surface water, wastewater and sludge samples by rapid resolution liquid chromatography-electrospray ionization tandem mass spectrometry. *Journal of Chromatography A*. 2011;**1218**(10):1367-1378
- [78] Jin SW, Yang FX, Liao T, Hui Y, Xu Y. Seasonal variations of estrogenic compounds and their estrogenicities in influent and effluent from a municipal sewage treatment plant in China. *Environmental Toxicology and Chemistry*. 2008;**27**(1):146-153
- [79] Zhou YQ, Zha JM, Wang ZJ. Occurrence and fate of steroid estrogens in the largest wastewater treatment plant in Beijing, China. *Environmental Monitoring and Assessment*. 2011;**184**(11):6799-6813
- [80] Zhou HD, Huang X, Wang XL, Zhi XH, Yang CD, Wen XH, et al. Behaviour of selected endocrine-disrupting chemicals in three sewage treatment plants of Beijing, China. *Environmental Monitoring and Assessment*. 2009;**161**(1-4):107-121
- [81] Chang H, Wan Y, Wu SM, Fan ZL, Hu JY. Occurrence of androgens and progestogens in wastewater treatment plants and receiving river waters: Comparison to estrogens. *Water Research*. 2011;**45**(2):732-740
- [82] Chang H, Hu JY, Shao B. Occurrence of natural and synthetic glucocorticoids in sewage treatment plants and receiving river waters. *Environmental Science & Technology*. 2007;**41**(10):3462-3468
- [83] Wang YQ, Hu W, Cao ZH, Fu XQ, Zhu T. Occurrence of endocrine-disrupting compounds in reclaimed water from Tianjin, China. *Analytical and Bioanalytical Chemistry*. 2005;**383**(5):857-863
- [84] Zhou XF, Dai CM, Zhang YL, Surampalli RY, Zhang TC. A preliminary study on the occurrence and behavior of carbamazepine (CBZ) in aquatic environment of Yangtze River Delta, China. *Environmental Monitoring and Assessment*. 2011;**173**(1-4):45-53
- [85] Reiner JL, Berset JD, Kannan K. Mass flow of polycyclic musks in two wastewater treatment plants. *Archives of Environmental Contamination and Toxicology*. 2007;**52**(4):451-457
- [86] Zeng XY, Sheng GY, Gui HY, Chen DH, Shao WL, Fu JM. Preliminary study on the occurrence and distribution of polycyclic musks in a wastewater treatment plant in Guangdong, China. *Chemosphere*. 2007;**69**(8):1305-1311
- [87] Zhang XL, Yao Y, Zeng XY, Qian GR, Guo YW, Wu MH, et al. Synthetic musks in the aquatic environment and personal care products in Shanghai, China. *Chemosphere*. 2008;**72**(10):1553-1558

- [88] Zhou HD, Huang X, Gao MJ, Wang XL, Wen XH. Distribution and elimination of polycyclic musks in three sewage treatment plants of Beijing, China. *Journal of Environmental Sciences*. 2009;**21**(5):561-567
- [89] Nakata H, Shinohara R. Concentration of benzotriazole UV stabilizers and polycyclic musks in wastewater treatment plant samples in Japan. In: *Interdisciplinary Studies on Environmental Chemistry—Environmental Specimen Bank*. Setagaya, Tokyo: Terrapub; 2010. p. 51-59
- [90] Li WH, Ma YM, Guo CS, Hu W, Liu KM, Wang YQ, et al. Occurrence and behavior of four of the most used sunscreen UV filters in a wastewater reclamation plant. *Water Research*. 2007;**41**(15):3506-3512
- [91] Weigel S, Bester K, Hühnerfuss H. 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. *Journal of Chromatography A*. 2001;**912**(1):151-161
- [92] Yang Y, Fu J, Peng H, Hou L, Liu M, Zhou JL. Occurrence and phase distribution of selected pharmaceuticals in the Yangtze Estuary and its coastal zone. *Journal of Hazardous Materials*. 2011;**190**(1):588-596
- [93] Hoyett Z, Owens MA, Clark CJ II, Abazinge A. A comparative evaluation of environmental risk assessment strategies for pharmaceuticals and personal care products. *Ocean & Coastal Management*. 2016;**127**:74-80
- [94] Benotti MJ, Brownawell BJ. Distributions of pharmaceuticals in an urban estuary during both dry- and wet-weather conditions. *Environmental Science & Technology*. 2007;**41**(16):5795-5802
- [95] Vidal-Dorsch DE, Bay SM, Maruya K, Snyder SA, Trenholm RA, Vanderford BJ. Contaminants of emerging concern in municipal wastewater effluents and marine receiving water. *Environmental Toxicology and Chemistry*. 2012;**31**(12):1-9
- [96] United States Environmental Protection Agency. *Methods for Measuring the Acute Toxicity of Effluents and Receiving Waters to Freshwater and Marine Organisms*. Washington, DC: EPA/600/4-90/027F; 1991
- [97] United States Environmental Protection Agency. *Ecological Effects Test Guidelines; OPPTS 850.1025 Oyster Acute Toxicity Test (Shell Deposition)*. Washington, DC: EPA 712-C-96-115; 1996
- [98] Suter GW. *Ecological Risk Assessment*. Boca Raton, FL: CRC Press; 2007
- [99] Comprehensive Environmental Response Compensation and Liability Act of 1980. 42 U.S.C. § 9601 et seq. (1986)
- [100] Daughton CG, Ternes TA. Pharmaceuticals and personal care products in the environment: Agents of subtle change? *Environmental Health Perspectives*. 1999;**107**(Suppl 3):907-938

- [101] Krock B, Pitcher GC, Ntuli J, Cembella AD. Confirmed identification of gymnodimine in oysters from the west coast of South Africa by liquid chromatography-tandem mass spectrometry. *African Journal of Marine Science*. 2009;**31**(1):113-118
- [102] Sumpter JP, Johnson AC. Lessons from endocrine disruption and their application to other issues concerning trace organics in the aquatic environment. *Environmental Science & Technology*. 2005;**39**(12):4321-4332
- [103] Fent K, Weston AA, Caminada D. Ecotoxicology of human pharmaceuticals. *Aquatic Toxicology*. 2006;**76**(2):122-159
- [104] Migliore L, Brambilla G, Cozzolino S, Gaudio L. Effect on plants of sulphadimethoxine used in intensive farming (*Panicum miliaceum*, *Pisum sativum* and *Zea mays*). *Agriculture, Ecosystems & Environment*. 1995;**52**:103-110
- [105] Kostopoulou M, Nikolaou A. Analytical problems and the need for sample preparation in the determination of pharmaceuticals and their metabolites in aqueous environmental matrices. *Trends in Analytical Chemistry*. 2008;**27**(11):1023-1035