Research Journal of Pharmaceutical Sciences E- ISSN 2319 – 555X
Vol. **5(3),** 1-15, August **(2016)** *Res. J. Pharmaceutical Sci.*

Pharmaceuticals and Personal Care Products (PPSPS) in the Aquatic Environment: Status and Issues in the Republic of Benin

Arouna Yessoufou[1*], Daouda Mama[1], Fidèle Suanon[1], Eric A. Alamou[1], Benjamin Fayomi[2], Cyriaque Degbey[3] and Comlan Achille Dedjiho[1]

[1]Laboratory of Applied Hydrology, University of Abomey-Calavi, Abomey-Calavi, Benin
[2]University Laboratory of Occupational Health and Environment, University of Abomey-Calavi, Abomey-Calavi, Benin
[3]Regional Institute of Public Health, University of Abomey-Calavi, Abomey-Calavi, Benin
arouna.yessoufou@yahoo.fr

Available online at: www.isca.in, www.isca.me
Received 21st June 2016, revised 24th August 2016, accepted 29th August 2016

Abstract

In Benin, next to the formal sales channel of pharmaceutical products there are informal channels that commercialize adulterated products. Pharmaceuticals and personal care products (PPSPS) containing various organic groups, such as antibiotics, hormones, antimicrobial agents, synthetic musks, etc., continue to raise concerns with their persistent and potential threat to the ecological environment and to human health. Although wastewater treatment systems are often faulty or non-existent in Africa and particularly in Benin, no study on the state of contamination in PPSPs is achieved in this continent.

Keywords: PPSPs, contamination, environmental risks, waste water, surface water.

Introduction

In recent decades, advances in technology and health-related research contributed to the development and the appearance of a large number of new pharmaceutical products[1]. About 3000 compounds are used in medicine and the annual production exceeds hundreds of tons[2]. The Pharmaceuticals and Personal Care Products (PPSPS) are biologically active molecules designed, developed and marketed for the treatment of diseases or infections and for improving the quality of life[3].

The use of varieties of pharmaceutical products by the population has not only beneficial effects. Indeed, their increased consumption leads to an increase in their concentration in the environment. Moreover, these emerging contaminants are often considered pseudo-persistent as they are continuously consumed and ubiquitous in the aquatic environment around the world[4-6], including in the sources of raw water from water treatment plants[7,8]. The residues of PPCPs in the environment can disrupt the metabolism or the normal functioning of organisms, producing a toxic effect on organisms or inducing the proliferation of drug-resistant strains[9]. Therefore potential environmental risks of these pollutants must not be ignored. Moreover, in recent years, Africa, particularly West Africa experienced a dramatic increase of adulterated pharmaceutical products or prohibited products on the market. The attraction of African populations to these prohibited products is justified by the relatively low cost of these products over those recommended by regulatory structures in charge of public health. Despite this global trend, in Africa particularly in Benin, no research has been done in this direction.

The purpose of this preliminary work is to summarize recent works on environmental concentrations (surface water and waste water) and aquatic toxicity of PPSPS to identify research needs and evaluate the risks of rejection of PPSPS in Benin aquatic environment that has never known such a study before.

Specifically, it will: i. Present the supply and distribution channels of medicines and medical supplies in Benin. ii. Inventory pharmaceutical products actually used in hospitals in Benin. iii. Present the data on the state of contamination of surface waters in the world.

This work will compile relevant information on PPSPs as well as updated data on the distribution methods and consumption of pharmaceutical products in Benin.

Materials and Methods

Study zone: The study area chosen are the five continents, Africa, Asia, America, Australia and Europe. In Africa, where a study of this kind has never been undertaken, we have focused in the sales channels of pharmaceutical products in Benin. For the other continents, the data on the state of water contamination in the cities of some countries have caught our attention.

Study Type: It is a descriptive and analytical retrospective study.

Study Population: Our study included sewage and water bodies in the vicinity or not of hospitals and water treatment plants.

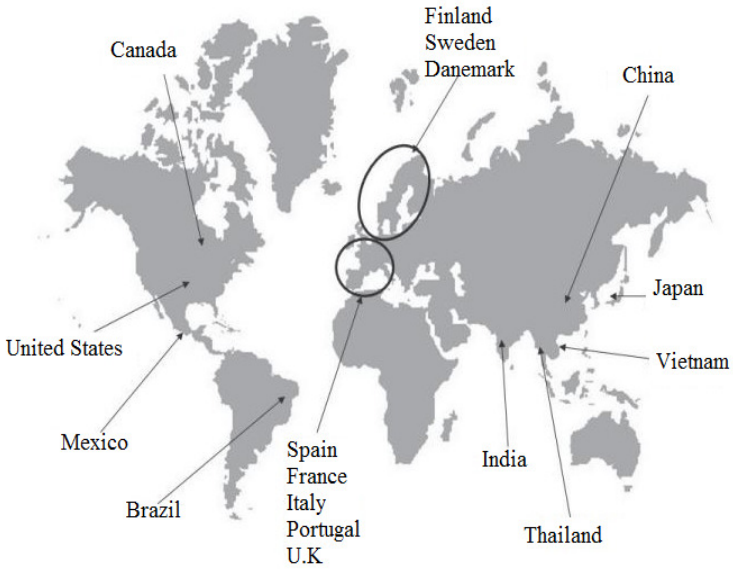

Figure-1
Geographical distribution of studies showing the presence of pharmaceutical compounds in aquatic environments[10]

Sampling and database: Countries and cities of study were selected based on availability of data on the PPSPS residue concentration in the water. Thus, 16 countries have been selected to host the investigation based on the presence of PPSPS residues in wastewater treatment plant. The following countries have therefore been identified: China, Korea, UK, Sweden, Finland, New Mexico, Colorado, Japan, Portugal, Canada, Norway and the United States. For surface water and drinking water source, 14 countries were selected. These are: China, Vietnam, France, UK, Finland, US, USA, Korea, Spain, the Netherlands, Australia, Japan, Brazil and India. The research unit is the presence of residues of PPCPs in water. Africa, to our knowledge, is the only continent that does not yet have data on water pollution in PPCPs. In Benin our investigations focused on the list of authorized medicines and the formal and informal sales channels pharmaceuticals.

The collection technique is the literature review with tools like the counting sheet.

Processing and analysis of data: The data were processed and analyzed with Microsoft Word for word processing and Microsoft Excel for illustrations.

Results and Discussion

Formal supply routes and distribution of drugs and medical consumables Republic of Benin: In Benin (Figure-2, Map-2), the supply channel and distribution of drugs and medical consumables is made by the public sector and the private sector.

Public sector: Benin has several private organizations that supply and distribute medicines and medical consumables. They are private wholesale distributors of companies whose top three: the Group Purchase of Pharmacists of Officines (GAPOB), the Union of Pharmacists Benin (UBPHAR) and Promotion of Pharmacies of Benin (PROMO-PHARMA). To those we will add some pharmaceutical industries such as dressing Society of Benin (SOPAB), Biological and Pharmaceutical Technological Cooperation (COPHARBIOTEC) PHARMAQUICK and API Benin. Founded in 1989, public wholesaler and under the supervision of the Directorate of Pharmacies , Medicines and Diagnostics Explorations (DPEMD), Essential Drugs Procurement for Central and Medical Consumables (CAM) is the only structure responsible for ensure the supply of drugs as generic public and private health facilities.

Private sector: Benin has several private organizations that supply medicines and medical consumables. They are private wholesale distributors companies. The top three are: Pharmacists of Officines Purchase Group (GAPOB), Union of Pharmacists of Benin (UBPHAR) and Promotion of Pharmacies of Benin (PROMO- PHARMA). To those, we can add some pharmaceutical industries such as Dressing Society of Benin (SOPAB), Biological and Pharmaceutical Technological Cooperation (COPHARBIOTEC), PHARMAQUICK and API Benin.

These companies ensure the implementation of the drug at the pharmacies who in turn supply the pharmaceutical depots located throughout the national territory. It should be noted that in 2012, there are a concentration of 59.34 % pharmacies in both departments of Atlantic and Littoral against 52.32 % in 2011[11]. This could be explained by the high concentration of the population in southern Benin.

According to the health statistics yearbook 2012, the pharmaceutical products consumption in Benin is growing and has doubled between 2004 and 2012[12].

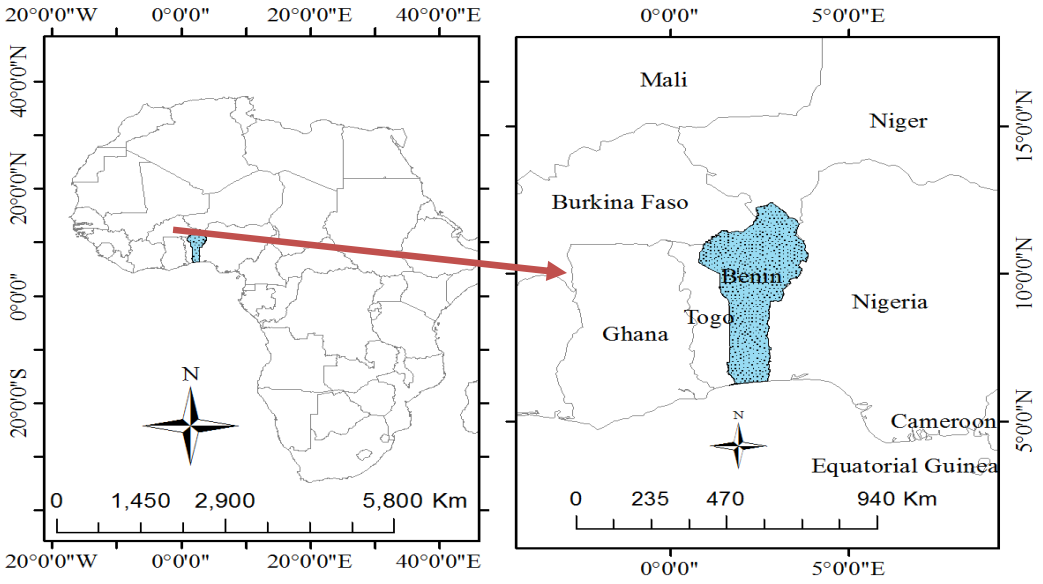

Figure-2
Presentation of Benin in Africa

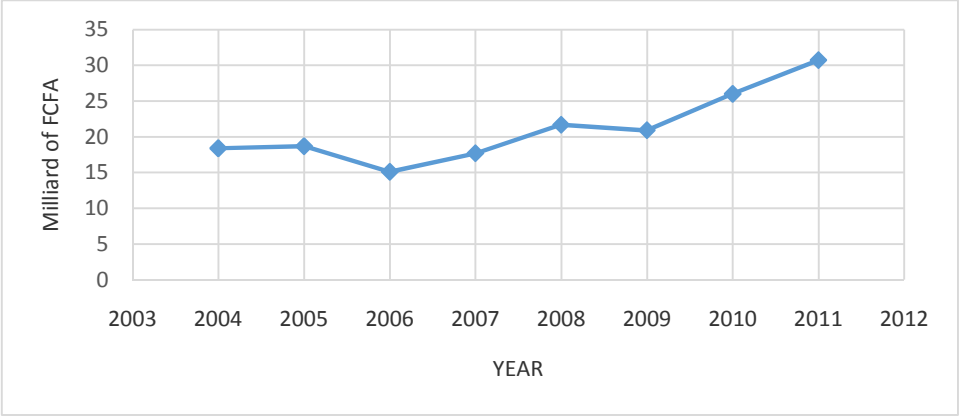

Figure-3
Evolution of imports of drugs 2004 to 2012 in Benin

Besides these formal structures, there are illegal pharmaceutical products markets.

Supply of the illegal market in pharmaceuticals: Two types of products are found in the market. Those officially permitted and other that are called illicit. This dual source of supply of parallel pharmaceutical market, both inside and outside the country is common to all of sub-Saharan Africa countries and still valid today[13,14].

Internal networks: The internal supply networks are grafted directly on the stocks of the official circuit and are the result of the weakness of the formal system or the need for easy money by some people in the pharmaceutical sector. These drugs are stolen from pharmacies or drug stores, wholesale distributors of pharmaceutical products by agents. These drugs often come from direct delivery of wholesale to street drugs sellers. This act is strictly prohibited by pharmaceutical regulation and constitutes an offense to the pharmaceutical monopoly. In many countries of Black Africa, this illicit market replenishment source is estimated (based on total replenishment informal total pharmaceutical sector) to 48% in Côte d'Ivoire, 40% in Niger and 57% in Benin[15]. Thus, a local manufacturer can sell big amount of defects or counterfeit products through this channel.

Consequently, external networks are organized with external agents to countries; they generally mobilize more consistent ways than the internal network resources. These products may be counterfeit, defect but also real drugs. This category is represented mainly by drugs smuggled by traffickers and, most often are not registered in Benin. Nigeria is known as the hub of drug trafficking in the Africa, expanding trade links with Indian

or Chinese manufacturers. In Benin, a study by the union of pharmacists on 351 pharmaceuticals from Dantokpa market, shows they come mainly from Nigeria at 24, 23%, while in Burkina Faso, the main external source would be Ghana[15]. However these figures are only very insignificant since manufacturers sometimes take the name of a manufacturer with the words "Made in England" in order to remove any suspicion at the consumer. This class of drug is more dangerous than the first. Indeed these drugs lack a marketing authorization. They have not undergone any quality control test. Their origin is often difficult to identify and they are often under-dosed, overdosed or contain have no active ingredient. Others contain ingredients that are toxic to human health.

Figure-4
Showcase of drugs to the international market at Adjegounlè in Dantokpa

Figure-5
Showcase of drugs from Nigeria to the international market Dantokpa

Classification of PPCPs: PPCPs can be classified into two categories: Pharmaceutical Products (PP) and Personal Care Products (PPCPs). In Benin over 150 pharmaceutical products in various therapeutic classes are sold. Several of these products molecules were detected in the world in various environmental matrices[16].

Sources of PPSPS and distribution channels in the various environmental compartments: These emerging contaminants are often considered pseudo-persistent as they are continuously consumed and released into the environment either in their unchanged form or in metabolites form and byproducts. In the literature, the presence of pharmaceuticals products in water has been detected for the first time, in the early 1970s. Generally Personal Care Products, the main transmission routes are domestic, industrial or agricultural[17-19]. It is noteworthy that among these various sources, humans and animals undergoing medical treatment mainly contribute to the introduction of these drugs via their natural excretion (urine, faeces, sweat and vomit) drugs as biologically active parent drug and not metabolized or biologically active or inactive metabolites.

Thus, when an individual consumes a drug, a part of this is expelled as original molecule (unmetabolized) by natural excretion routes such as urine or feces. The other part of the drug is generally metabolized (as hydroxylation and cleavage) by the liver and eliminated by the body by the same natural excretion routes in the form of one or more metabolites. For example, by analyzing the mode of excretion of several hundred pharmaceutical products[20] showed that on average 64% (± 27%) was excreted via the urine and 35% (± 26%) via the faeces. In the urine, 42% (± 28%) of these was excreted as metabolites. A significant portion of ingested drugs is therefore found in domestic wastewater and wastewater from hospitals. At the level of human use, the disposal of unused or expired drugs in the toilet or sink contributes to the incorporation of PPCPs in wastewater systems. In the case of human medication, it often happens that the active ingredients of drugs are not completely absorbed by the body and reach the treatment plants of urban waste water. However, the treatment methods of the current wastewater can not completely eliminate these substances even less in Benin where the treatment system is inadequate and does not even meet the international standards.

Consequently, these residues can pass through sewage treatment plants and reach surface waters such as rivers and lakes. Other emissions may also be the result of leaks in sewers, because of the excesses of storm basins during heavy rainfall or come from sewage sludge when used in agriculture.

The consequence of these emissions is that pharmaceutical residues, even in very low concentrations, can be detected in surface water or in water intended for drinking water production. In Benin, various studies have shown that ecosystems of Trench of Cotonou and Nokoué Lake are heavily polluted by chemical substances, organic substances of all kinds, PAHs, PCBs and pesticides[21], heavy metals and waste solid (plastic containers or cardboard, cans, scrap, wood, rubber, adulterated or expired pharmaceutical products, human or animal waste).

Pollution by heavy metals is one of the most serious sources of threats that the majority of these studies revealed[22]. Large quantities of solid waste from the town are discharged on the banks of the Trench of Cotonou; the main outfalls of wastewater collectors and gutters of the Hospital of the Mother and the Child (HOMEL) lead there without any treatment.

Table-1
Classification of PPCPs commonly used in Benin[12]

Category	Group	Pharmaceutical Product
Pharmaceutical products	Antibiotiques	Oflaxacin, chlortetracycline, oxytetracyclin, Streptomycin, Flumequine, Ciprofloxacin, Trometoprim, Lincomycin, Penicillin, Lincomycin, Amoxycillin, Spiramycin. Azithromycin, Clarithromycin, Erythromycin, N4 -Acetyl - Sulfamethoxazole, Sulfamethoxazole, Roxithromycin, Sulfamethazin
	antimalarials	Quinine,artemether, artesunate, sulfadoxine + pyrimethamine, artemether - lumefantrine, artesunate - amodiquine
	Estrogen and Hormones	17 - β -estradiol , 17 - α - ethinylestradiol, diethylstilbestrol, Estrone, Estriol, acetate Diethylstilbestro
	Anti -inflammatory / analgesics	Acetylsalicylicacid (Aspirin), Diclofenac, Ibuprofen, Metamizol, Acetaminophen, codeine, indomethacin, naproxen, Phenazone, Fenoprofen, Paracetamol
	Antiepileptic	Carbamazepine, Primidone
	Lipidregulators	Bezafibrate, Clofibric acid, fenofibrate, gemfibrozil
	β -blockers	Metoprolol, Propanolol, Nadolol, Atenolol, Sotalol, Betaxolol
	Antidepressants	Mianserin
	Tranquilizers	Diazepam
	Anticancer	IfosfamidecyclophosphamideMetotrexate
Personal Care Products	Antimicrobial agents / disinfectants	Triclosan Triclocarban
	Syntheticmusks / Perfume	Galaxolide (HHCB) Toxalide (AHTN)
	Repellents	N, N-diéthyl-m-toluamide (DEET)
	Conservatives	Parabens (alkyl-p-hydroxybenzoates)
	UV sunscreen filters	2-ethylhexyl-4-triméthoxycinnamate (EHMC), 4-methyl- benzilidin-camphor (4MBC)

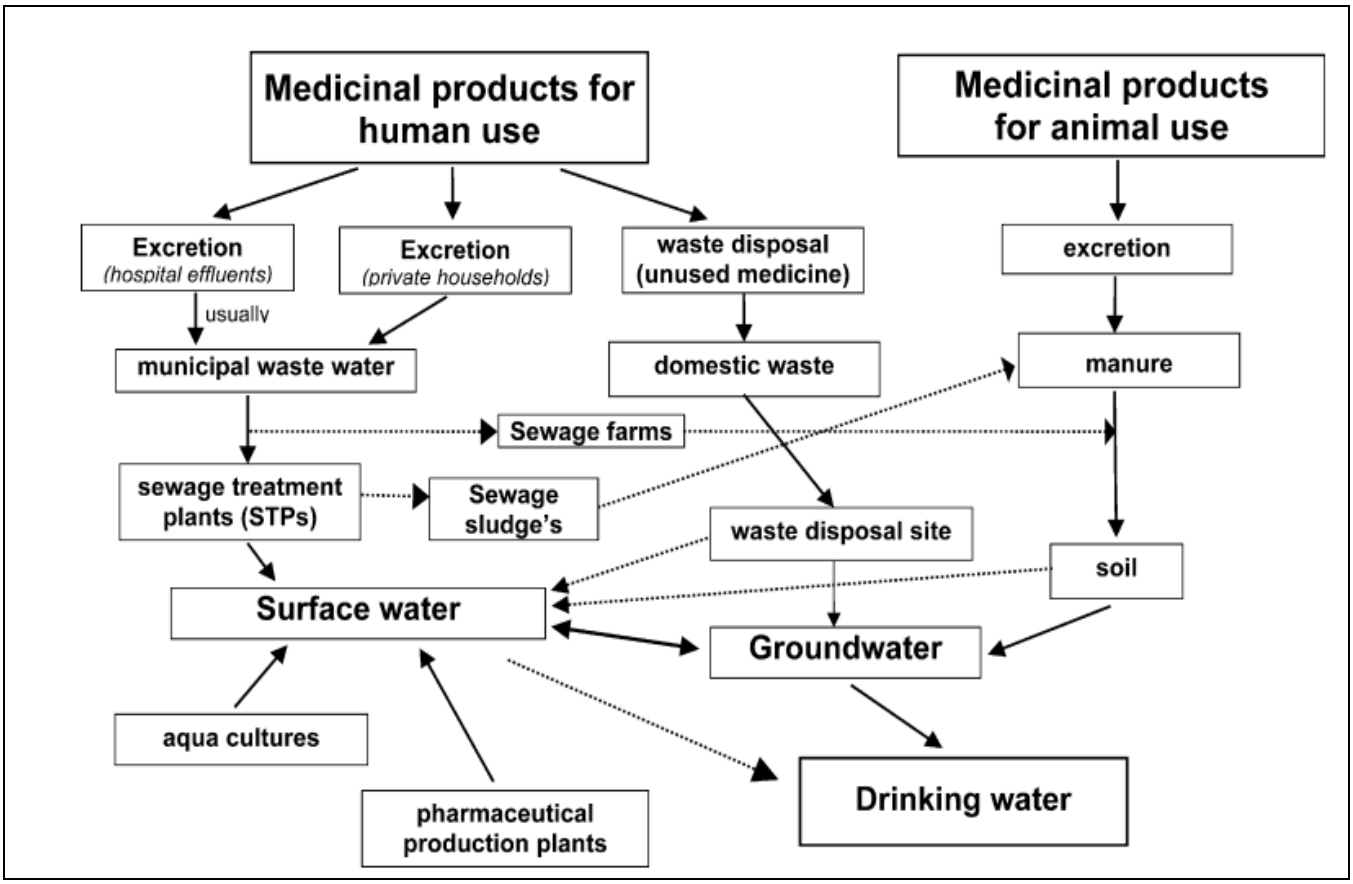

Figure-6
Sources and possible ways of the presence of residues of pharmaceuticals in the aquatic environment[23]

Water Contamination: Extraction and analysis techniques: PPCP detection techniques use gas chromatography coupled with mass spectrometry (GC-MS)[24] and mass spectrometry (GC-MS-MS)[25]. But these are limited to compounds that are volatile. Until 2010, liquid chromatography's sensitivity, specificity and reliability have dramatically improved spectrometry of mass-liquid chromatography (LC-MS) and LC-MS-MS.

The recently developed chromatography, the ultra-liquid with high performance (HPULC), which uses analytical columns packed with 1.8 microns particles, provides increased speed and improved sensitivity, selectivity and specificity compared to a conventional HPLC analysis. HPULC not only offers very low chromatographic analysis waiting time but also has a higher resolution; narrow peaks which help prevent analytescoelution with interference, which may decrease the effects of the matrix. Advances in analytical instrumentation have confirmed the presence of a compound at very low levels by using liquid chromatography coupled with mass spectrometry. Today, triple quadrupole (QqQ) is a very common and useful tool for analyzing target with high sensitivity.

Since pharmaceuticals products are at low concentrations in the environment, the enrichment and concentration steps of the latter are required. The solid phase extraction (SPE) was the preferred technique, although the liquid-liquid extraction (LLE) and the solid phase micro extraction (SPME)[26] were used in some cases. Sometimes antibiotics extracts were analyzed by liquid chromatography-ion at high-performance and by electro spray tandem mass spectrometry (HPLC-ESI-MS-MS) with multiple reactions monitoring (MRM).

Other methods such as gas chromatography (GC)[26], capillary electrophoresis (CE)[27] and the high performance liquid chromatography (HPLC) were used to determining residues of PPCPs in biological samples.

In general, the determination of residues of pharmaceuticals in aqueous environmental matrices, whatever the origin of the sample is based essentially now on a solid foundation phase extraction (SPE) and separation methods chromatography coupled with mass spectrometry.

Sewage contamination: The sophisticated analysis techniques developed have detected the presence of drug residues and their metabolites in all compartments of the aquatic environment: wastewater, groundwater, surface water and drinking water[28]. These analyzes require highly specialized equipment, time and associated costs are also relatively high.

Table-2
Figures on the contamination of PPCPs in wastewater treatment plants

Family	Compound	Concentration (in ng/L)	Country	Reference
Analgesics	Paracetamol	201000	Spain	29
		nd-5990	Croatia	30
		35-70229	France	31
		218000	China	32
		246000	England	6
	Diclofenac	59-243	Korea	33
		223-800	Italy	34
		120	Sweden	35
		30-4470	Norway	36
		65-280	Netherlands	37
		211-486	France	31
	Ketoprofene	nd-23	Italy	34
		130-620	Croatia	30
		22-1080	France	31
		330	Sweden	35
	Naproxene	42-289	France	31
		nd-20	Italy	34
		nd-269	U.K	6
		250	Sweden	35
	Ibuprofene	40-800	Croatia	30
		18-219	France	31
		15100	Spain	29
		120-16000	Norway	36
		1599-2853	Korea	34
		65-491	U.K	6
Anticonvulsant	Carbamazepine	94-265	Italy	34
		1080	Sweden	35
		nd-630	Croatia	30
		5-175	Spain	38
		100-280	Netherlands	37
		157-1308	France	31
		230-1110	China	39
		65-474	Italia	34
		160	Sweden	35
		1094	Spain	40
		5113-11239	Korea	34
		1292-3168	U.K	6
	Soltalol	152-366	Italy	34
		nd-210	Croatia	30
		11-168	Spain	38
		830-1600	Netherlands	37
		196-4358	France	41

Family	Compound	Concentration (in ng/L)	Country	Reference
	Propanolol	30	Sweden	35
		100-470	Croatia	30
		130-523	U.K	6
		2	France	41
	Bisoprolol	59-114	Spain	38
		1 and 56-450	France	41
	Metoprolol	161-219	Italy	34
		190	Sweden	35
		13 113-398	Spain	40
Stimulants	Cafeine	220	Sweden	35
		1608-3217	Korea	34
		19-873	Spain	42
		70-293000	Norway	36
		9-4378	France	31
lipid-lowering	Gemfibrozil	180	Sweden	35
		368	Spain	42
		2-34	France	31
Macrolides	Azithromycine	19-944	France	43
		22-209	Italy	35
		50-210	Croatia	30
	Clarithromycine	8-73 89-374	Italie	44 35
		247 1020	Spain	29 40
	Érythromycine	197 82	Spain	40 29
		23-2772	U.K	6
	Roxithromycine	18	Spain	29
		10-13	Italy	34
		1-161	Italy	44
	Tétracycline	620-32670	China	45
		15-120	Italy	44
Quinolones	Ciprofloxacine	313 2292	Spain	40 46
		10-499 27-514	Italy	34 44
	Norfloxacine	310	Spain	29
		85-339	China	47
	Ofloxacine	169 925	Spain	42 29
		150-1081	Italy	44
		503-1208	China	47
	acidpipemidic	430	Spain	46

Family	Compound	Concentration (in ng/L)	Country	Reference
Sulfamides	Sulfamethoxazole	35-185	Italy	34
		70	Sweden	35
		nd-820	Croatia	30
		1010	China	45
		4-44	U.K	6
		4-39	Luxembourg	48
	Sulfapyridine	36	Spain	42
		94-1112	U.K	6
	Sulfadimethoxine	nd-9	Luxembourg	48
		9830	China	45
	Sulfamethazine	73 11 33	Spain	42 29 40
		600-1400	Mexico	49
		21-39	Italy	34
		232	Spain	46
		70-310	Croatia	30
		40	Sweden	35
		385-1218	U.K	6
Hormones	Estriol	125-802	Corea	34
	Estrogen	nd-4100	China	39
	Estrone	103-2884	Portugal	50
		19-78	Canada	51
β -agonists	Terbutaline	4	France	31
	Salbutamol	9-26 1-18	Italy	34 44
		102	Spain	40
		nd-22	U. K	6
Antidepressants	Amitriptyline	nd-355	U.K	6
		nd-6	France	31
	Fluoxetine	21	Spain	40
Personal care products	Mucsynthétique	280-1400	Japan	52
		1-11463	Portugal	50
		304-12700	United States	53
	Anti microbal	27-65381	U.K	6
	Triclosan	160-2380	Norway	36

n.d : not detected.

Drug residues concentrations are in the range a few tens of ng/L to several tens of µg/L. This concentration varies from one country to another. The pharmaceutical classes detected in high proportion are analgesics, antibiotics and hormones.

Analgesics are drugs mostly used in the treatment of pain and fever. Paracetamol, most widely used product is obtained up to 201 µg/LL in Spain[32,33,46], 218 µg/LL in China, 246 µg/L and England. Ibuprofen is found up to 15.1 µg/L in Spain[46], 16 µg/L in Norway[36].

The charge in antibiotics in urban waste water is generally low. However, it is highin the effluent of hospitals. Such is the case of clarithromycin, ciprofloxacin in Spain whose values are of the order of µg/ L[40,46]. The very high concentrations (32.67µg/L) were registered in China. Frequently detected antibiotics are macrolides, quinolones and sulfonamides.

This massive use of antibiotics is linked to agriculture. Indeed, the largest producer of aquaculture is China with about 61% of the world market[54]. The extensive use of veterinary antibiotics in the breeding[39,55] and their significant presence in wastewater may constitute a threat to surface water and affect the quality of groundwater.

Hormones, in most studied cities, had concentrations below 1µg/L, and thus relatively smaller than those of antibiotics. It should be noted that higher concentrations are obtained in Portugal (103-2484 ng/L) and low concentrations in Canada (2.4 to 78 ng/L). In China, the estrogen concentrations in pharmaceutical industries and hospitals wastewater are higher than those in poultry and aquaculture waters[39]. This suggests that the main pollution sources may rely on municipal wastewater and pharmaceutical factories wastewater. The most detected hormones are the steroidal oestrogens, natural estrogen steroids which are mainly excreted by humans and animals. Their concentrations, which are sometimes very high, can pose potential harm to the aquatic ecosystem.

Contamination of surface waters: Since the pharmaceutical residue concentration is low in drinking water sources, rivers and lakes, we have presented the results here in the form of groups of antibiotics, hormones and other drugs.

Table-3
Figures on the contamination of certain bodies of water in tailings PPSPS

Country	Nature of pharmaceutical Product	Concentration (in ng/L)	Sample source	Reference
China (10 cities)	Antibiotics	nd to 776	River	55
Vienam (delta of Mekong)	Antibiotics	7 to 360	River	56
France (Seine)	Antibiotics	nd to544	River	57
United Kingdom (Taff and Ely River)	Antibiotics	<0,5 to 183	River	6
Finnish (Vantaanjoki)	Antibiotics	<1,6 to 36	Drinking water	7
United States (Choptank River)	Antibiotics	nd to 694	River	25
United States (flux in Iowa)	Antibiotics	nd to 300	River	58
United States (139 rivers)	Antibiotics	nd to1900	River	18
Korea (Youngsan River)	Hormones	1,7 to 5,0	River	59
Spain (Llobregat River)	Hormones	2-5	River	60
Netherlands (Escautestuairy)	Hormones	0,4 to 10	River	61
United States (Choptank River)	Hormones	nd to20	River	25
United States (139 rivers)	Hormones	nd to872	River	18
Australia (Little River)	Hormones	0,03 to 18,9	River	62
Korea (Youngsan River)	Drugs	1,1 to 361	River	59
Japan (37 rivers and estuairies Tamagawa)	Drugs	nd to 749	River	63
United KIngdom (Taff and Ely River)	Drugs	nd to5970	River	6

Country	Nature of pharmaceutical Product	Concentration (in ng/L)	Sample source	Reference
Uited Kingdom (5 rivers)	Drugs	<1 to 928	River	64
(Vantaanjoki)	Drugs	3 to 107	Drinking water	7
United States (flux in Iowa)	Drugs	nd to 1950	River	58
US (139 rivers)	Drugs	nd to10000	River	18
Brasil (Rivers at Rio de Janeiro)	Drugs	20 to 500		65
India (Kaveri, Vellar and Tamiraparani River)	Triclosan	5160	River	66
United Kingdom (Taff and Ely River)	Antimicrobals Conservatives UV filters	1 to 358 0,2 to 305 0,3 to 323	River	6
United States (Michigan lake)	Syntheticmusks	0,03 to 4,7	Lake	67
United States (flux in Iowa)	HHCB and ANTH Triclosan DEET	nd to 1200 nd to 140 nd to 130	River	58

n.d : not detected.

The concentration range usually encountered is rather in the range of nd ng/L to 10 ng/L. The concentrations of antibiotics in surface waters are generally in the order pg / L. China's water (ND-776 ng/L) and US (ND-1900 ng/L) were the most contaminated.

Risks residues PPSPS: The large presence of PPSPS in various environments raises concerns about their potential danger to the ecosystem and human health.

In Pakistan and India, the accumulation of veterinary diclofenac residues by carnivores and vultures caused the significant drop of the population of these wild animals[68]. The environmental exposure to antibiotics can speed the persistence or the appearance of antibiotic resistance genes. In 2010, the National Ministry of Health of China has collected more than 270,000 samples of bacteria isolated from 128 hospitals across the country to study the situation of antibiotic resistance. The results showed that resistance rates have reached almost 80%, creating a serious situation for public health. The level of antibiotic resistance in this country compared to that of Kuwait and the United States reveals that China has the highest rate[55]. Hormones can cause endocrine disruptions. These disruptions can have a wide range of negative effects on reproduction and development, for example, reduced fertility, feminization of males[9].

A number of aquatic species, for example, crucian carp, trout, minnows and turtles have been reported to be inhibited or reversed by the presence of estrogen in the environment[69,70]. For the group of personal care products, parabens and UV filters may also act as endocrine disruptors[71], while triclosan is suspected to exert disruptive effects of the endocrine system[72].

Conclusion

Current knowledge indicates that pharmaceutical residues are widespread in aquatic systems in the form of trace. It has been shown that chronic exposure of aquatic organisms to these substances contributes to the appearance of various phenomena such as hormonal imbalance, antibiotic resistance and some harmful environmental impacts. Therefore, water stock in Benin (rivers, lakes) especially wastewater and sludge from treatment plants in Benin need special attention. This will allow us to know the current state of PPSPS residue pollution in our water stocks, the quality of effluent and sludge from treatment plants, discharged into receiving waters, and their environmental risks. Thus, studies on the behavior and the control of these pollutants on the environment should be conducted. Acute and chronic toxicities of different groups of PPSPS should be examined to assess the potential environmental and health risks in Benin.

References

1. Zuccato E., Calamari D., Natangelo M. and Fanelli R. (2000). Presence of therapeutic drugs in the environment. *The lancet*, 355(9217), 1789-1790.

2. Calisto V. and Esteves V. I. (2009). Psychiatric pharmaceuticals in the environment. *Chemosphere*, (77), 1257-1274.

3. Baran W., Adamek E., Ziemiańska J. and Sobczak A. (2011). Effects of the presence of sulfonamides in the environment and their influence on human health. *Journal of Hazardous Materials*, 196, 1-15

4. Carballa M., Omil F., Lema J.M., Lompart M., García-Jares C. and Rodríguez I. (2004). Behavior of pharmaceuticals, cosmetics and hormones in a sewage treatment plant. *Water Res*, (38), 2918-2926.

5. Nakada N., Tanishima T., Shinohara H., Kiri K. and Takada H. (2006). Pharmaceutical chemicals and endocrine disrupters in municipal wastewater in Tokyo and their removal during activated sludge treatment. *Water Res*, (40), 3297-3303.

6. Kasprzyk-Hordern, Dinsdale R. M. and Guwy A. J. (2009). 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 Res.*, 43, 363-380.

7. Vieno N. M., Härkki H., Tuhkanen T. and Kronberg L. (2007). Occurrence of pharmaceuticals in river water and their elimination in a pilot-scale drinking water treatment plant. *Environ Sci Technol*, (41), 5077-5084.

8. Radjenovic J., Petrovic M., Ventura F. and Barcelo D. (2008). Rejection of pharmaceuticals in nanofiltration and reverse osmosis membrane drinking water treatment. *Water Res*, (42), 3601-3610.

9. Sridevi P., Chaitanya R. K., Prathibha Y., Balakrishna S. L., Dutta-Gupta A. and Senthilkumaran B. (2015). Early exposure of 17α-ethynylestradiol and diethylstilbestrol induces morphological changes and alters ovarian steroidogenic pathway enzyme gene expression in catfish, *Clarias gariepinus*. *Environmental Toxicology.*, 30(4), 439-451.

10. Alighardashi A., Marie-Noëlle P. and Olivier P. (2008). Occurrence and fate of pharmaceutical substances in urban wastewater, a literature mini-review. *Journal of Water Sciences*, 21(4), 413-426.

11. Assanh J. M. C. (2013). The fight against counterfeit drugs: drug quality control from the markets of Parakou, Cotonou and Porto Novo. Pharmacy PhD thesis at the University of Abomey Calavi.

12. Directorate of Pharmacies and Medicines (DPM) (2012). National List of Essential Drugs for Human Medicine in the Republic of Benin. Directorate of Pharmacies and Medicines Nigeria.

13. Lergis C. (2005). The detection of counterfeit drugs by investigation of their authenticity. Pilot study on the illicit drug market in Côte d'Ivoire. Pharmacy doctoral thesis, Nancy I, 99-100.

14. Fayomi E., Bissagnéne E. and Zohoun T. (1996). Illegal sale of antibiotics to the international market "Dantokpa" Cotonou : a serious public health problem (Vente illicite d'antibiotiques au marché international « Dantokpa » de Cotonou : un grave problème de santé publique.). *Med Mal Infect*, (11), 77-81.

15. Martioux J. (1999). Pharmaceutical market parallel, illegal sales and public health. *Journal of Re Me D*, 8-22.

16. Hernando M.D., Mezcua M., Fernández-Albaand A.R. and Barceló D. (2006). Environmental risk assessment of pharmaceutical residues in wastewater effluents, surface waters and sediments. *Talanta*, 69(2), 334-342.

17. Sim W.J., Lee J.W., Lee E.S., Shin S.K., Hwang S.R. and Oh J.E. (2011). Occurrence and distribution of pharmaceuticals in wastewater from households, livestock farms, hospitals and pharmaceutical manufactures. *Chemosphere*, (82), 179-186.

18. Chang X., Meyer MT, Liu X., Zhao Q., Chen H., Chen J., Qiu Z., Yang L., Cao J. and Shu W. (2010). Determination of antibiotics in sewage from hospitals, nursery and slaughter house, wastewater treatment plant and source water in Chongqing region of Three Gorge Reservoir in China. *Environ. Pollut.*, (158), 1444-1450.

19. Kolpin D. W., Furlong E. T., Meyer M. T., Thurman E. M., Zaugg S. D., and Barber L. B. (2002). Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999–2000: a national reconnaissance. *Environ Sci Technol*, (36), 1202-1211.

20. Linert J., Burki T. and Escher B. L. (2007). Reducing micro pollutants with source control: substance flow annalysis of 212 pharmaceuticals in faeces and urine. *Water Sciences and Technology.*, (56), 87-96.

21. Soclo H. H., Garrigues P.H. and Ewald M. (2000). Origin of polycyclic aromatic hydrocarbons (PAHs) in coastal marine sediments: case studies in Cotonou (Bénin) and Aquitaine (France) areas. *Marine Pollution Bulletin*, 40(5), 387-396.

22. Youssao A., Soclo H.H., Bonou C. and Fayomi B. (2011). Assessment of bioaccumulation of lead in marine animal species and identification of sources of metal contamination by a multi-element analysis of metals (Al, Cd, Cr, Cu, Pb) in the coastal waters of Benin. *Int. J. Biol. Chem. Sci.*, 5(1),188-195.

23. Heberer T. (2002). Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. *Toxicology Letters*, 131(1-2), 5-17.

24. Alder A. C., McArdell C. S., Golet E. M., Ibric S., Molnar E., Nipales N. S. and Giger W. (2001).

Pharmaceuticals and Care Products in the Environment. ACS Symposium Series, American Chemical Society, 791, 56.

25. Arikan O. A., Rice C. and Codling E. (2008). Occurrence of antibiotics and hormones in a major agricultural watershed. *Desalination*, 226, 121-133.

26. Moeder M., Schrader S., Winkler M. and Popp P. (2000). Solid-phase micro extraction–gas chromatography–mass spectrometry of biologically active substances in water samples. *J. Chromatogr. A*, 873, 95.

27. Pedersen-Bjergaard S. and Grounhaug Halvorsen T. (2000). Analysis of pharmaceuticals by micro emulsion electro kinetic chromatography in a suppressed electro osmotic flow environment Chromatographia. *Chromatographia*, 52, 593.

28. Houeto P., Carton A., Guerbet M., Auclair AC, Gatignol C. and Lechat P. (2012). Assessment of the health risks related to the presence of drug residues in water for human consumption: Application to carbamazepine. *Regulatory Toxicology and Pharmacology*, 62(1), 41-48.

29. Gracia-Lor E., Sancho J. V. and Hernández F. (2011). Multi-class determination of around 50 pharmaceuticals, including 26 antibiotics, in environmental and wastewater samples by ultra-high performance liquid chromatography – tandem mass spectrometry. *Journal of Chromatography A*, 1218, 2264-2275.

30. Gros M., Petrović M. and Barceló D. (2006). Development of a multi-residue analytical methodology based on liquid chromatography–tandem mass spectrometry (LC–MS/MS) for screening and trace level determination of pharmaceuticals in surface and wastewaters. *Talanta*, 70, 678-690.

31. Togola A. and Budzinski H. (2008). Multi-residue analysis of pharmaceutical compounds in aqueous samples. *Journal of Chromatography A*, 1177, 150-158.

32. Yu Y., Wu L. and Chang A. C. (2013). Seasonal variation of endocrine disrupting compounds, pharmaceuticals and personal care products in wastewater treatment plants. *Science of the Total Environment*, 442, 310-316.

33. Behera S. K., Kim H. W, Oh J. E. and Park H. S. (2011). Occurrence and removal of antibiotics, hormones and several other pharmaceuticals in wastewater treatment plants of the largest industrial city of Korea. *Sci Total Environ*, 409, 4351-4360.

34. Aukidy M., Verlicchi P., Jelic, A., Petrovic M. and Barcelò D. (2012). Monitoring release of pharmaceutical compounds: Occurrence and environmental risk assessment of two WWTP effluents and their receiving bodies in the Po Valley, Italy. *Science of the Total Environment*, 438, 15-25.

35. Bendz D., PaxéusN. A., Ginn T. R. and Loge F. J. (2005). Occurrence and fate of pharmaceutically active compounds in the environment, a case study: Höje River in Sweden. *Journal of Hazardous Materials*, 122, 195-204.

36. Weigel S., Berger U., Jensen E., Kallenborn R., Thoresen H. and Hühnerfuss H. (2004). Determination of selected pharmaceuticals and caffeine in sewage and seawater from Tromsø/Norway with emphasis on ibuprofen and its metabolites. *Chemosphere*, (56), 583-592.

37. Oosterhuis M., Sacher F. and terLaak T. L. (2013). Prediction of concentration levels of metformin and other high consumption pharmaceuticals in wastewater and regional surface water based on sales data. *Science of the Total Environment*, 442, 380-388.

38. Huerta-Fontela M., Galceran M. T. and Ventura F. (2010). Fast liquid chromatography–quadrupole-linear ion trap mass spectrometry for the analysis of pharmaceuticals and hormones in water resources. *Journal of Chromatography A*, 1217, 4212-4222.

39. Zhou Y.Q., Zha J.M., Xu Y.P., Lei B.L. and Wang Z. J. (2011). Occurrences of six steroid estrogens from different effluents in Beijing, China. *Environ Monit Assess*, 184, 1719-1729.

40. Gros M., Petrović M., Ginebreda A. and Barceló D. (2010). Removal of pharmaceuticals during wastewater treatment and environmental risk assessment using hazard indexes. *Environment International*, 36, 15-26.

41. Piram A., Salvador A., Gauvrit J. Y., Lanteri P. and Faure R. (2008). Development and optimisation of a single extraction procedure for theLC/MS/MS analysis of two pharmaceutical classes residues in sewage treatment plant. *Talanta*, 74, 1463-1475.

42. Cabeza Y., Candela L., Ronen D. and Teijon G. (2012). Monitoring the occurrence of emerging contaminants in treated wastewater and groundwater between 2008 and 2010. The Baix Llobregat (Barcelona, Spain). *Journal of Hazardous Materials*, 239-240, 32-39.

43. Van H. B. (2014). Contribution to the study of the presence and future of drug residues in aquatic compartments. PhD thesis at the University of Bordeaux, 1.

44. Castiglioni S., Bagnati R., Calamari D., Fanelli R. and Zuccato E. (2005). A multi residue an analytical method using solid-phase extraction and high-pressure liquid chromatography tandem mass spectrometry to measure pharmaceuticals of different therapeutic classes in urban wastewaters. *Journal of Chromatography A*, 1092, 206-215.

45. Ben W., Qiang Z., Adam C., Zhang H. and Chen L. (2008). Simultaneous determination of sulfonamides, tetracyclines and tiamulin in swine wastewater by solid-phase extraction and liquid chromatography–mass spectrometry. *J Chromatogr A*, 1202, 173-180.

46. García-Galán M.J., Díaz-Cruz M. S. and Barceló D. (2011). Occurrence of sulfonamide residues along the Ebro river basin: Removal in wastewater treatment plants and environmental impact assessment. *Environment International*, 37, 462-473.

47. Xiao Y., Chang H., Jia A. and Hu J. (2008). Trace analysis of quinolone and fluoroquinolone antibiotics from wastewaters by liquid chromatography–electro spray tandem mass spectrometry. *J Chromatogr A*, 1214, 100-108.

48. Pailler J. Y., Krein A., Pfister L., Hoffmann L. and Guignard C. (2009). Solid phase extraction coupled to liquid chromatography-tandem mass spectrometry analysis of sulfonamides, tetracyclines, analgesics and hormones in surface water and wastewater in Luxembourg. *Science of The Total Environment*, 407, 4736-4743.

49. Brown K. D., Kulis J., Thomson B., Chapman T. H. and Mawhinney D. B. (2006). Occurrence of antibiotics in hospital, residential, and dairy effluent, municipal wastewater, and the Rio Grande in New Mexico. *Sci Total Environ*, 366, 772-783.

50. Salgado R., Noronha J. P., Oehmen A., Carvalho G. and Reis M. A. M. (2010). Analysis of 65 pharmaceuticals and personal care products in 5 wastewater treatment plants in Portugal using a simplified analytical methodology. *Water Sci Technol*, (62), 2862-2871.

51. Servos M. R., Bennie D. T., Burnison B. K., Jurkovic A., McInnis R. and Neheli T. (2005). Distribution of estrogens, 17beta-estradiol and estrone in Canadian municipal wastewater treatment plants. *Sci Total Environ*, (336), 155-170.

52. Nakata H. and Shinohara R. (2010). Concentration of benzotriazole UV stabilizers and polycyclic musks in wastewater treatment plant samples in Japan. T. Isobe, K. Nomiyama, A. Subramanian, S. Tanabe (Eds.), Interdisciplinary studies on environmental chemistry—environmental specimen bank, 51-59

53. Reiner J. L., Berset J. D. and Kannan K. (2007). Mass flow of polycyclic musks in two wastewater treatment plants. *Arch Environ Contam Toxicol*, (52), 451-457.

54. Adam L., Ailbhe M. and Kevin V. T. (2015). Recommendations for the inclusion of targeted testing to improve the regulatory environmental risk assessment of veterinary medicines used in aquaculture. *Environnement international*, 185, 1-4.

55. Jin-Lin L. and Ming-Hung W. (2013). Pharmaceuticals and personal care products (PPCP): A review on environmental contamination in China. *Environment International,* (59), 208-224.

56. Managaki S., Murata A., Takada H., Tuyen B. C. and Chiemn H. (2007). Distribution of macrolides, sulfonamides, and trim ethoprim in tropical waters: ubiquitous occurrence of veterinary antibiotics in the Mekong Delta. *Environ Sci Technol*, (41), 8004-8010.

57. Tamtam F., Mercier F., Le Bot B., Eurin J., TucDinh Q. and Clément M. (2008). Occurrence and fate of antibiotics in the Seine River in various hydrological conditions. *Sci Total Environ*, (393), 84-95.

58. Kolpin D. W., Skopec M., Meyer M., Furlong E. and Zaugg S. (2004). Urban contribution of pharmaceuticals and other organic wastewater contaminants to streams during differing flow conditions. *Sci Total Environ*, (328), 119-130.

59. Kim S. D., Cho J., Kim I. S., Vanderford B. J. and Snyder S. A. (2007). Occurrence and removal of pharmaceuticals and endocrine disruptors in South Korean surface, drinking, and waste waters. *Water Res.*, (41), 1013-1021.

60. Brix R., Postigo C., González S, Villagrasa M., Navarro A. and Kuster M. et. al. (2009). Analysis and occurrence of alkylphenolic compounds and estrogens in a European river basin and an evaluation of their importance as priority pollutants. *Anal Bioanal Chem*, 396, 1301-1309.

61. Noppe H., Verslycke T., De Wulf E., Verheyden K., Monteyne E. and Van Caeter P. (2007). Occurrence of estrogens in the Scheldt estuary: a 2-year survey. *Ecotoxicol Environ Saf*, (66),1-8.

62. Ferguson E. M., Allinson M., Allinson G., Swearer S. E. and Hassell K. L. (2013). Fluctuations in natural and synthetic estrogen concentrations in a tidal estuary in south-eastern Australia. *Water Res*, (47), 1604-1615.

63. Nakada N., Kiri K., Shinohara H., Harada A., Kuroda K. and Takizawa S. (2008). Evaluation of pharmaceuticals and personal care products as water-soluble molecular markers of sewage. *Environ Sci Technol*, (42), 6347-6353.

64. Thomas K.V. and Hilton M.J. (2004). The occurrence of selected human pharmaceutical compounds in UK estuaries. *Mar Pollut Bull*, (49), 436-444.

65. Stumpf M., Ternes T.A., Wilken R.D., Rodrigues S.V. and Baumann W. (1999). Polar drug residues in sewage and natural waters in the state of Rio de Janeiro, Brazil. *Sci Total Environ*, (225), 135-141.

66. Ramaswamy B. R., Shanmugam G., Velu G., Rengarajan B. and Larsson D. G. J. (2011). GC–MS analysis and ecotoxicological risk assessment of triclosan, carbamazepine and parabens in Indian rivers. *J Hazard Mater*, (186), 1586-1593.

67. Peck A. M. and Hornbuckle K. C. (2004). Synthetic musk fragrances in Lake Michigan. *Environ Sci Technol*, (38), 367-372.

68. Karl Fent, Anna A. Weston and Daniel Caminada (2006). Ecotoxicology of human pharmaceuticals. *Aquatic Toxicology*, 78(2), 122-159.

69. Tabata A., Kashiwada S., Ohnishi Y., Ishikawa H., Miyamoto N. and andtoh M. (2001). Estrogenic influences of estradiol-17 beta, p-nonylphenol and bis-phenol-A on Japanese medaka (*Oryziaslatipes*) at detected environmental concentrations. *Water Sci Technol*, 43, 109-116.

70. Zha J. M., Sun L. W., Zhou Y. Q., Spear P. A., Ma M. and Wang Z. J. (2008). Assessment of 17α-ethinylestradiol effects and underlying mechanisms in a continuous, multigeneration exposure of the Chinese rare minnow (*Gobiocyprisrarus*). *Toxicol Appl Pharmacol*, 226, 298-308.

71. Gomez E., Pillon A., Fenet H., Rosain D., Duchesne M. J. and Nicolas J. C. (2005). Estrogenic activity of cosmetic components in reporter cell lines: parabens, UV screens and musks. *J Toxicol Env Health*, 68, 239-251.

72. Foran C.M., Bennett E.R. and Benson W.H. (2000). Developmental evaluation of a potential non-steroidal estrogen: triclosan. *Mar Environ Res*, 50, 153-156.