

# Pharmaceuticals and Personal Care Products: Sources, Toxicity in the Environment, Regulations and Removal Technologies

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## ABSTRACT

The intensive concern and research about micro pollutants started within the last several decades; the daily occurrence of these micro pollutants has increased the risk to streams, aquatic life and for human life since some of the micro pollutants contain endocrine disrupting chemicals and have complex molecules that is not easy to degrade by biological process. Pharmaceuticals and personal care products (PPCPs), which form one category of micro pollutants, are widely found in wastewater and even can be found in drinking water. The sources and fate of PPCPs, their toxicity to the environment, PPCP emission regulations and removal technologies are discussed in this review, and the concept of green technology is a focal point.

**KEY WORDS:** Micro pollutants, pharmaceuticals and personal care products (PPCPs), fate, toxicity, regulations.

## 1. INTRODUCTION

Micro pollutants comprise trace amounts of organic contaminants found in waters with very small concentrations  $\mu\text{g/l}$  to  $\text{ng/l}$ . Swiss Federal Institute of Aquatic Science and Technology (EAWAG) describes the occurrence of micro pollutants as nano gram per litre, which is roughly like the concentration of the active ingredient of a headache tablet dissolved in a 25-metre swimming pool or to 1 kg of an active substance dissolved in a lake. The dissimilar types of micro pollutants include pesticides, pharmaceuticals, detergents, paints, and ingredients in personal care products, biocides, and waterproofing agents. "Pharmaceuticals and personal care products (PPCPs)" is a term that represents a broad group of chemicals, including prescription, veterinary, and illicit drugs, fragrances, sunscreen agents, nutraceuticals, and other active ingredients found in personal care products, besides all their metabolites. PPCPs can find their way into natural waters from many diversity of sources, including agriculture, construction, households and transportation. In the future, PPCP is predictable to increase due to the increasing population.

In the last two decades, the concern regarding micro pollutants has increased due to the continuous development around the world. The presence of micro pollutants in the natural environment became prominent during the early 2000 (Kolpin, 2002). The concern regarding micro pollutants is related to their possible ecological and human health impacts. Moreover, micro pollutants obstruct water recycling, which could otherwise mitigate water shortages. Attention has been paid to the existence of micro pollutants in wastewater, surface water and drinking water (Daughton 2004; Daughton & Ternes 1999; Heberer, 2002; Petrovic, 2009). The existing wastewater treatment plants (WWTPs) are not definitely designed to remove micro pollutants. Therefore, a lot of these micro pollutants can pass by the wastewater treatment processes by their persistency and/or continuous introduction. In addition, protections and monitoring actions for micro pollutants have not established in most of the WWTPs (Bolong, 2009). Consequently, these compounds may end up in the marine environment, becoming threats to wildlife and spelling trouble for the drinking water industry. In this review the causes and the regulations of PPCPs will be reviewed.

**Occurrence of Micropollutants in the Aquatic Environment:** Micro pollutants, which are also called emerging contaminants, are composed of different substances, including pharmaceuticals, personal care products, steroid hormones, industrial chemicals, pesticides, waterproofing agents, paints, detergents, and many other compounds that enter the natural environment. Micro pollutants are usually found in water system like wastewater and can found also in other water streams (Gros, 2012; Petrovic, 2009). Fig.1, shows the major types of micro pollutants that can be found in the aquatic environment with the amount of micro pollutants found in the environment can depend on several aspects, for example the rate of production, and water consumption per person per day (Petrovic, 2009).

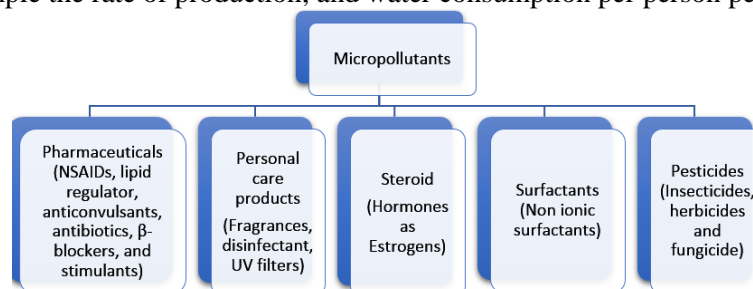


Fig.1. Types of Micro pollutants

Kolpin (2004), showed that climatic conditions can cause fluctuating micro pollutant inputs. Some medicines had found in wastewater streams with higher concentrations in winter due to the increased frequency of illnesses, e.g., flu and infections, during this season. Luo (2014), found that most micro pollutants occurred in WWTP influent at concentrations between 0.1 and 10 µg/L. Focusing on the micro pollutants that appear most frequently in wastewater, pharmaceutical and personal care products (PPCP) are the most found in water streams because of the daily use of pharmaceuticals and the presence and usage of personal care products everywhere. The raw wastewater from three hospitals in Jordan were measured for some pharmaceuticals, showing concentrations on the order of 100 µg/L to 100 mg/L for antibiotics, estrogens, acidic, and neutral pharmaceuticals (Fares, 2016). In India, it was found that Atorvastatin (a medicine that prescribed mostly for anti-hyper cholesterol emic in India), paraxanthine, and mefenamic acid were found in wastewater in India for the first time at the mean concentrations of 395, 1100 and 13,000 ng/L, respectively (Subedi, 2017).

The main sources for a variability of micro pollutants in surface water are municipal and rural wastewater treatment plant effluents, animal manure, septic tank, and effluents (Dodgen, 2016), also from the runoff of WWTP effluent; the micro pollutant concentrations in surface water are less than in the effluent due to several factors, e.g., watering in surface water and sorption onto sediments and suspended solids (Pal, 2010). Furthermore, river water dilution can be affected by rainfall. Consistent increases in micro pollutant concentrations during dry weather conditions and reductions during rainy weather conditions have been reported. Wang (2011), indicated that pharmaceuticals in summer water samples have found to be lower in rate levels than those measured in winter due to the biodegradation of pharmaceuticals at warmer temperatures and raised dilution during wetter summers. However, rainfall does not always reduce the micro pollutant concentrations. In some cases, rainfall has been identified as a contributor to the emission of micro pollutants to the surface water. Luo (2014), found that rainfall events may intensify combined sewer overflows, resulting in higher levels of contamination discharge.

**Types and Routes of PPCPs in the Environment:** PPCPs represent a wide-ranging group of chemicals, including prescription, veterinary, and illicit drugs, fragrances, sunscreen agents, and other active ingredients found in personal care products, in addition to all their metabolites. PPCPs find their way into the waters streams from a different sources, like agriculture, construction, households and transport. Due to the proliferation of chemical applications and the ageing of the population, the consumption of these complexes will continue to rise in the future. Sources of PPCPs in the environment are shown in fig.2 (Esplugas, 2007; Luo, 2014; Pal, 2010).

Sources of PPCPs				
Hospitals discharge of wastes and expired drugs	Hormones fed to fish and antibiotics	Discharge of drugs into waste water and septic systems	Companies manufacturing drugs and Industrial wastes	Landfill leachate

**Fig.2. Sources of micro pollutants in the environment**

PPCP products in their native form or as metabolites are introduced continuously to sewage primarily through excreta, disposal of unused or expired drugs, or directly from pharmaceutical discharges. Hospital waste water (HWW) is considered the main source of PPCPs due to the high loading of these pollutants in this water stream. Moreover, urban waste water (UWW) is also considered a major source of PPCPs, although HWW exceeds it by approximately 5-150 times (Verlicchi, 2010). The human body may metabolize only a section of administered pharmaceuticals; they enter the water streams as parent compounds and/or its metabolites through excretion, primarily in urine (55–80%) and to a lesser through feces (4–30%) (Jjemba, 2006). The most common PPCP categories are analgesic, antibiotics, and anti-inflammatory compounds. However, other groups, e.g., diuretics, anticoagulants, anti-diabetics, psychiatric drugs, lipid regulators, and histamine H<sub>2</sub> antagonists (Jelic, 2011; Miege, 2009), anti-epileptic drugs (Miege, 2009; Petrovic, 2009), antifungals, antineoplastics, disinfectants, antiseptics, antidepressants, hormones, and vasodilators (Miege, 2009), antifungals, barbiturates, vasodilators, and anti-cancers, anticonvulsant (Onesios, 2009), and anti-hypersensitive and anti-lipidemics are also common (Beherea, 2011). It is very difficult to detect typical PPCP concentrations because they can vary from hundreds of pg/L up to hundreds of µg/L (Boleda, 2011; Miege, 2009), depending on the target PPCP and the type of wastewater.

**Impact and Toxicity of PPCPs:** The concern for PPCPs comes from the fact that these micro pollutants are known to have biological effects to humans and animals through direct exposure via inhalation, ingestion, dermal contact and drinking water. However, until lately, only limited information has been available to assess the potential ecotoxicological impacts of PPCPs. Some researchers have applied various toxicity tests, e.g., using freshwater invertebrates such as daphnids, fish, algae, mussels, (Hoeger, 2005; Lai, 2009) and even human embryonic cells (Pomati, 2006), to determine that these compounds also have ecotoxicological effects. Among these compounds, sex hormones, including both estrogens and androgens, are viewed to have the highest potential concern, followed by

cardiovascular medicines, antibiotics, antineoplastics and medicines used to cure abnormal tissue growth in neoplasms, daphnids and water fleas, which are the most susceptible to environmental pharmaceutical contaminants, followed by fish and algae (Sanderson, 2004). Certain lipid-lowering agents in the blood, such as fenofibrate, bezafibrate and gemfibrozil, have shown high estrogenic activity, especially in the proliferation tests of breast cancer cells (Isidori, 2009). Also, it was found that a bioaccumulation of 145 PPCPs were measured in mussels downstream and upstream of WWTPs in Canada and 43 PPCPs from many types of PPCP were detected in muscle tissue and the PPCP in water changed seasonally and the exposures were the highest in late summer during low river flow (Solla, 2016). Table.1, summarizes selected studies for toxicity risk analysis, showing the effects of pharmaceuticals and personal care products on human and aquatic life. The effects of chronic exposure on aquatic organisms during the initial stages of life may not be observed until adulthood. Some emerging contaminants like PPCP may have specific manners of action that may affect individual certain types of aquatic animals (e.g., vertebrates such as fish), thus, traditional toxicity test endpoints may not be sufficiently sensitive for emerging contaminants (Noguera and Aga, 2016).

**Table.1. Toxicity of selected pharmaceuticals and personal care products**

Compounds causing risks	Type of risks involved	Reference
Ibuprofen, diclofenac, E2 and EE2; ~0.01 µg/l	Risk to the aquatic environment with chronic toxic effects (such as inhibited polyp regeneration and reduced reproduction)	Carlsson, 2006
Mixture of atenolol, bezafibrate, carbamazepine, cyclophosphamide, ciprofloxacin, furosemide, hydrochlorothiazide, ibuprofen, lincomycin, ofloxacin, ranitidine, salbutamol and sulfamethoxazole; 10–1000 ng/l	Inhibit the growth of human embryonic kidney cells HEK293, with the highest effect observed as a 30% decrease in cell proliferation compared to controls.	Pomati, 2006
17α-ethinylestradiol (EE2); 5–50 ng/l	Brain and inter-renal steroidogenic acute regulatory protein and cytochrome P-450-mediated cholesterol side-chain cleavage expressions of juvenile salmon were modulated with time and concentration	Lyssimachouet, 2007
HHCB (Synthetic musk); 1.5 µg/l	Oxidation stress in goldfish ( <i>Carassius auratus</i> )	Chen, 2012

**Regulations on PPCPs:** Discharge guidelines and standards do not currently exist for most micro pollutants. Some regions or countries have implemented regulations for a few micro pollutants (Luo, 2014). For example, environmental quality standards for a subgroup of micro pollutants (e.g. bisphenol A, nonylphenol, DEHP and diuron) have been agreed in Directive 2008/105/EC (European Parliament and The Council, 2008). Moreover, nonylphenol and nonylphenol ethoxylates have been documented as toxic substances by the Canadian government (Canadian Environmental Protection Act, 1999). Additional micro pollutants, such as pharmaceutical and personal care products (PPCPs) and the steroid hormones, have not been listed of regulated substances list until recently. To set monitoring limits for micro pollutants, additional research on biological responses for these compounds (both acute and chronic effects) is required. Furthermore, the scientific community and regulatory agencies should improve insight into synergistic, additive, and antagonistic effects not only the impact of individual micro pollutants (Luo, 2014).

In Malaysia, the occurrence of human medical pollution in the environment has only been examined in very few studies (Al-Odaini, 2010); therefore, conducting such studies is crucial to obtaining primary information about the pollution status in Malaysia. Al-Qaim (2014), conducted the first study inspecting the occurrence of human pharmaceuticals and synthetic hormones in the Tangkas River, Malaysia. The Tangkas River is a tributary of the Langat River, a main river in the Hulu Langat district in the state of Selangor, Malaysia; he found several compounds in the water samples, such as caffeine, carbamazepine and levonorgestrel. These are among the most consumed compounds in Malaysia according to the latest Malaysian statistics on medicine report for 2010 (Al-Qaim, 2014).

In the U.S., the assessment of environmental risks from pharmaceuticals has been required by the U.S. Food and Drug Administration (U.S. FDA) under the National Environmental Policy Act (NEPA) since 1969 (U.S. FDA, 1969), and in 1998, the guidance for a tiered risk assessment method was published by Centre for Drug Evaluation and Research (CDER) of the U.S. FDA (CDER, 1998). In the same year, the U.S. Environmental Protection Agency (U.S. EPA) enacted reviewed regulations for the pharmaceutical industry to control both air emissions and effluent discharges (U.S. EPA, 1998). The European Union's (EU's) first Guideline for Environmental Risk Assessment of Human Medicines was published by the European Medicines Agency (Liu and Wong, 2013). The global pharmaceutical market in 2005 was \$606 billion U.S. dollars, with more than 268 billion located in North America.

An American survey of more than 100 compounds in a drinking water treatment plant, found 22 persisted in treated water (Rahman, 2016).

Switzerland, which is a non-member of the EU, uses only ecotoxicity information about human pharmaceuticals and both ecotoxicity and potential environmental risks for veterinary drugs (AMZV 2001). Human health risk assessments of new drugs are required under the Pharmaceutical Administration Law; thus, environmental risk assessments of drugs and cosmetics are not currently regulated. In the future, environmental risk assessment regulations and assessment guidelines for PPCPs should be established. The awareness of PPCPs should be increased via source control, which is a direct and efficient strategy to reduce the disposal of PPCPs. Another option is that expired drugs should be collected through the formation of a drug management and reclamation program. In addition, sewage, landfill waste, and reclaimed water irrigation require more careful evaluation considering the possible introduction of PPCPs into the soil and groundwater environments. More wastewater treatment facilities should be established to increase the current sewage treatment rate and to avoid direct sewage discharge into the aquatic environment. Moreover, wastewater treatment plants, hospitals, livestock agriculture, and cosmetic plants should not be near drinking water sources, and any illegal wastewater discharge should be strictly forbidden (Liu and Wong, 2013).

**Removal Technologies for PPCPs:** During the treatment at wastewater treatment plants (WWTPs), PPCPs are either partially retained in the sludge or metabolized to a more hydrophilic compound. Regardless, they pass the wastewater treatment plant and end up in the receiving waters. A blend of conventional and advanced treatment can be used also to remove the PPCP from the water stream with better removal efficiency, from a study investigation done by a pilot plant to understand the optimal combination of unit process for treating PPCPs, 12 treatment trains with their additive and synergistic contributions were investigated; processes included dissolved air flotation (DAF), pre- and intermediate-ozonation with and without H<sub>2</sub>O<sub>2</sub> intermediate, filtration, chlorination, granular activated carbon (GAC), and UV/H<sub>2</sub>O<sub>2</sub> (Zhang, 2016).

The removal of pharmaceuticals in WWTPs varies and depends on the properties of the substance and process parameters. The importance of recognizing and assessing the toxicity of transformation products (biotic and abiotic) of pharmaceuticals in engineered treatment systems and under natural environments should not be ignored. In general, most of these emerging micro pollutants are not completely removed in WWTPs via conventional treatments. Therefore, they remain in the effluent and contaminate surface and ground waters, which are the main sources of drinking water and need more effective and specific treatments are required to reduce the environmental and potential impacts of contaminated effluents by PPCPs and comply with increasingly strict legislation. Like using advanced oxidation processes (AOPs) which are effective for removing contaminants from wastewater for the degradation of PPCPs. The UV/peroxide (H<sub>2</sub>O<sub>2</sub>) AOP producing hydroxyl radicals (HO) has been reported to unselectively oxidize many PPCPs such as, metronidazole, diatrizoic acid, phenazone, phenytoin (Xiang, 2016). The removal of contaminants from wastewater by advanced oxidation processes is built on the generation of hydroxyl radicals, which can oxidize organic and inorganic complex compounds. Hydroxyl radicals are not ionic species and they are formed from an equal splitting of a two-electron bond: OH• is uncharged. The hydroxyl radical is a strong oxidant which can destroy compounds that are not typically oxidized by conventional oxidants (e.g., oxygen and chlorine). Hydroxyl radicals react with dissolved compounds; the first reaction initiates a series of various oxidation reactions. The goal of the oxidation of compounds is mineralization, whereby the organic compounds are converted to carbon dioxide, water, and harmless inorganic molecules. The use of ozonation can be optimized if the extent of degradation of the trace-level contaminants can be observed and/or predicted in real time. This is difficult to accomplish based solely on chromatographic determinations because, while extremely sensitive and precise, they remain labor- and time-intensive (Li, 2016). Table.2, shows the removal during ozonation and AOPs for various PPCPs from different reviews. Most AOPs are generally accomplished of removing micro pollutants; the most popular AOP processes are Fenton photocatalysis with semiconductors and ozonation, which have the highest removal efficiencies.

**Table.2. PPCP removal via AOPs and ozonation**

Treatment condition	Compound	Removal (%)	Reference
O <sub>3</sub> (15) mg/l for 15 min	Carbamazepine	> 90	Sui, 2010
	Diclofenac	> 90	
	DEET	50-80	
UV 254 nm for 10 min	Ibuprofen	34	De La Cruz, 2012
	Diclofenac	100	
	Carbamazepine	23	
	Atrazine	69	
O <sub>3</sub> (15 mg/l)	Tonalide	79	Hernandez-Leal, 2011
	Galaxolide	87	

	Nonphenol	79	
O <sub>3</sub> (1.5) mg/l	17 $\alpha$ -ethynylestradiol	100	Alum, 2004
O <sub>3</sub> 5-15 mg /l at pH=6	Natural estrogen (17 $\beta$ -estradiol)	99	Kim, 2004
O <sub>3</sub> 1-5 mg/l at pH=7	Ibuprofen Diclofenic Clofibrac acid		Zwiener and Frimmel, 2000
UV at 254 nm at pH 5-6	Diclofenic	95	Vogna, 2004
UV at 254 nm at pH 5	Clofibrac acid	95	Andreozzi, 2003
O <sub>3</sub> (10-5) M at pH 5	Clofibrac acid	100	Andreozzi, 2003
Fe <sup>3+</sup> /H <sub>2</sub> O <sub>2</sub> /UV 254 nm at pH=2.8	Diclofenac at TOC=20 mg/l	100	Ravina, 2002

## 2. CONCLUSIONS

The occurrence and the destiny of micro pollutants in the environment and in aquatic regions have received considerable attention by the environment community and engineers during the last two decades. Pharmaceuticals and personal care products, which compose a single type of micro pollutants that are continuously discharged into the water system, are designed to be biologically active substances, usually lipophilic and are resistant to biodegradation, leading to accumulation and persistence in the environment. Although they found at low concentrations ranging between ng/L and  $\mu$ g/L and sometimes to mg/l, they may cause serious effects on the environment and humans. In searching for suitable technologies to destroy such a xenobiotic, many methods and studies have been put additional efforts to achieve high removal efficiencies. Several points have been discussed herein. The removal of pharmaceuticals from ground and surface waters destined for drinking water production is necessary. The conventional waste water treatment approaches (i.e., coagulation, sedimentation, and filtration) have failed to remove these compounds; therefore, AOPs have become a critical component of the treatment of PPCPs due to their high treatment efficiency. Moreover, PPCPs have been found in hospital wastes and in drug manufacturing effluents with concentrations that are relatively very high, i.e., several hundreds of mg/l or even g/L, compared with wastewater treatment plants for domestic use. The absence of regulations is thought to be a cause for the increased PPCP percentage in the water streams. Applying green chemistry is a significant step to reduce the effects of PPCPs in the water and waste systems. One such technique is take-back systems that focus on returning the expired and unwanted medicine to pharmacies and companies.

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