Tung Pham Thanh

Occurrence of pharmaceutical residues in water and treatment solutions

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Author	Thanh Tung Pham
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Abstract

Pharmaceutical residues as micropollutants in water resources is a growing concern. This thesis presents a review of the global occurrence of pharmaceutical waste leftover in water after treatment in common sewage plants, the potential toxic effects of these chemicals as well as the pathways in which they enter and accumulate in the ecosystems. Awareness of these pollutants has been increased over the years and steps have been made by the authorities to remove these substances and restore the water quality. However, current technology and treatment process within existing wastewater treatment plants are insufficient in degrading these compounds effectively. Fortunately, several advanced treatment technologies have been found to effectively treat these pollutants with high removal percentage, such as activated carbon, advanced oxidation process using ultraviolet (UV) and/or ozone, biological treatment using fungi and macrophytes. Each of these technologies follows a different process, working mechanism as well as having their advantages and limitations. Overall, not any of the discovered technologies are able to totally remove all pharmaceutical residues presented in water sources. The best method currently is to combine these technologies within a wastewater treatment process in order to maximize all-around removal effectiveness and mitigate some of the limitations. Further research and development are still being made in this field and better treatment techniques will hopefully be discovered in the near future.

Keywords	pharmaceuticals, wastewater, micropollutants, ozone, activated carbon, ultraviolet, biological treatment

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List of Abbreviations

WWTP	Wastewater treatment plant
PAC	Powdered activated carbon
GAC	Granular activated carbon
UV	Ultraviolet
DOC	Dissolved organic carbon
HRT	Hydraulic retention time
HRAP	High rate algal ponds

1 Introduction

The consumption and manufacturing process of pharmaceutical products (e.g. medicines, personal care products) is prevalent in today's society. While bringing many benefits, these products leave a trace after usage. After consumption, drugs are ingested and undergo metabolic reactions. However, a considerable fraction of the original products remain unchanged and leave the living organisms (humans & animals) along with an amount of their metabolites via excretion and enter the sewage. Chemicals discharge from pharmaceutical manufacturing, hospital services, animal husbandry and agricultural activities also find its way into the sewage system (aus der Beek et al., 2016). These factors result in the presence of pharmaceutical traces in the raw influent of the WWTPs. Small doses of these chemical continue to remain in the effluent after the treatment process and are discharged into the environment (Kolpin et al., 2002).

Over the last years, the occurrence of pharmaceuticals in water bodies has attracted more attention from environmental administrative authorities as potential dangerous pollutants to the environment as well as to the living entities (Kümmerer, 2009). They are found to be present in all type of water bodies: surface water, ground water, tap/drinking water, sewage, wastewater treatment plants (WWTPs) influent/effluent, animal manure and agricultural soil with low concentration (ng/L to µg/L range). These substances are usually water soluble, biologically active compounds but not biodegrade easily (Jiang et al., 2013). They can remain in water bodies and accumulate until reaching a critical dose which can pose a harmful effect towards the ecosystem and human health (Sirés and Brillas, 2012). With population continues to age and living quality raising every year, pharmaceutical consumption and discharge quantity might be set to increase in future years.

Typical types of pharmaceutical pollutants found in the sewage and water environment are (according to Verlicchi et al., 2012):

- Analgesics/anti-inflammatories: painkillers and drugs that reduce inflammation.
- Antibiotics: antimicrobial medicine applied in the treatment of bacterial infections.
- Antidiabetic: drugs used in diabetes treatment.

- Antifungal: medication used to treat and prevent mycoses (fungal infections)

- Anti-hypertensives: drugs prescribed for curing hypertension (high blood pressure) and their complications.

- Beta-blockers: pharmaceuticals used to treat abnormal heart rhythms, hypertension, heart attacks and their complications.

- Diuretics: drugs that promote diuresis i.e. increased production of urine and excretion of water from bodies.

- Lipid regulators: cholesterol-reducing drugs used in treatment of high fat (lipids) levels in the blood.

- Psychiatric drugs: medications for mental illnesses.

- Receptor antagonists: drugs that dampen or completely block the neurotransmitter-mediated response to another chemical substance.

- Synthetic Hormones/Estrogens: artificial female human hormones used in treatment of menopausal symptoms.

- Antiseptic: chemicals applied to living skin tissue to destroy bacteria to treat and prevent infection.

- Contrast agent (or contrast medium): compounds used in improving the contrast of structures or fluids in medical imaging.

2 Pharmaceutical residues in water

2.1 Occurrence

The presence of pharmaceutical residues has been shown to be global (aus der Beek et al., 2016). Figure 1 shows that every single continent on the planet has records on detection of pharmaceuticals in the aquatic system. Within Europe and North America, painkillers, cardiovascular drugs, and antibiotics are the most popular form of pharmaceutical residues. The heavy occurrence is obviously apparent in developed countries since it is a known fact that the application of pharmaceuticals in medical treatment, agriculture, research is copious in nowadays modern era. However, developing regions of the world such as Africa and South America also find their water contaminated with these chemicals. Carbamazepine, sulfamethoxazole, ibuprofen, trimethoprim, and paracetamol are presented most abundantly in Africa, while very high concentrations of synthetic hormones such as estrone, estradiol, and ethinylestradiol were commonly found in South America. Asian water especially has very high concentration of antibiotics (ciprofloxacin, erythromycin, norfloxacin, and ofloxacin) which can be attributed to the heavy consumption and production of these drugs. While limited severe cases of adverse effect have been reported, the Earth's water source should be kept clean and free of unwanted leftovers for our present and future generations.

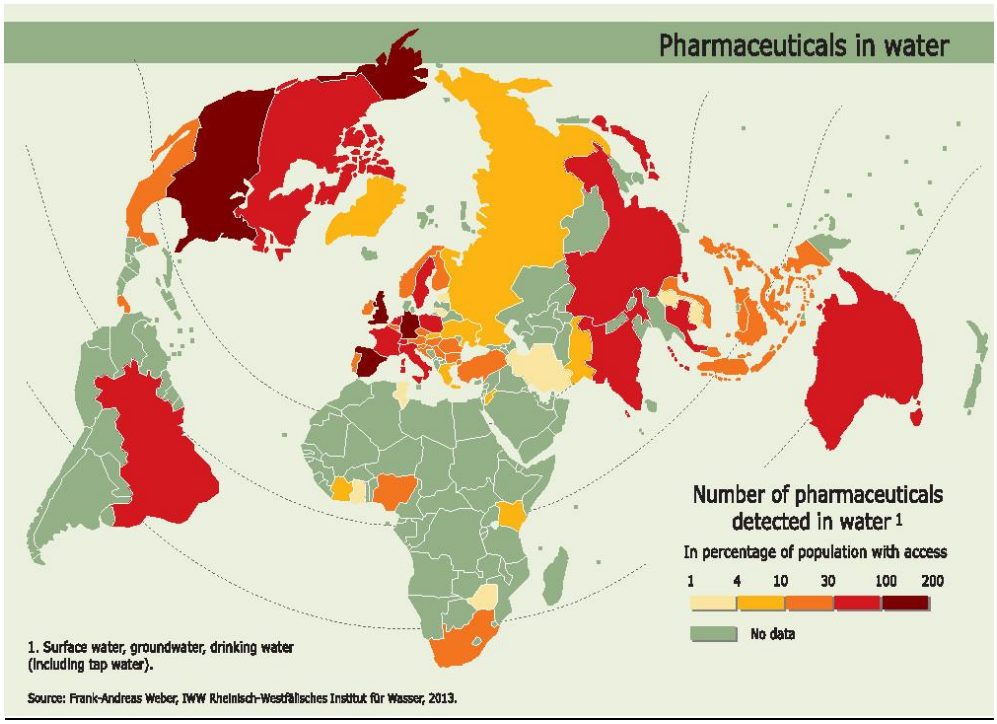
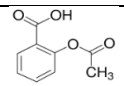
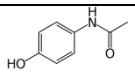
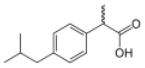
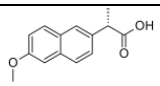
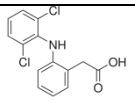
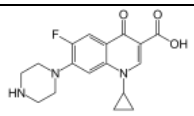
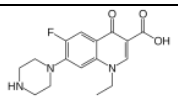
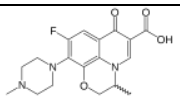
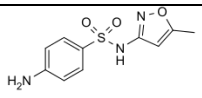
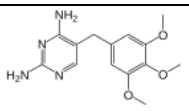
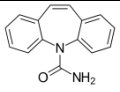
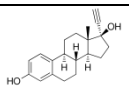
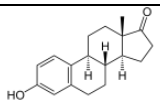
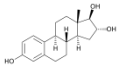
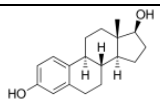


Figure 1. Occurrence of pharmaceuticals in surface water, ground water and drinking water in the world (Weber, 2013)

Table 1 depicts the most common chemicals detected in aquatic systems and their recorded concentrations from all over the globe. They are medicines that are used today to treat and prevent diseases in humans and animals. Globally, the most popular pharmaceuticals pollutants are painkillers (Naproxen, Aspirin, Diclofenac, Paracetamol) with detected frequency of 31 % of all total records with median concentration of 230 ng/L. Second most important pharmaceutical group is antibiotics group (Sulfamethoxazole, Ciprofloxacin, Trimethoprim, Ofloxacin, Norfloxacin) with a 21 % detection frequency and a 8128 ng/L median concentration (Hughes et al., 2013). As can be seen in Table 1, the concentration of each individual residue is very low, with the two highest being the Antibiotics Ciprofloxacin (18.99 µg/L) and Norfloxacin (3.457 µg/L); the rest of them are in the range of 0.003 to less than 1 µg/L. Maximum concentrations are recorded from different locations globally, with each one of those pharmaceuticals being popular in usage within a particular region. Despite the fact that the concentrations are low, it should be noted that these chemicals should not have been released into the water at the first place.

Table 1. Common pharmaceutical pollutants in water bodies, their average and maximum global concentration (aus der Beek et al., 2016)

Type of pharmaceutical	Compound name	Compound structure	Average concentration (µg/L)	Maximum concentration (µg/L)
Analgesics/anti-inflammatories	Acetylsalicylic acid (aspirin)		0.922	20.96
	Paracetamol		0.161	230.0
	Ibuprofen		0.108	303.0
	Naproxen		0.050	32.0
	Diclofenac		0.032	18.74
Antibiotics	Ciprofloxacin		18.99	6500.0
	Norfloxacin		3.457	520.0
	Ofloxacin		0.278	17.7
	Sulfamethoxazole		0.095	29.0
	Trimethoprim		0.037	13.6
Anti-epileptics	Carbamazepine		0.187	8.05

Type of pharmaceutical	Compound name	Compound structure	Average concentration (µg/L)	Maximum concentration (µg/L)
Synthetic Estrogens	Ethinylestradiol		0.043	5.9
	Estrone		0.016	5.0
	Estriol		0.009	0.48
	Estradiol		0.003	0.012

2.2 Pathways

Pharmaceutical residues can enter the environment through multiple complex routes. Figure 2 presents some of the most common exposure pathways of pharmaceutical products from manufacturing source to wastewater then into living bodies.

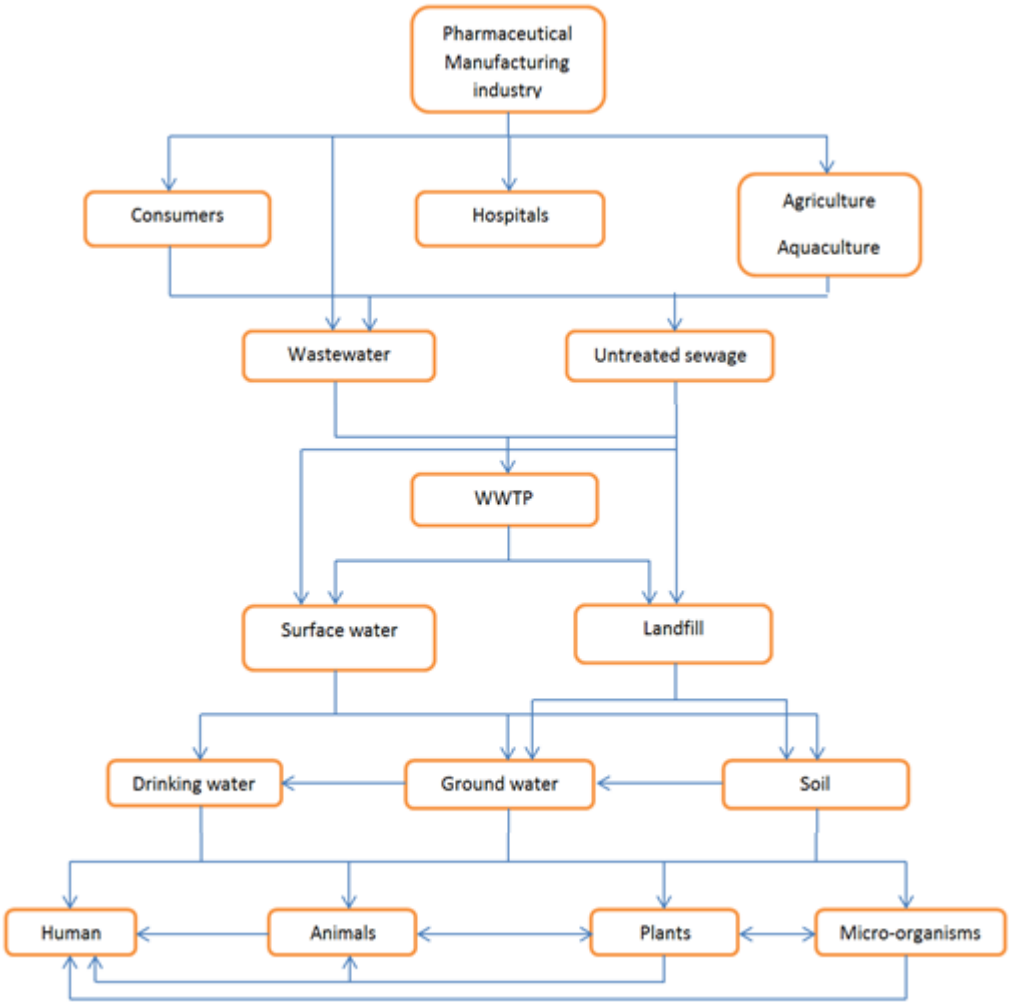


Figure 2. Exposure pathways of pharmaceutical products

Pharmaceuticals can enter the wastewater as early as during the production process. It had been found that effluent from pharmaceutical production site contains a large amount of chemicals which arises from the manufacturing process (Larsson et al., 2007). After the production phase, pharmaceutical products are delivered to pharmacies, health facilities then to the consumers. Most of the pharmaceuticals are consumed by hospitals, healthcare facilities, private consumers and agriculture (with farming, animal husbandry being the most notable) to treat and prevent diseases. When consumed by humans or animals, pharmaceutical products are metabolized to a range of degrees. Their discharged metabolites and parent (original) compounds can be found in urine or feces which go to the sewage system. After that, the biological, chemical and physical processes within WWTPs and the receiving water bodies can further alter these substances'

structure (Deblonde et al., 2011; Fatta-Kassinos et al., 2011). Pharmaceutical residues in animal excretion from agriculture activities through surface runoff can be further exposed to upper soil layer and surface water. They may continue accumulating in the soil layer or penetrating into the groundwater system through leaching (Jongbloed and Lenis, 1998). Hospitals are another source of pharmaceutical discharge. As hospitals do not usually accommodate a sewage water treatment unit to immediately treat their effluent after discharge, a large amount of chemicals resulted from healthcare services are discharged directly into the urban wastewater (aus der Beek et al., 2016). High concentration of various drugs has been found in hospitals' sewage effluent (Orias F, Perrodin Y. 2013).

In general, municipal wastewater treatment plants (WWTPs), even with activated sludge process, are not well equipped to remove all complex pharmaceutical residues since most of them were built with the main goal of removing biodegradable carbon, nitrogen, phosphorus and microorganisms. The removal rates are from less than 20 % up to more than 80 % for most chemicals (Weber et al., 2014). However, it is not complete removal; therefore, pharmaceuticals find their way into the receiving water bodies after the effluent has been discharged from the WWTPs. From there, they can be moved along to accumulate in water bodies, soil, groundwater then drinking water and eventually living organisms.

2.3 Eco-toxicology

So far research has revealed that although the acute toxicity of pharmaceuticals within water bodies is insignificant due to very low concentration (ng/L level), their chronic toxicity may pose a threat to non-target aquatic species in the future (Enick et al., 2007). Pharmaceutical residues, difficult to biodegrade in the environment, can accumulate and be exposed to aquatic beings throughout a long period of time (sometimes their whole life cycle), which may cause undesirable side effects to the ecosystem function (Kümmerer, 2009). Presently, some compounds have already reached the concentration level of displaying chronic/acute toxicity effects, such as diclofenac, propranolol and fluoxetine (Fent et al., 2006). Some examples of the toxicity of pharmaceuticals are reported in Table 2. However, more research and data are still required in the future in order to reach the final conclusion on the eco-toxicological aspect of pharmaceutical residues (Santos et al., 2010).

Table 2. Examples of eco-toxicological effects of pharmaceutical pollutants

Class	Name	Non-target organism	Observed effects	References
Analge-sics/anti-in-flammatory	Diclofenac	Vultures	Enormous de-crease in num-ber of vultures on the Indian subcontinent	Oaks et al.,2004
		Rainbow trouts	Damage of liver, kidney and gills	Triebskorn et al., 2007
Antibiotics	Sulfadiazine	Hazel	Effects on pho-tosynthesis ability and leaf transpiration	Michelini et al., 2015
		Maize	Effect on growth and yield Death at high concentration	Michelini et al., 2012
		Willow	Effect on water uptake Stress at high concentration	
	Enrofloxacin Ciprofloxacin	Cyanobacte-rium Duckweed	Decrease growth	Ebert et al., 2011

Class	Name	Non-target organism	Observed effects	References
Estrogen	17α-ethylny-lestradiol	Fathead min-now	Feminization of males leads to near extinc-tion of the spe-cies within the experimental lake	Kidd et al., 2007
Antidepressant	Fluoxetine	Leopard frog	Later tadpole development	Foster et al., 2010
Anxiolytics	Oxazepam	European perch	Change in habits	Brodin et al., 2013
Veterinary par-asiticide	Ivermectin	Dung fly Beetle	Death of eggs and larvaes	Liebig et al.,2010

Antibiotic resistance is another concern regarding pharmaceuticals in aquatic environment. Antibiotics after consumed by humans and animals can lead to the development of bacteria which are resistant to those drugs in the gut. These bacteria can be released into the environment through excretion. Antimicrobial resistant genes can also be promoted in the aquatic system when antibiotic traces are available. Afterwards, these genes can be passed on to pathogenic bacteria, making them to be more potent as they may become more resistant to current treatment (Kümmerer 2009).

3 Current efforts in pharmaceutical residues removal

3.1 Pharmaceutical removal ability of municipal wastewater treatment plants (WWTPs)

Overall, common WWTPs have limited ability to fully degrade complex pharmaceutical pollutants due to the fact that they are not built with the intention of removing these substances at the first place. Figure 3 presents the basic layout of a standard WWTP.

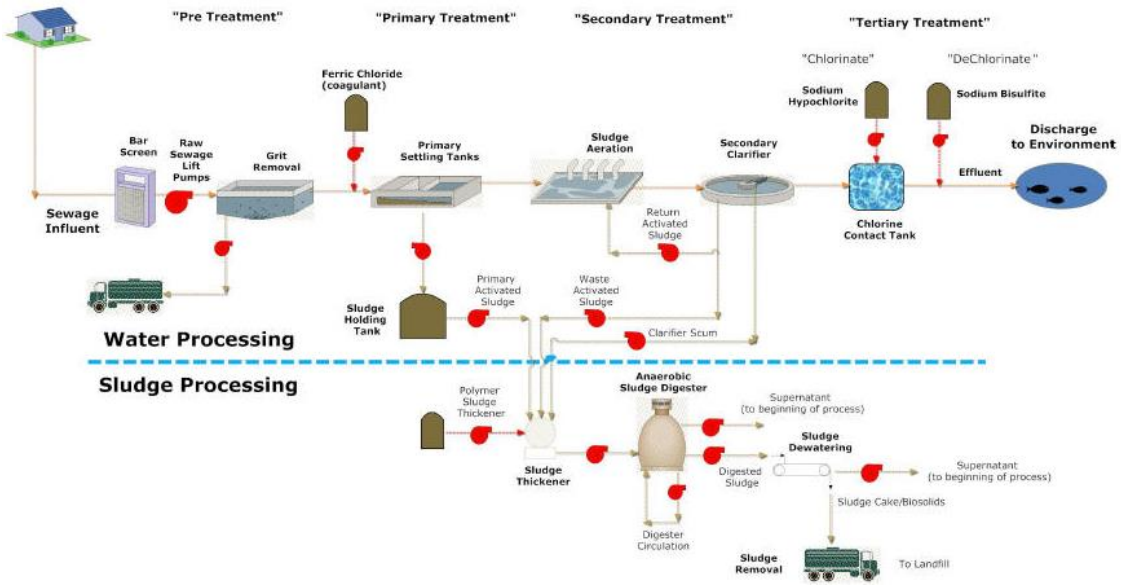


Figure 3. Basic layout of a standard municipal WWTP (the McIlvaine Company)

The wastewater treatment process composes of four main stages: pre-treatment, primary treatment, secondary treatment and tertiary treatment. First, the influent wastewater arrives from the sewage system and passes through the pre-treatment process. During this process the influent undergoes physical screening by bar racks, fine screens and aerated chamber for grit and fat removal. Next, the water is mixed with coagulant chemicals and delivered to the sedimentation tanks, where the primary treatment progresses (sedimentation process). Within the tanks, sludge settles towards the bottom and scraped out while fat/grease float to the surface and skimmed off. This is followed by the secondary treatment step, in which primary removal of organic matter (dissolved and suspended) occurs. This aim can be achieved through multiple different systems for secondary treatment, being fixed-film or attached growth systems (e.g. trickling filters, constructed wetlands and rotating biological contactors) or suspended growth

system (e.g. activated sludge and membrane biological reactors). The final step, tertiary treatment includes biological nutrient removal (nitrogen and phosphorus) and disinfection (reduces the majority of microorganisms) to further improve the water quality. Lastly, the water (WWTP effluent) is discharged into a receiving water body.

The sludge after being separated from the water goes through the sludge treatment process. The aim of this treatment is to reduce the amount of organic matter and microorganisms in the sludge before disposal. Common employed technologies are anaerobic digestion, aerobic digestion composting and incineration.

From influent throughout the whole treatment process to effluent, most pharmaceuticals are removed to a degree but mainly remain in the effluent with low concentrations. Table 3 and figures 4-7 show the levels of drug in the water before and after the treatment procedure in µg/L.

Table 3. Influent-Effluent from various WWTPs (average concentration in µg/L) (References: Verlicchi et al., (2012))

Types of pharmaceutical	Compound name	Average Influent concentration (µg/L)	Average Effluent concentration (µg/L)
Analgesics/Anti-inflammatories	Acetaminophen	38.00	0.89
	Ibuprofen	37.00	3.60
	Tramadol	32.00	20.00
	Salicylic Acid	17.00	0.17
	5-Aminosalicylic acid	14.00	0.64
	Dipyrone	14.00	4.90
	Codeine	6.90	1.70
	Naproxen	6.00	1.00

	Aspirin	3.10	0.36
	Ketoprofen	1.10	0.36
	Ketorolac	1.10	0.42
	Mefenamic acid	1.10	0.63
	Diclofenac	1.00	0.80
	Indomethacin	0.47	0.21
	Hydrocodone	0.12	0.01
	Fenoprofen	0.05	0.02
	Propyphenazone	0.05	0.04
	Phenazone	0.04	0.16
	Dextropropoxy-phene	0.03	0.10
Antibiotics	Ofloxacin	5.10	0.45
	Sulfapyridine	3.30	0.33
	Cefalexin	3.20	0.13
	Erythromycin	1.80	0.73
	Ciprofloxacin	1.60	0.86
	Roxithromycin	1.50	0.50
	Clarithromycin	1.30	0.29
	Chloramphenicol	1.00	0.05
	Sulfamethoxazole	0.92	0.28
	Trimethoprim	0.76	0.36
	Cefaclor	0.74	0.01

	Azithromycin	0.40	0.16
	Metronidazole	0.36	0.25
	Tetracycline	0.33	0.14
	Amoxicillin	0.24	0.01
	Norfloxacin	0.23	0.06
	Sulfachloro-pyridazine	0.19	0.06
	Sulfathiazole	0.11	0.01
	Sulfadimethoxine	0.07	0.09
	Cefotaxime	0.014	0.02
Anti-diabetics	Glibenclamide	8.70	No data
Anti-hypertensives	Hydrochlorothia-zide	3.90	3.30
	Diltiazem	0.70	0.12
Beta-blockers	Atenolol	4.50	3.70
	Sotalol	0.60	0.75
	Propranolol	0.32	0.17
	Metoprolol	0.24	0.32
Diuretics	Furosemide	2.40	0.66
	Bendroflumethia-zide	0.05	0.004
Lipid-regulators	Benzafibrate	3.50	0.90
	Gemfibrozil	2.40	0.93
	Pravastatin	0.49	0.02

	Clofibric acid	0.22	0.21
	Fenofibric acid	0.21	0.11
Psychiatric drugs	Gabapentin	13.00	2.60
	Amitriptyline	3.10	0.14
	Carbamazepine	1.20	1.04
	Fluoxetine	0.54	0.24
Receptor antagonist	Cimetidine	4.10	3.50
	Famotidine	0.08	No data
	Loratadine	0.03	No data
	Omeprazole	0.85	0.63
	Ranitidine	2.70	0.51
	Valsartan	2.50	0.33
Hormones/Estrogens	Estradiol	0.25	0.01
	Estriol	0.17	0.016
	Estrone	0.08	0.03
	Ethinylestradiol	0.02	0.003
Antiseptics	Triclosan	1.90	0.32
Contrast media	Iopromide	2.20	2.50

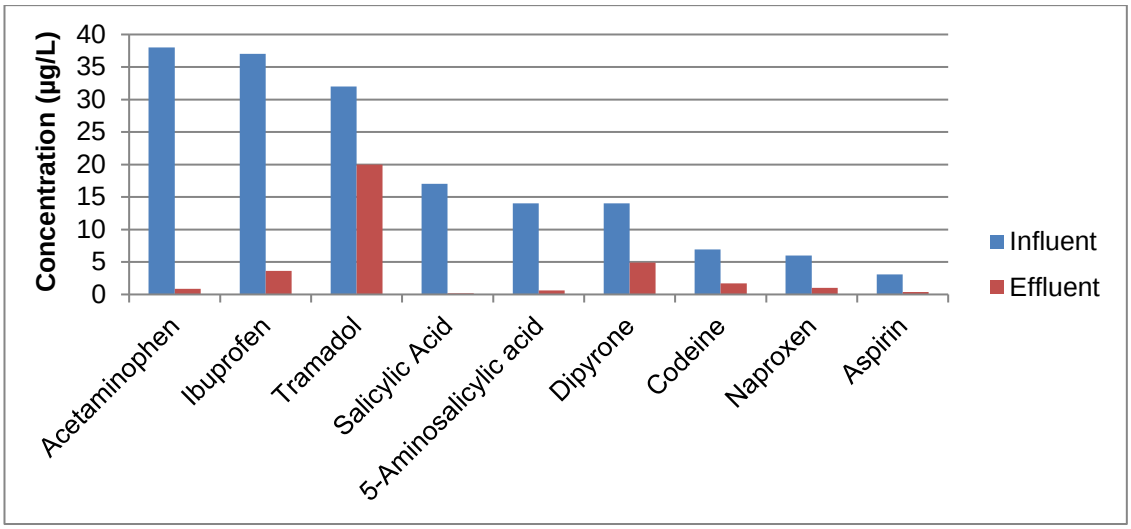


Figure 4-1. Average concentration levels of analgesics and anti-inflammatories (in µg/L) before and after WWTP

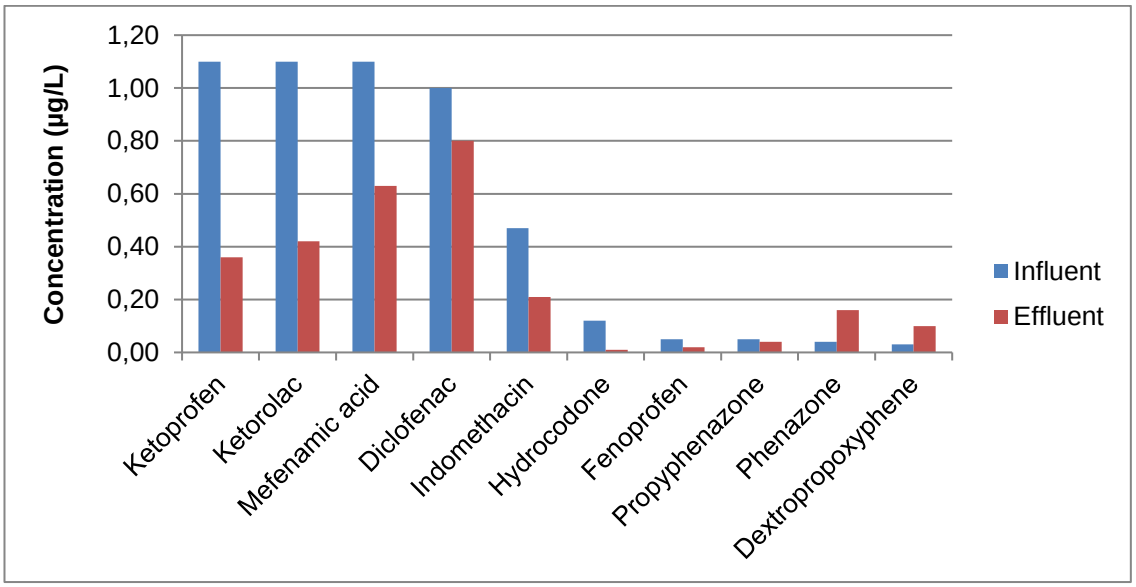


Figure 4-2. Average concentration levels of analgesics and anti-inflammatories (in µg/L) before and after WWTP (continued)

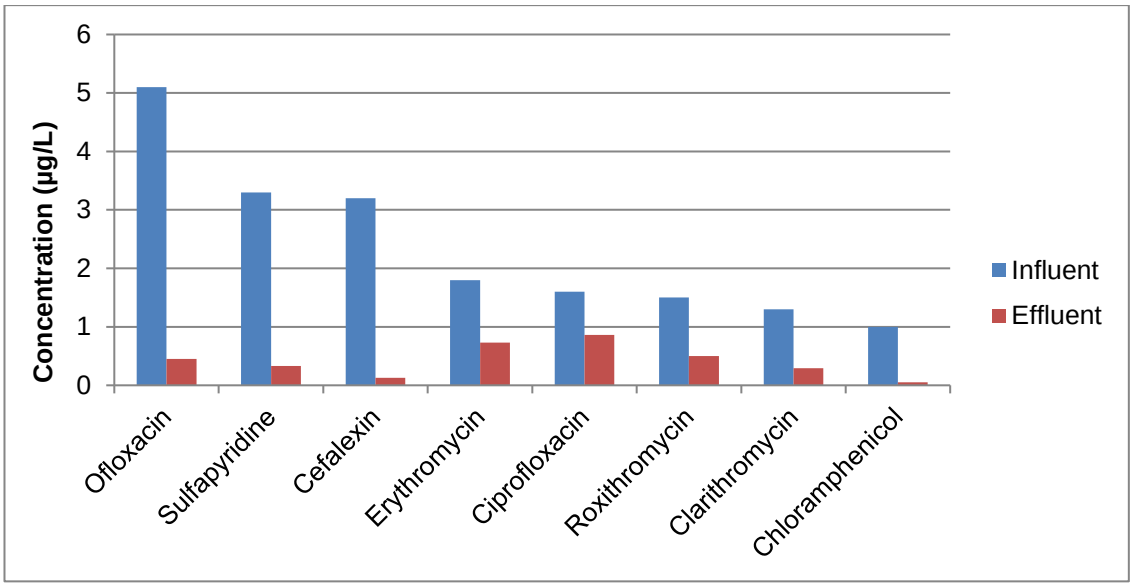


Figure 5-1. Average concentration levels of antibiotics (in µg/L) before and after WWTP

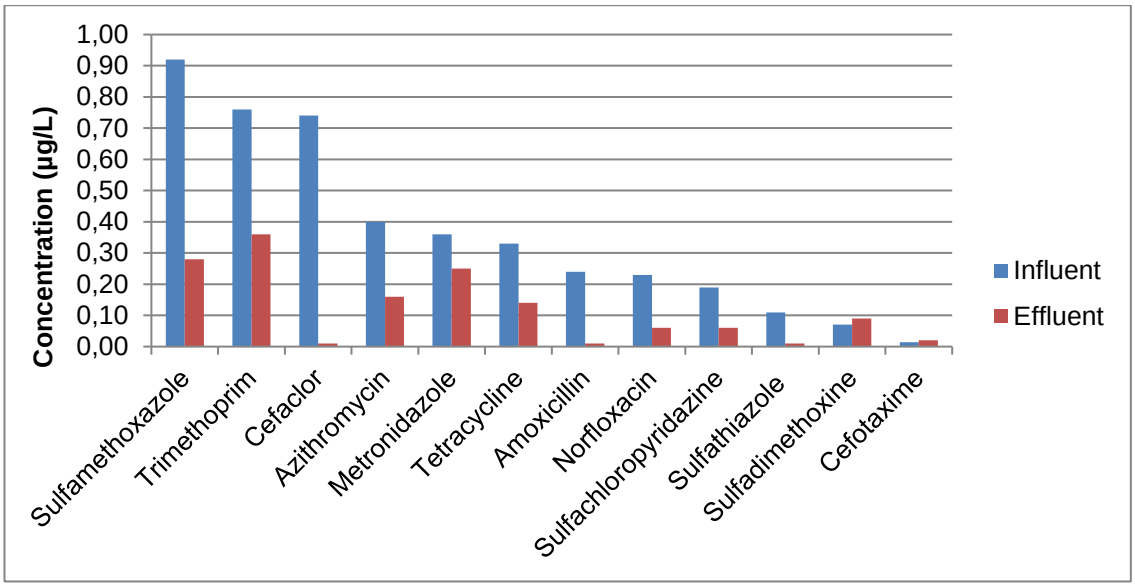


Figure 5-2. Average concentration levels of antibiotics (in µg/L) before and after WWTP (continued)

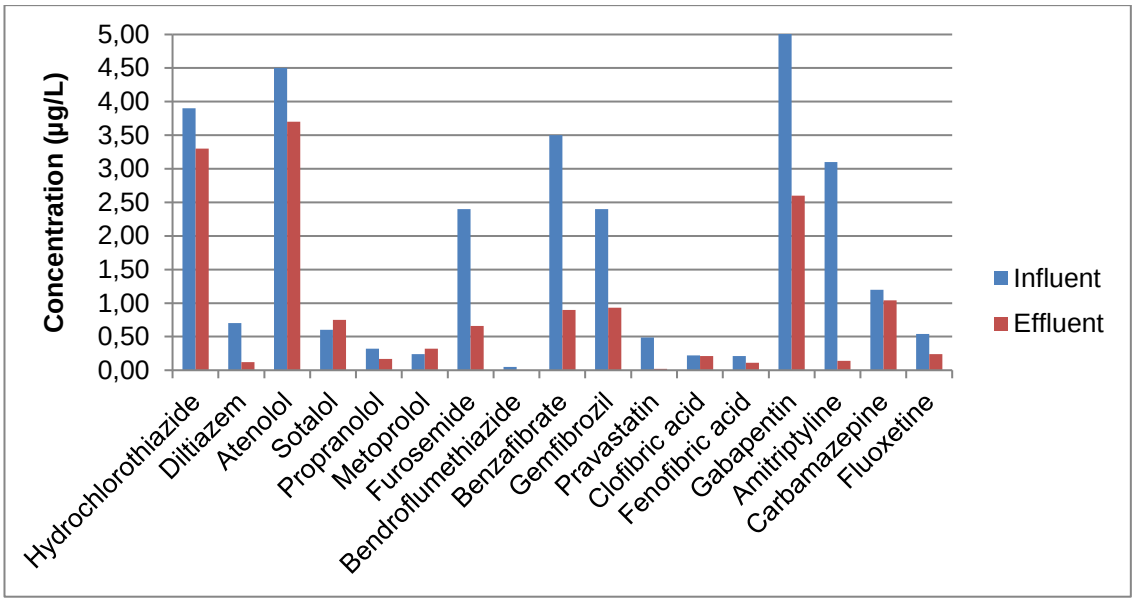


Figure 6. Average concentration levels of anti-hypertensives / Beta-blockers / Diuretics / Lipid regulators / Psychiatric drugs (in µg/L) before and after WWTP

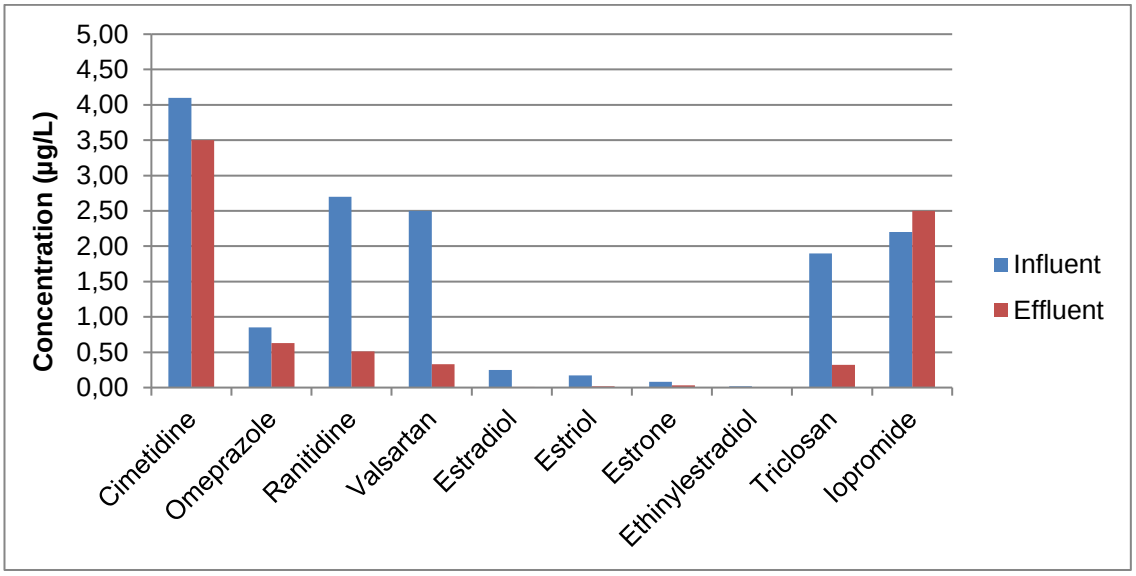


Figure 7. Average concentration levels of receptor antagonist/Hormones/Antiseptic/Contrast media (in µg/L) before and after WWTP

As observed from the data, WWTP's process is mostly not successful in complete removal of all pharmaceutical products, leaving small amount of each in the effluent which is discharged into the receiving water bodies. Additionally, some irregular trends can be seen: for some substances, their concentrations increase after undergoing wastewater

treatment (negative removal efficiency). The reason for this may be due to deconjugates intervening with biological conversion of deconjugated substances. Another reason could be that some particular pharmaceuticals which are sorped onto the particulate dissolving are released after the biological treatment phase. Lastly, this could be the result of instrumental errors when measuring pharmaceuticals with very low concentrations. (Verlicchi et al., 2012)

Throughout the whole treatment process, the removal of residual drugs occurs during preliminary, primary treatment (by absorption onto solids and sedimentation) and secondary biological treatments (by biodegradation and absorption on to particles, flocs and sludge). The removal ability of preliminary and primary treatment has been noted by many to be poor (Khan and Ongerth, 2005; Yasojima et al., 2006; Watkinson et al., 2007; Zorita et al., 2009). Most drug compounds are present in aqueous phase, while having low sorption ability onto coarse solids and sludge (Ternes et al., 2004); therefore, it is reasonable to observe that the physical screening of the pre-treatment and the sedimentation process fail to remove a significant amount of them. Sometimes pharmaceuticals may even be released during these steps due to the simultaneous presence of deconjugable substances of these substances in the influent (Göbel et al., 2005). Most notable for low removal percentage are ibuprofen and naproxen, with their quantity experienced little reduction during preliminary treatment and sedimentation; hormone estrone concentration was found to be increased at the end of primary treatment (Carballa et al., 2004).

The main mechanisms of removal during secondary treatment are biodegradation and sorption (absorption and adsorption). However, with the sorption ability onto sludge to be poor and low capacity for biodegradable (Jia et al., 2012), their removal seems to be due to the sorption onto flocs which are formed by hydrophobic and electrostatic interactions of microorganisms (Lindberg et al., 2006; Jia et al., 2012). Overall, secondary treatment is generally more effective than pre-treatment and primary treatment in chemical residue removal (Carballa et al., 2004).

3.1.1 Pharmaceutical removal efficiency of conventional wastewater treatment plants (WWTPs)

Call *P* is the overall pharmaceuticals removal efficiency of WWTPs, assuming influent and effluent flowrate are constant throughout the day as well as concentration of pharmaceuticals unchanged, *P* can be represented as followed:

$$P = \frac{C_{\text{in}} - C_{\text{out}}}{C_{\text{in}}} * 100\ \%$$

P is the average removal efficiency

C_{in} is the average concentration of a pharmaceutical in the influent

C_{out} is the average concentration of a pharmaceutical in the effluent

Removal efficiency *P* for all pharmaceuticals are presented in Figure 8-11.

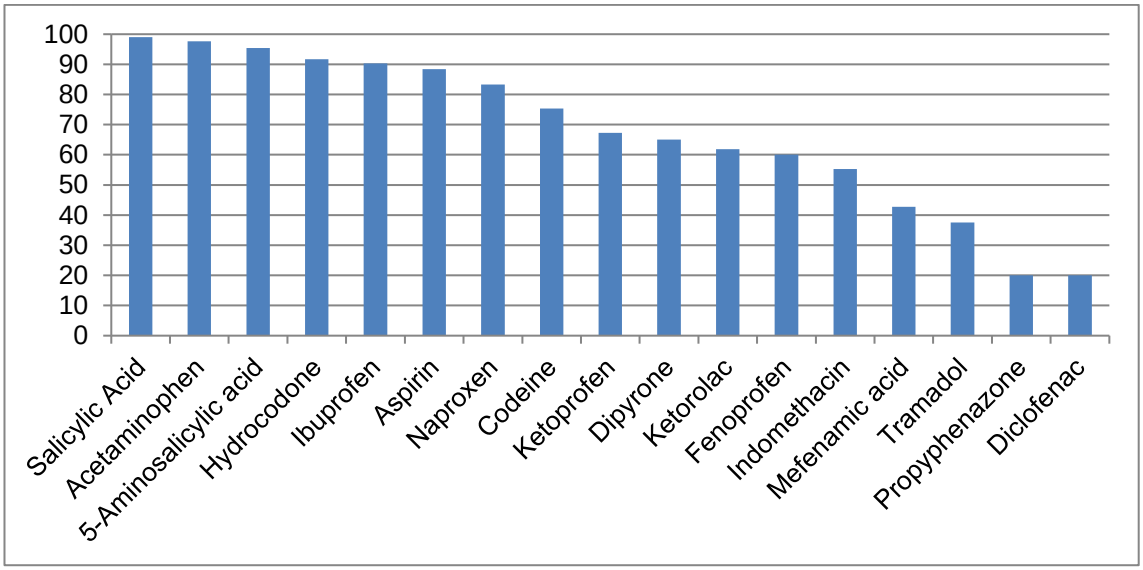


Figure 8. Average removal efficiency (*P*) of analgesics and anti-inflammatories (%) in common municipal WWTPs

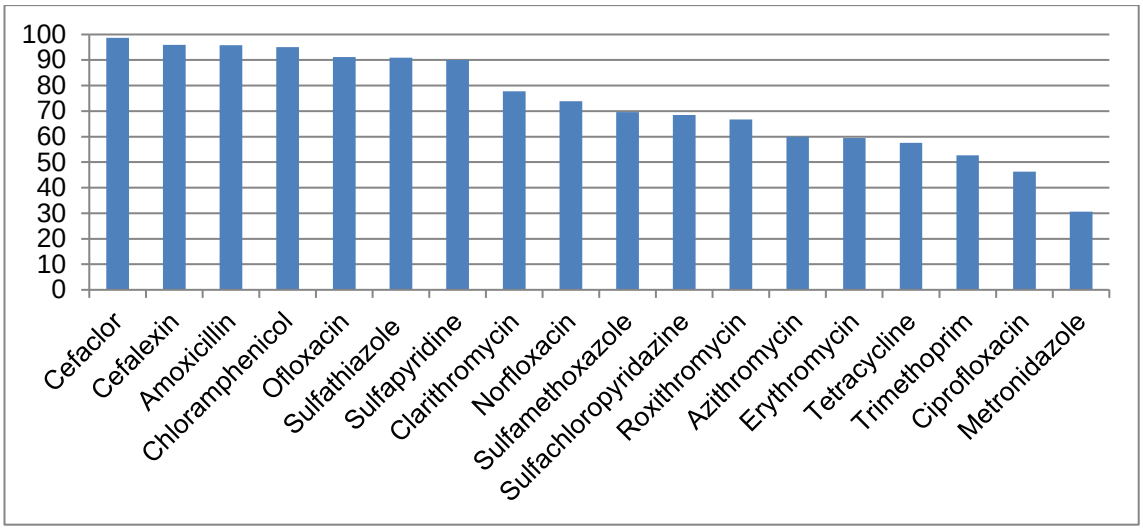


Figure 9. Average removal efficiency (*P*) of antibiotics (%) in common municipal WWTPs

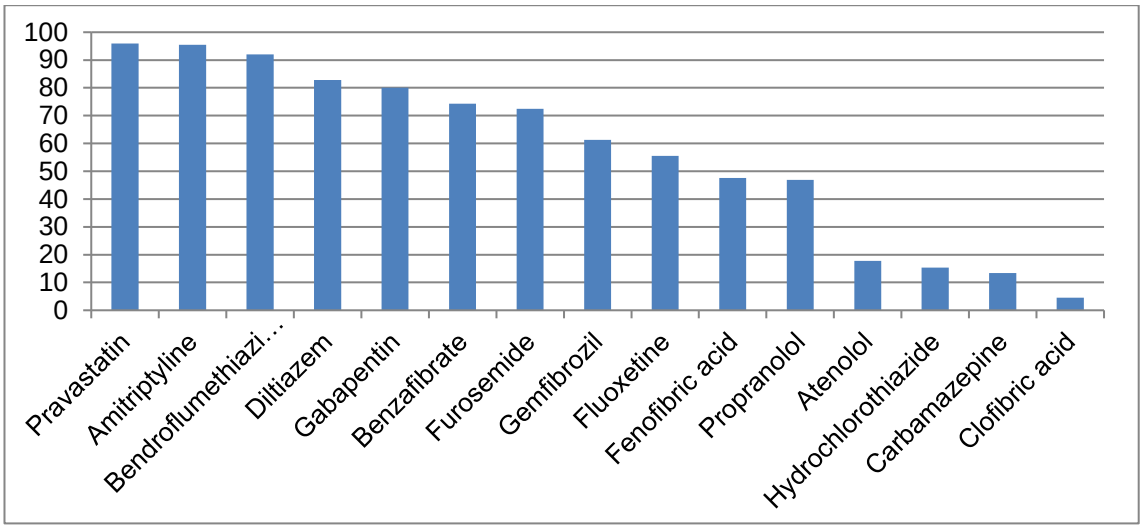


Figure 10. Average removal efficiency (*P*) of anti-hypertensives/beta-blockers/diuretics/lipid regulators/psychiatric drugs (%) in common municipal WWTPs

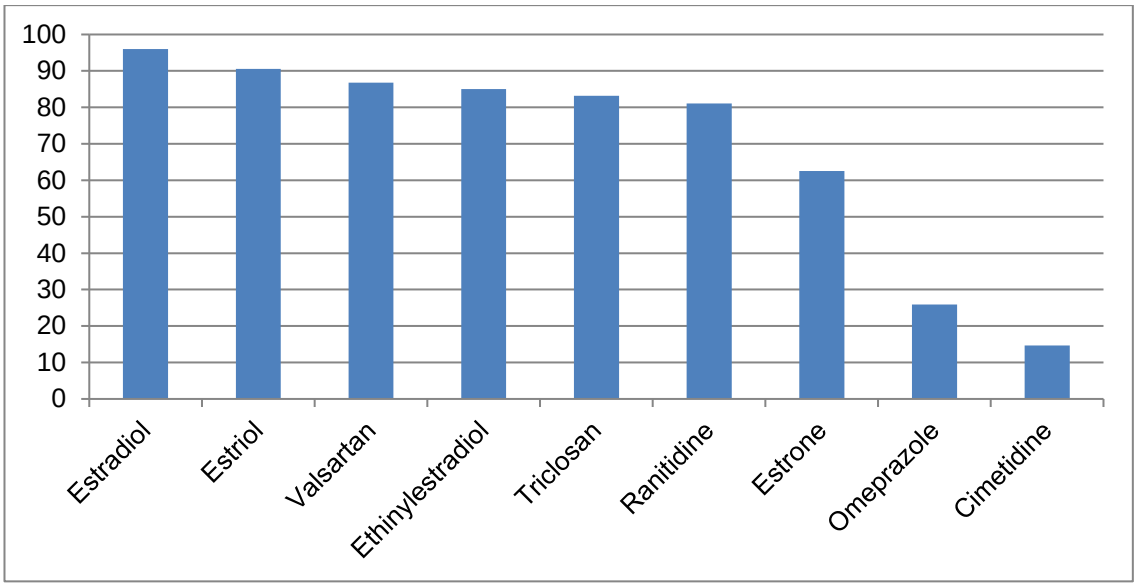


Figure 11. Average removal efficiency (*P*) of receptor antagonist/hormones/antiseptic/contrast media (%) in common municipal WWTPs

As these charts depicts, the removal efficiencies for pharmaceutical products vary widely from less than 20 % to more than 90 %. Some cases show even up to 99 % removal rate. Some pharmaceuticals show good record for example salicylic acid, acetaminophen, 5-aminosalicyclic acid, hydrocodone, ibuprofen (analgesics/anti-inflammatories), cefaclor, cefalexin, amoxicillin, ofloxacin, chloramphenicol, sulfathiazole, sulfapyridine (antibiotics), bendroflumethiazide, pravastatin, amitriptyline, estradiol, estriol (other groups) with high removal rate (90 % and higher). Some of the poor efficiency marks are diclofenac, propyphenazone (analgesics/anti-inflammatories), hydrochlorothiazide, atenolol, clofibric acid, carbamazepine, cimetidine (other groups) with insignificant removal volume (20 % and less). While common municipal WWTPs show good prowess in removing some chemicals with more than 90 % of their original amount, it should be noted that very low loads of these still get released into the environment daily and can accumulate with time, considering typical municipal WWTPs release thousands cubic meter of effluent daily.

In conclusion, pharmaceutical residues compose of a great variety of compounds, many different chemical and physical characteristics and react differently under the same circumstance. Therefore, more complex, well-rounded and specified treatments must be

utilized within WWTPs to successfully remove the majority if not all of the residual substances. Currently, there are several technologies employed specifically for chemicals removal, their pros and cons will be discussed in the next section.

3.2 Current pharmaceutical removal technologies

3.2.1 Adsorption on activated carbon

3.2.1.1 Overview

Activated carbon is a form of processed carbon with high quantity of small, low volume pores which increase the overall surface area for adsorption. Further chemical treatment of carbon can further enhance adsorption capacity. Activated carbon usage in pharmaceuticals removal has been reported by several literatures to be effective with high capacity for pollutants adsorption. (Snyder et al., 2007; Choi et al., 2008; Kårelid et al., 2017). There are several types of activated carbon; however, only two main types are studied extensively for pharmaceuticals adsorption: powdered activated carbon (PAC) and granular activated carbon (GAC). PAC is characterized as fine granules with less than 1 mm in size and average diameter between 0.15 and 0.25 mm. GAC mainly differs from PAC that it has larger grain size, which is typically in range of 1.2 to 1.6 mm. Both types of activated carbon can be prepared from charcoal or natural high carbon content sources such as bamboo, wood and coconut husk. These materials are heated slowly in oxygen-free environment at above 400 °C (carbonization phase), then treated with oxidizing agent (steam or carbon dioxide is commonly utilized) at high temperature to create the submicroscopic spores and increase surface area (activation phase). For example, Mestre et al.,2007 reported using cork powder waste to produce activated carbon by mixing the waste with K_2CO_3 (weight ratio 1:1) and heating at 700 °C for 1 h. The sample was then let to be cool down then washed with distilled water until pH is 7 and dried at 100 °C. To finish, the sample is activated using steam at 750 °C for an hour.

3.2.1.2 Operating mechanism

Activated carbon removes chemicals from water by mechanism called adsorption. It is the adhesion of dissolved chemical molecules (adsorbate) to the surface of activated carbon (adsorbent), which creates a film of adsorbate on it. When introduced into the water, carbon molecules actively seek out other molecules they can adsorb. With high surface area and porous nature activated carbon has good capacity for chemical adsorption.

3.2.1.3 Factors affecting performance

There are several factors influencing the effectiveness of activated carbon adsorption:

- Ingredients types and production methods affect adsorption capacity (i.e. different materials and different treatment procedures can create activated carbon with different adsorption capacity).
- Contact time: the longer the exposure time, the more drug residues activated carbon can adsorb (until it reaches capacity limit).
- The amount of carbon in the system: More activated carbon molecules means more residues could be removed
- Surface area: For example, powdered activated carbon (PAC) is considered to give better results with regard to carbon consumption compared to the granular form (GAC) due to the larger surface area of the finer grains (Meinel et al., 2015).
- Temperature: temperature between 5 to 40 °C does not seem to affect the effectiveness of activated carbon in pharmaceuticals removal. Mestre et al., 2007 and Baccar et al., 2012 showed that temperatures range 25–40 °C has insignificant influence on the adsorption process onto powder activated carbon. Villaescusa et al., 2011 also noted that the temperature between 5 and 30 °C has negligible influence on paracetamol sorption onto activated carbon made from grape stalk.
- pH: Increase in pH reduces the uptake of drug compounds, and this effect is even more noticeable when the pH becomes high (alkaline region). For example, Baccar et al., 2012 reported gradual decrease in removal efficiency of Diclofenac, Naproxen, Ketoprofen and Ibuprofen in activated carbon adsorption system when pH increases from 2 to 8.61. Similarly, Cho et al., 2011 and Bhera et al., 2010 also noticed a reduction in activated carbon effectiveness when increasing pH

level from 3 to 10 in an activated carbon utilization (for removing ibuprofen and triclosan, respectively).

- Hydrophobicity (log K_{ow}): Westerhoff et al., 2005 concluded that compounds with low log K_{ow} seem to be more challenging to adsorp with powder activated carbon (PAC). For example, diclofenac and naproxen have the same pK_a, but diclofenac is adsorbed better due to higher hydrophobicity (diclofenac's log K_{ow} = 4.51 and naproxen's log K_{ow} = 3.18).
- Availability of natural organic matters: activated carbon's performance decreases significantly when the amount of natural organic matters within the water is high, due to the fact that these matters competes with pharmaceuticals for binding sides and thereby block available spores for adsorption of target compounds (Luo et al., 2014).

3.2.1.4 Advantages and limitations of using activated carbon

Activated carbon treatment has several advantages as well as limitations as follows:

Advantages:

- Activated carbon does not generate toxic or pharmacologically active products during the introduction into water as well as the adsorption process.
- Environmental friendly. Activated carbon production can employ recycling materials (coconut husk, biomass residues,etc…)
- Less complicated setting and operation
- High removal rate of several common pharmaceuticals from wastewater such as Atenolol, Carbamazepine, Diclofenac, Trimethroprim, Triclosan, Fluoxetine. (As shown in table 4)

Limitations:

- Total energy demand for application with activated carbon is considerably higher (Mousel et al., 2017). Therefore, the cost of utilizing activated carbon for wastewater treatment is high.

- There is a need for regular regeneration or disposal of used activated carbon to sustain high removal efficiency, which adds more overall cost.

3.2.1.5 Removal efficiency

Table 4 demonstrates the removal rate of several popular pharmaceutical drugs in wastewater using powdered and granular activated carbon. Overall, activated carbon treatment is able to remove a wide range of pharmaceutical pollutants with high success. For example, Kårelid et al., 2017 tested the effectiveness of both PAC and GAC in a wastewater treatment plant scenario and reported a removal rate of over 95 % (for PAC) and over 90 % (for GAC) for all 22 tested compounds, including commonly found substances such as carbamazepine, clarithromycin and diclofenac. The dosage of 15-20 mg/L for PAC is proved to be sufficient to achieve such results. Additionally, within the dosage range of 30-100 mg/L, PAC was found to produce better performance than GAC (with the exception of atenolol, clarithromycin and metoprolol). The overall effectiveness of PAC can be comparable with that of ozone treatment (Luo et al., 2014).

Table 4. Removal rate of several popular pharmaceutical drugs in wastewater using activated carbon (PAC and GAC).

Adsorbent	Pharmaceutical(s)	Removal efficiency or adsorption capacity	References
GAC	Trimethoprim	118-345 mg/g	Liu et al.,(2012)
GAC	Ibuprofen Ketoprofen Naproxen Diclofenac	12.6 mg/g 24.7 mg/g 39.5 mg/g 56.2 mg/g	Baccar et al.,(2012)
GAC	Paracetamol	113-267 mg/g	Cabrita et al.,(2010)
GAC	Ciprofloxacin	119-320 mg/g	Carabineiro et al.,(2011)

Adsorbent	Pharmaceutical(s)	Removal efficiency or adsorption capacity	References
GAC PAC	Trimethoprim	257.9 mg/g	Kim et al.,(2010)
GAC	Paracetamol Ibuprofen	119.1-151.9 mg/g 121.2-166.3 mg/g	Mestre et al.,(2011)
GAC	Tetracycline	95 %	Choi et al.,(2008b)
PAC	Ibuprofen Iopromide Sulfamethoxazole Gemfibrozil Diclofenac Naproxen	16-30 % 30-50 % 36-56 % 37-55 % 38-46 % 52-58 %	Snyder et al.,(2007)
GAC	Acetaminophen Carbamazepine Trimethoprim Triclosan Fluoxetine	73-84 % 74-86 % 76-96 % 90-96 % 91-92 %	Snyder et al.,(2007)
PAC and GAC	Atenolol Carbamazepine Diclofenac Trimethroprim	99 % 94-95 % 97-99 % 98-99 %	Kårelid et al., 2017

3.2.2 Advance oxidation process and photocatalytic process using Ultraviolet radiation (UV)

3.2.2.1 Overview

Ultraviolet (UV) is an invisible electromagnetic radiation with frequency higher than visible light - lower than x-rays and wavelength in the region of 10 nm – 400 nm. UV is present naturally in sunlight and has high energy. UV light has long been known for its effective disinfection ability: it penetrates harmful pathogens in water and destroy microorganisms' DNA and RNA, hence eliminating their reproductive ability. UV can disinfect very efficiently with up to 99 % harmful microorganisms with very simple set up and without chemical addition that affects water quality and taste. Therefore, UV radiation systems are already commonly used in water treatment plants during the tertiary treatment phase for water disinfection. In water treatment, UV radiation are employed at the wavelength range of 250 nm – 270 nm, with the most frequently used wavelength being 254 nm. Recently, UV light has also been discovered for its utility in pharmaceuticals degradation (Lazarova and Savoye, 2004). Main applications of UV light in pharmaceuticals removal are UV, UV/H_2O_2, UV/H_2O_2/Fe^{2+}, UV/TiO_2. UV usage alone is direct photolysis process where UV cause the degradation in organic compounds that are able to absorb UV photons (usually at 254 nm wavelength). UV/H_2O_2, UV/H_2O_2/Fe^{2+} are advance oxidation processes which utilize hydroxyl radicals (·OH) as another oxidation pathway to degrade organic compounds. UV/TiO_2 is a photocatalytic process, where TiO_2 acts as a semiconductor material which upon UV radiation produces hydroxyl radicals, in the end works similar to advance oxidation process.

3.2.2.2 Operating mechanism

Two main pathways of UV technology are the direct photolysis under UV radiation exposure and oxidation process created by hydroxyl radicals. Direct photolysis is the process when compounds absorb UV photons, increasing its energy to reach an excited state, leading to bond breaking and degradation. The substance structure is the main determinant of whether that substance is able to absorb UV energy. Many pharmaceutical products are photoactive (i.e. they can absorb UV photons), hence photodegradable. Nevertheless, the photolysis process produces several unwanted side products which are also highly toxic. Drug residues which do not go through direct photolysis can degrade

through another pathway: under the effect of hydroxyl radicals' reaction. Hydroxyl radicals are produced from the photolytic dissociation of additional reagents (most commonly H_2O_2) under UV exposure. In UV/TiO_2 photocatalytic process, hydroxyl radicals are produced through the reduction of oxygen and water by electron-hole pairs, created when the semiconductor TiO_2 is exposed to UV radiation. Additionally, they can also be generated in a photo-Fenton system (UV/H_2O_2/Fe^{2+}), where not only the UV + H_2O_2 interaction makes radicals but also the H_2O_2 + Fe^{2+} and UV + Fe^{2+} reactions. Hydroxyls radicals reacts unselectively with many pharmaceutical residues to break down those compounds and also destroy many toxic side products of UV photolysis. However, it also affects radicals performance as many other micropollutants are present in WWTPs effluent, which can also reacts with hydroxyls radicals, making less available for the degradation of main priority targets.

Equations:

$H_2O_2 + UV \rightarrow 2 \cdot OH$ (hydroxyl radicals generated by UV radiation)

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+}OH \cdot + OH^-$ (hydroxyl radicals generated by Fenton process)

$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HO_2 \cdot + H^+$ (Fe(III) reverts to Fe(II) to continue the hydroxyl radicals generation cycle)

3.2.2.3 Factors affecting performance

There are several factors influencing the effectiveness of advanced oxidation process using UV:

- pH affects the generation of hydroxyl radicals (alkaline pH level is favored)
- The chemical structure of the target pharmaceutical determines if that pharmaceutical could absorb UV photons to degrade or not.
- A large number of suspended particles makes UV light less effective because it prevents the penetration of UV light into the water.
- The amount of additional chemicals (H_2O_2 or Fenton's reagent) affects the quantity of available hydroxyl radicals for degradation.
- The availability of interfering radicals which react with hydroxyl radicals reduces the amount available to degrade target compounds.

3.2.2.4 Advantages and limitations of UV techniques

UV treatment has several advantages as well as limitations as follows:

Advantages:

- UV techniques are less affected by drastic pH and temperature change compared to other technologies.
- UV radiation is already used widely in WWTPs for disinfection.
- UV techniques are simple set up and usage.
- UV treatment is cost-effective and highly sustainable (relatively low cost equipment, low energy input and cheap chemical reagents addition).

Limitations:

- UV radiation can only work efficiently on clear water, murky water affects the UV ray ability to infiltrate the whole water body and reduces its effectiveness.
- The addition of H_2O_2 is frequently needed to maximize the treatment efficacy, since UV light alone is not able to degrade a wide variety of drug residues.
- Photodegradation process of some pharmaceutical compounds produces highly toxic side products.

3.2.2.5 Removal efficiency

Table 5 demonstrates the removal efficiency for various pollutants utilizing several common UV technologies. Generally, UV is not particularly a great treatment method when applied alone as it can only remove a few pharmaceuticals with significant effectiveness (>90 % removal rates for those such as tetracycline, ketoprofen,diclofenac and antipyrine) (Kim et al., 2009; Gomez-Pacheco et al., 2012). The capability of UV treatment is improved greatly when used in conjunction with H_2O_2, Fenton's reagent or TiO_2 which boost the generation of hydroxyl radicals. For instance, in a study conducted by Kim et al., (2009) which examined the effect of 254 nm UV/ H_2O_2 combination in the elimination of 41 pharmaceutical compounds found that the addition of 7.8 mg/L H_2O_2 increases the

efficacy of the UV treatment greatly from >90 % removal of a few substances to >90 % removal of 39 pollutants. Another research by De la Cruz et al., (2012) which investigated difference between 254 nm UV alone and the combination of 254 nm UV and Fenton's reagent ($Fe^{2+,3+}/H_2O_2$) also confirmed a similar conclusion. Out of 32 targeted micropollutants, UV standalone treatment could only degrade successfully diclofenac, ketoprofen, mefenamic acid with 100 % amount while showing low results on others. Meanwhile, the mix of UV and 50 mg/L H_2O_2 produced a total degradation rate of 81 %, which was further increased to 97 % after another 30 minutes of treatment. Similarly, the $Fe^{2+,3+}/H_2O_2$/UV combo generated an appealing result as a global degradation of 97 % was observed.

Table 5. Removal efficiency of several UV technologies

Treatment method	Target pollutant	Removal efficiency	References
UV	Metronidazole	83 %	Prados-Joya et al., (2011)
	Dimetridazole	82 %	
	Tinidazole	76 %	
	Ronidazole	73 %	
	Carbamazepin	<5 %	Lekkerkerker-Teunissen et al., (2012)
	Tetracycline	100 %	Gomez-Pacheco et al.,(2012)
UV/H_2O_2	Doxycycline	100 %	Andreozzi et al.,(2004)
	Ciprofloxacin		
	Diclofenac	100 %	Andreozzi et al.,(2004)
	Amoxicillin	99 %	Jung et al.,(2012)
	Carbamazepine	100 %	Andreozzi et al.,(2004)
	Ofloxacin	100 %	Andreozzi et al.,(2004)

Treatment method	Target pollutant	Removal efficiency	References
UV/TiO_2 (with and without H_2O_2)	Atenolol	100 %	Yang et al., 2010
	Metoprolol		
	Propranolol		
	Amoxicillin	100 % with H_2O_2 and much lower without	Elmolla and Chaudhuri (2010)
	Ampicillin		
	Cloxacillin		
UV/H_2O_2/Fe^{2+}	Carbamazepine	100 %	De la Cruz et al ., 2012
	Diclofenac		
	Ibuprofen		
	Ketoprofen		
	Naproxen		
	Ciprofloxacin		

3.2.3 Ozonation (O_3)

3.2.3.1 Overview

Ozone is a molecule that consists of three oxygen atoms (O_3). It is basically the normal atmospheric oxygen (O_2) with an additional oxygen atom attached by a weak bond. This weak bond makes ozone unstable under normal conditions and readily revertible to O_2 which is the more stable form. This also gives ozone a high oxidizing power with various kinds of organic compounds and microorganisms, especially those with electron-rich functional groups such as double bonds or aromatic rings. Therefore, ozonation is widely

utilized in drinking water treatment in order to disinfect, remove inorganic materials and eliminate odor/taste. Recently, with the increased awareness of pharmaceutical residues in water, ozone has been tested for the ability to decompose these harmful substances. It has been reported that ozonation is a promising post treatment as it significantly reduces pharmaceutical load in a full scale WWTP, with a relatively low dose and high efficiency (Hollender et al., 2009). This method has been shown to be able to remove a wide range of pharmaceutical residues with a high removal rate up to 90-100 % (Sui et al., 2010; Gerrity et al., 2011). However, ozonation is not without drawbacks. Ozone is not very effective in oxidizing some popular pharmaceuticals such as perindopril, phenytoin, sertraline or ketoprofen (Ahmed et al., 2017) Furthermore, research has indicated the formation of the potentially carcinogenic substances such as bromate and N-nitrosodimethylamine (NDMA) can be facilitated with ozone usage and reduce overall water quality (von Gunten 2003, Hollender et al., 2009; Yang et al., 2009). The ozone system also consumes a high amount of energy and thereby has high operating cost: Ahmed et al., 2017 studied and reported that an ozone treatment system can boost the energy consumption in a common sewage treatment plant by 40–50 %. Overall, despite of its limitations, ozonation is currently still a very viable option to remove unwanted micropollutants with high efficiency and restore the water quality.

3.2.3.2 Operating mechanism

There are two main mechanisms operating the oxidation of organic compounds in ozonation process: the direct pathway in which ozone reacts directly with the contaminants and the indirect pathway in which ozone decomposes to create hydroxyl radicals (·OH), which react non-selectively with organic molecules. H_2O_2, Fenton reagent and ultraviolet are frequently used in combination with ozone as they promote the generation of OH radicals.

Generation of hydroxyl radicals by ozone can be expressed as follows:

$$O_3 + OH^- \rightarrow HO_2^- + O_2$$

$$O_3 + HO_2^- \rightarrow HO_2 \cdot + O_3^- \cdot$$

$$O_3^- \cdot + H^+ \rightarrow HO_3 \cdot$$

$$HO_3 \cdot \rightarrow OH \cdot + O_2$$

Generation of hydroxyl radicals by the addition of Fe(II) and H_2O_2 can be expressed as follows:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+}OH \cdot + OH^-$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HO_2 \cdot + H^+$$

Some organic compounds readily react to ozone through both mechanisms (naproxen and carbamazepine); some only react to OH radicals and not to ozone directly (atrazine and meprobamate) and some are resistant to both forms of oxidation (e.g. tris(2-carboxyethyl)phosphine and tris(2-chloroisopropyl)phosphate) (Gerrity et al., 2011). Overall, molecular ozone can only react selectively with organic substances (such as those with electron-rich functional groups) and this direct pathway has smaller reaction rates, while OH radicals are not discriminating; therefore, the reaction rates are much faster.

3.2.3.3 Factors affecting performance

There are several factors influencing the effectiveness of ozone treatment:

- Dosage: Antoniou et al., (2013) tested the effectiveness of ozone in removing 42 different pharmaceuticals and showed that a dosage of 1.4 g O_3 per g DOC (dissolved organic carbon) is required to achieve a removal rate of at least 90 %. For chemicals that are resistant to ozone treatment, a double amount (2.8 g O_3 per g DOC) is required, thus increase the cost of treatment significantly.
- pH: It has been proved that even though the formation of hydroxyl radicals is enhanced under alkaline conditions, lower pH is beneficial for overall pharmaceuticals removal efficiency (Zhang et al. 2012).
- Interfering ions: some ions (such as bromate (Br^-)) can interfere with the ozonation process.
- Wastewater composition: suspended particles in the wastewater may also react with ozone, decreasing the amount available for the degradation of pharmaceuticals. Therefore, wastewater with high amount of suspended particles may need a higher amount of ozone. However, this effect seems to be minor (Hernández-Leal et al., 2011; Huber et al., 2003)
- Chemical structure of pollutants: Since ozone readily reacts with electron-rich functional groups, the chemical structure of pharmaceuticals available in the wastewater (whether it has the electron-rich functional groups) determine if the pharmaceutical would be effectively degraded by O_3. Positive functional groups for degradation are C-C double bonds, tertiary amines, aniline, phenol and methoxy groups. Meanwhile, electron-withdrawing functional groups, such as fluoro, nitro, chloro, amide and carboxyl, prevent direct oxidation reactions from ozone

(Nakada et al., 2007; Hollender et al., 2009; Antoniou et al., 2013). Additionally, pollutants that are resistant to ozone's direct oxidation may still be degraded through the hydroxyl radical pathway.

3.2.3.4 Advantages and limitations

Ozone treatment has several advantages as well as limitations as follows:

Advantages:

- Capable of removing a wide range of pharmaceuticals in a relatively short time duration
- Very effective, offering a high removal rate of pharmaceutical residues (>90 %)

Limitations:

- High energy consumption
- Formation of carcinogenic by-products such as bromate, N-Nitrosodimethylamine (NDMA) (von Gunten 2003; Hollender et al., 2009; Yang et al., 2009)
- Interference of radical scavengers

3.2.3.5 Removal efficiency

Table 6 shows the removal efficiencies for several commonly found pharmaceuticals using ozone technologies. Overall, ozone treatment is capable of breaking down a large variety of micropollutants within the wastewater with high efficiency. Sui et al., (2010) studied the application of ozone in treating pharmaceutical residues within four WWTPs' effluent. An ozone dose of 5 mg/L was shown to decrease the concentrations of carbamazepine, diclofenac, indomethacin, sulpiride and trimethoprim by more than 95 %. However, the reduction of N, N-Diethyl-meta-toluamide (DEET), metoprolol and bezafibrate was only moderate, especially bezafibrate (removal rate of 14 %). Similarly, another study conducted by Gerrity et al., (2011) showed that the application of ozone/ H_2O_2

combination can produce a respectable performance with > 90 % for 17 target contaminants including carbamazepine, diethyltoluamide (DEET), diclofenac and fluoxetine. Meprobamate (80 %) and ibuprofen (83 %) also were removed by an acceptable amount. However, TCEP (13 %), TCPP (26 %) and atrazine (69 %) was proved to be more resistant to this type of treatment.

Table 6. Removal efficiency of ozone treatment towards various target compounds

Treatment	Targeted compounds	Removal (%)	Reference
O_3 (5 mg/L) for 15 min	Carbamazepine	>90	Sui et al., 2010
	Diclofenac	>90	
	Metoprolol	80-90	
	Bezafibrate	0-50	
	Trimethoprim	>90	
O_3 (5 mg/L) + H_2O_2 (3.5 mg/L)	Ibuprofen	83	Gerrity et al., 2011
	Diclofenac	>99	
	Carbamazepine	>99	
	Sulfamethoxazole	98	
	Triclosan	>99	
	Estradiol	>83	
	Estrone	>98	

3.2.4 Biological based treatment

3.2.4.1 Overview

Recently, biological-based water treatment technologies have emerged and gained considerable attention. These types of treatment utilize natural ingredients such as fungi, microalgae or macrophyte species, simulating the ability of natural ecosystems to minimize the effect of micropollutants. There are some significant benefits of these treatment methods compared to other advanced treatments such as lower overall cost, less toxic side products, production of ecology-rich water effluent and biomass for biofuel production. Several setups are available as biological-based treatment including high-rate algal ponds (using microalgae), constructed wetlands (using macrophytes), fungal reactors

(using fungi). Several studies have shown a trend of high effectiveness of these methods in removing pharmaceutical residues (Rodríguez-Rodríguez et al., 2012; Ávila et al., 2013; Garcia-rodríguez et al., 2013; Matamoros et al., 2015). Overall, biological-based treatments are promising solution for the future of micropollutants removal due to the competitive edges and versatility they bring. Table 7 demonstrates the main features of several biological treatments.

Table 7. Description of several biological-based wastewater treatment technologies

Treatment name	Ingredients	Description	Main mechanisms involved
High-rate algal ponds	Microalgae (Stigeoclonium sp., diatoms, Chlorella sp.) and heterotrophic bacteria	Passos et al., (2014:351) described the high-rate algal ponds as “shallow raceway reactors in which microalgae and bacteria grow in symbiosis”. Within the systems, heterotrophic bacteria degrade organic matter and expend oxygen provided by microalgal photosynthesis activity; thus, no aeration is required.	Phytoremediation
Constructed wetlands	Macrophytes (Phragmite australis, Typha angustifolia)	Constructed wetlands utilize shallow ponds, beds containing floating or emergent rooted wetland vegetation, which wastewater runs through. Microcontaminants are removed either by plant uptake, photodegradation or biodegradation (by rhizosphere microbial community) (Garcia-Rodríguez et al., 2013)	Phytoremediation Biodegradation Photodegradation Sorption

Treat-ment name	Ingredients	Description	Main mechanisms involved
Fungal reactors	White-rot fungi (Phanero-chaete chrys-osporium, Trametes ver-sicolor)	White-rot fungi species excrete oxida-tive enzymes that are able to degrade a wide variety of organic pollutants. Fungal treatment can be used in packed bed bioreactor, fluidized bed bioreactor, trickle-bed bioreactor, stirred tank bioreactor, rotating biolog-ical contactor, and membrane biore-actor.	Biodegradation

3.2.4.2 Operating mechanisms

There are several mechanisms involved in biological-based treatments depending on the set-up and the materials used. Dominant mechanisms are as follows:

- *Biodegradation* is the process in which microorganisms such as bacteria and fungi produce enzymes which are responsible for the decomposition organic pol-lutants into simpler chemical substances which pose no harm to the environment (Cajthaml et al., 2009). The process can be performed under aerobic or anaero-bic conditions.

- *Phytoremediation* is the direct use of living plants (macrophytes and algae) to remove hazardous chemicals. It can occur through plant uptake, plant exudates or enzymes produced by plants that break down chemical substances or with the participation of rhizosphere organisms (i.e. microorganisms within the region of soil that is directly influenced by root secretions) (Pilon-Smits 2005; Susarla et al. 2002).

- *Photodegradation* does not involve plants but the effect of sun ray. Some chemicals that can be difficult to break down under other process (i.e. diclofenac and triclosan), are decomposed under the effect of solar energy. Photodegradation composes of direct and indirect pathway. Direct photodegradation involves the absorption of solar energy by chemical pollutants, which in turn enter the sequence of chemical reactions, which break them down into simpler substances. Indirect photodegradation is the pathway in which pollutants are broke down by the high oxidizing power of hydroxyl radicals generated by the effect of radiation.

- *Sorption* includes absorption and adsorption. Adsorption is the process in which the pollutants are adhered physically onto the surface of a sorbent. Absorption is the incorporation of the contaminants into the sorbent.

3.2.4.3 Factors affecting performance

There are several factors influencing the effectiveness of biological treatment:

- Hydraulic retention time (HRT): Matamoros et al., (2013) have shown that pharmaceuticals removal rates in biological-based treatment systems increases with longer HRT due to the fact that biodegradation and sorption processes have more time to function.

- pH: The appropriate pH level has a positive impact on the optimal development and function of plants and microbial community.

- Sunlight and temperature (or seasonal factors): The amount of sunlight and temperature level affect plants and microbial development. These factors also directly influence algal and microbial activity. Research has shown that algal activity was clearly higher in summer than in winter, when the temperature is better suited, whereas average microalgal biomass concentration and production were noticeably better in hot seasons due to the higher amount solar radiation exposure (Matamoros et al., 2015).

- Dissolved particles and suspended particles: A high amount of dissolved particles and suspended particles reduces sunlight penetration in water. Therefore, it affects the effectiveness of photodegradation as well as the growth of algae (Garcia-Rodríguez et al., 2013).

- Micropollutants' properties and their interaction with the plant system: Micropollutants' properties affect phytoremediation mechanism. Different types of plants can uptake a different range of micropollutants. Also, only certain chemicals with fitting structure, appropriate solubility, polarity, and partitioning coefficients can be uptaken by plants (Tsao 2003).

3.2.4.4 Advantages and limitations

Biological treatment has several advantages as well as limitations as follows:

Advantages:

- Overall cost-effectiveness and sustainablity: low energy consumption, low maintenance and operation cost.

- Recovery of biomass for other purposes, such as biofuel production or fertilizing.

- Production of high quality and ecology-rich effluent.

Limitations:

- Plants' development as well as microbial activity are affected by seasonal variables such as temperature, sunlight intensity and duration. Therefore, there is a noticeable decline in the percentage removal rate in the cold season (Matamoros et al., 2015).
- Biological-based treatments can remove a wide range of pharmaceutical pollutants, but they are not particularly effective in removing some substances which resist these treatments. For example, high-rate algal ponds remove poorly (<30 % removal rate) carbamazepine or benzothiazole (Matamoros et al., 2015).

3.2.4.5 Removal efficiency

Overall, the ability of biological based treatment to degrade unwanted pharmaceutical residues seems very promising. Fungal reactors are capable of degrading some commonly found chemicals such as codeine, atendol, propranolol, sotalol, acetaminophen, erythromycin, sulfathazole, sulfapyridine and sulfamethazine with up to complete removal rate. The fungi based treatment system seems to remove betablockers at the highest effectiveness, followed by gastroesophageal, anti-inflammatory and stimulants, antibiotics, analgesics and lastly lipid regulators (Ahmed et al., 2017).

Macrophytes-based treatment applied in constructed wetland also produces good results. For example, diclofenac, ibuprofen, and naproxen can be completely removed. However, some pharmaceuticals such as carbamazepine, clofibric acid, amoxicillin, clarithormycin are resistant to this method and must be removed by different technology (Hijosa-Valsero et al., 2011; Garcia-Rodríguez et al., 2013).

Microalgae-based treatment, most notably the high rate algal ponds (HRAPs), has been shown to be excellent in degrading caffeine, acetaminophen, ibuprofen and hydrocinnamic acid with an overall removal rate of >90 % in a study by Matamoros et al., (2015). HRAPs also showed moderate success in removing ketoprofen, 5-methyl/benzotriazole, naproxen and triclosan (60 % to 90 % removal) but proved to be ineffective at treating carbamazepine, benzothiazole and tris(2-chloroethyl) phosphate (TCEP). Table 8 presents the pharmaceutical removal efficiency of some biological treatments.

Table 8. Removal efficiency of various biological-based wastewater treatment methods

Type of treatment	Targeted pharmaceuticals	Removal rate (%)	References
Microalgae-based	Caffeine	98	Matamoros et al., 2015
	Triclosan	95	

	Acetaminophen	99	
	Ketoprofen	95	
Fungi-based	Codeine	100	Garcia-rodríguez et al., 2013
	Ibuprofen	92	
	Sotalol	100	Rodríguez-Rodríguez et al., 2012
	Atendol	100	Rodríguez-Rodríguez et al., 2012
Macrophytes based	Ibuprofen	85	Ávila et al., 2013
	Acetaminophen	>95	
	Tetracycline	94	Carvalho et al., 2013
	Naproxen	99	Ávila et al., 2010

3.3 Discussion

Although considerable efforts has been put in discovering and testing different technologies to remove unwanted pharmaceutical residues and to restore the water quality, and while these methods have yielded results, they have yet to become perfect and limitations are present. Not one technology is able to remove every pharmaceutical substance with great effectiveness, and each technology has a certain group of pharmaceuticals that are resistant to it. Furthermore, some treatment methods were shown to produce serious downsides which cannot be ignored (the production of highly toxic side products such as carcinogenic bromate substance in ozonation, for example). In order to minimize the disadvantages and maximize the effectiveness of these technologies, coupling treatments was suggested. For instance, advance oxidation method (UV or ozone) can be paired with activated carbon so as to improve the global degradation ability, as activated carbon can control some substances that ozonation cannot and vice versa. Additionally, activated carbon can help collect toxic side products formed from oxidation process (Sánchez-Polo et al., 2008).

4 Conclusion

Pharmaceutical residues have emerged and attracted considerable attention recently as potentially hazardous pollutants to the environment. There is evidence showing traces of these micropollutants in water resources and wastewater treatment plants' effluent across the globe. Even though their concentrations are low (in the ng/L to µg/L range), if left unchecked and allowed to accumulate over the years, this chemical waste can pose a serious threat to the balance of the ecosystems and human health. These pollutants are composed of drug groups such as analgesics/anti-inflammatories, antibiotics, antidiabetic, antifungal, psychiatric drugs and synthetic hormones, to name a few. Some commonly found substances in the water body all over the world are naproxen, diclofenac, acetaminophen, aspirin and caffeine. These chemicals are originated from mainly medical, agriculture and animal husbandry activities. Humans and animals digestive system cannot convert all of the drugs consumed in these activities. These drugs then are released into the waste system, going through sewage treatment plants without being completely degraded and then discharged into the environment. There is evidence showing that when these micropollutants are allowed to accumulate, they can seriously affect

living entities within the natural food chains, which in turn can be harmful towards the ecosystems.

Although much effort has been made to improve existing technologies, current common wastewater treatment is not effective in removing pharmaceutical residues from the water influent. Traces of a wide variety of drugs have been detected in analyzing the effluent of common wastewater treatment plants. Therefore, more advance treatment techniques must be applied in order to reduce the micro-waste load in the wastewater. Currently, there are many techniques available with various effectiveness, and more will be invented in the future. Some of the most commonly researched methods are adsorption using activated carbon, advance oxidation methods using ultraviolet (UV rays), ozonation, biological treatment using fungi, microalgae and macrophytes. Activated carbon is effective in removing a lot of commonly found drugs, and produces effluent without toxic or pharmaceutical active side products, but very costly in terms of operation and maintenance. Carbon ingredients, contact time, total carbon load, pores size, surface area, temperature, pH, hydrophobicity and available NOM amount are factors which can affect the adsorption strength of activated carbon. Advance oxidation processes can be based on UV light or ozone, with Fenton's reagent, TiO_2 and H_2O_2 being popular addition in order to improve its effectiveness. These methods can also produce appealing results, capable of degrading a wide range of pollutants with a rate of 90 % or higher. However, they also suffer from expensive operation costs. Moreover, advance oxidation processes can generate unwanted toxic side products. Biological treatments are some recent efforts in imitating the ability of nature to degrade micropollutants. Usage of fungi, microalgae and macrophytes deliver promising results in removing these substances, while costing less and producing valuable biomass for other purposes. However, some pharmaceuticals are resistant to this method and seasonal/environmental factors can decrease its effectiveness. Also, the combination of advanced treatment techniques can be an effective way to combine their strengths and compensate for the weaknesses of each technique. In conclusion, more studies must be conducted in order to find a proper technology that is versatile in removing pharmaceutical pollutants, has reasonable costs, produces no unwanted side-effects and could be integrated perfectly into the existing wastewater treatment systems.

References

A. W. Jongbloed, N. P. Lenis, 1998. Environmental concerns about animal manure. *Journal of Animal Science*, 76(10), pp. 2641–2648.

A.S. Mestre, J. Pires, J.M.F. Nogueira, A.P. Carvalho, 2007. Activated carbons for the adsorption of ibuprofen. *Carbon*, 45(10), pp. 1979-1988.

Ai Jia, Yi Wan, Yang Xiao, Jianying Hu, 2012. Occurrence and fate of quinolone and fluoroquinolone antibiotics in a municipal sewage treatment plant. *Water Research*, 46(2), pp. 387-394.

Aida Garcia-Rodríguez, Víctor Matamoros, Clàudia Fontàs, Victòria Salvadó, 2014. The ability of biologically based wastewater treatment systems to remove emerging organic contaminants—a review. *Environmental Science and Pollution Research*, 21(20), pp. 11708–11728.

Alette Langenhoff, Nadia Inderfurth, Teun Veuskens, 2013. Microbial Removal of the Pharmaceutical Compounds Ibuprofen and Diclofenac from Wastewater. *BioMed Research International*, 2013(325806).

Ana S. Mestre, Ana S. Bexiga, Margarida Proença, Marta Andrade, Moisés L. Pinto, Inês Matos, Isabel M. Fonseca, Ana P. Carvalho, 2011. Activated carbons from sisal waste by chemical activation with K_2CO_3: Kinetics of paracetamol and ibuprofen removal from aqueous solution. *Bioresource Technology*, 102(17), pp. 8253-8260.

Anke Göbel, Angela Thomsen, Christa S. McArdell, Adriano Joss, Walter Giger, 2005. Occurrence and Sorption Behavior of Sulfonamides, Macrolides, and Trimethoprim in Activated Sludge Treatment. *Environmental Science & Technology*, 39(11), pp. 3981-3989.

aus der Beek T, Weber FA, Bergmann A, Hickmann S, Ebert I, Hein A, Küster A, 2016. Pharmaceuticals in the environment--Global occurrences and perspectives. *Environmental Toxicology and Chemistry*, 35(4), pp. 823-835.

Bokun Lin, Jinling Lyu, Xian-jin Lyu, Han-qing Yu, Zhong Hu, James C.W. Lam, Paul K.S. Lam, 2015. Characterization of cefalexin degradation capabilities of two Pseudomonas strains isolated from activated sludge. *Journal of Hazardous Materials*, 282, pp. 158-164.

C.V. Gómez-Pacheco, M. Sánchez-Polo, J. Rivera-Utrilla, J.J. López-Peñalver, 2012. Tetracycline degradation in aqueous phase by ultraviolet radiation. *Chemical Engineering Journal*, 187, pp. 89-95.

Carlos E. Rodríguez-Rodríguez, Enrique Barón, Pablo Gago-Ferrero, Aleksandra Jelić, Marta Llorca, Marinella Farré, M. Silvia Díaz-Cruz, Ethel Eljarrat, Mira Petrović, Glòria Caminal, Damià Barceló, Teresa Vicent, 2012. Removal of pharmaceuticals, polybrominated flame retardants and UV-filters from sludge by the fungus Trametes versicolor in bioslurry reactor. *Journal of Hazardous Materials*, 233–234, pp. 235-243.

Cristina Ávila, Anna Pedescoll, Víctor Matamoros, Josep María Bayona, Joan García, 2010. Capacity of a horizontal subsurface flow constructed wetland system for the removal of emerging pollutants: An injection experiment. *Chemosphere*, 81(9), pp. 1137-1142.

Cristina Ávila, Carolina Reyes, Josep María Bayona, Joan García, 2013. Emerging organic contaminant removal depending on primary treatment and operational strategy in horizontal subsurface flow constructed wetlands: Influence of redox. *Water Research*, 47(1), pp. 315-325.

D.G. Joakim Larsson, Cecilia de Pedro, Nicklas Paxeus, 2007. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *Journal of Hazardous Materials*, 148(3), pp. 751-755.

Dana W. Kolpin, Edward T. Furlong, Michael T. Meyer, E. Michael Thurman, Steven D. Zaugg, Larry B. Barber, and Herbert T. Buxton, 2002. Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999−2000: A National Reconnaissance. *Environmental Science & Technology*, 36(6), pp. 1202-1211.

Daniel Gerrity, Sujanie Gamage, Janie C. Holady, Douglas B. Mawhinney, Oscar Quiñones, Rebecca A. Trenholm, Shane A. Snyder, 2011. Pilot-scale evaluation of ozone and biological activated carbon for trace organic contaminant mitigation and disinfection.
Danièle Mousel, Laurence Palmowski, Johannes Pinnekamp, 2017. Energy demand for elimination of organic micropollutants in municipal wastewater treatment plants. *Science of The Total Environment*, 575, pp. 1139-1149.

David T. Tsao, 2003. Overview of Phytotechnologies. *Phytoremediation*, pp. 1-50.
Despo Fatta-Kassinos, Sureyya Meric, Anastasia Nikolaou, 2011. Pharmaceutical residues in environmental waters and wastewater: current state of knowledge and future research. *Analytical and Bioanalytical Chemistry*, 399(1), pp. 251–275.

Ebert, I., Bachmann, J., Kühnen, U., Küster, A., Kussatz, C., Maletzki, D., Schlüter, C., 2011. Toxicity of the fluoroquinolone antibiotics enrofloxacin and ciprofloxacin to photoautotrophic aquatic organisms. *Environmental Toxicology and Chemistry*, 30, pp. 2786-2792.

Emad S. Elmolla, Malay Chaudhuri, 2010. Photocatalytic degradation of amoxicillin, ampicillin and cloxacillin antibiotics in aqueous solution using UV/TiO_2 and UV/H_2O_2/TiO_2 photocatalysis. *Desalination*, 252(1–3), pp. 46-52.

F. Meinel, A. S. Ruhl, A. Sperlich, F. Zietzschmann, M. Jekel, 2015. Pilot-Scale Investigation of Micropollutant Removal with Granular and Powdered Activated Carbon. *Water, Air, & Soil Pollution*, 226:2260.

Fabiana Passos, Mariona Hernández-Mariné, Joan García, Ivet Ferrer, 2014. Long-term anaerobic digestion of microalgae grown in HRAP for wastewater treatment. Effect of microwave pretreatment. *Water Research*, 49, pp. 351-359.

Foster, H. R., Burton, G. A., Basu, N. and Werner, E. E., 2010. Chronic exposure to fluoxetine (Prozac) causes developmental delays in Rana pipiens larvae. *Environmental Toxicology and Chemistry*, 29, pp. 2845-2850.

Frank-Andreas Weber, Tim aus der Beek, Axel Bergmann, 2014. *Pharmaceuticals in the environment – the global perspective; Occurrence, effects, and potential cooperative action under SAICM*. [pdf] German Environment Agency. Available at: <https://www.umweltbundesamt.de/en/publikationen/pharmaceuticals-in-the-environment-the-global> [Accessed 1 March 2018].

Frédéric Orias, Yves Perrodin, 2013. Characterisation of the ecotoxicity of hospital effluents: A review. *Science of The Total Environment*, 454–455, pp. 250-276.

G. Prados-Joya, M. Sánchez-Polo, J. Rivera-Utrilla, M. Ferro-garcía, 2011. Photodegradation of the antibiotics nitroimidazoles in aqueous solution by ultraviolet radiation. *Water Research*, 45(1), pp. 393-403.

Garcia-rodríguez, A., Matamoros, V., Fontàs, C. & Salvadó, V., 2014. The ability of biologically based wastewater treatment systems to remove emerging organic contaminants--a review. *Environmental science and pollution research international*, 21(20), pp. 11708-28.

Hai Liu, Jian Zhang, Nan Bao, Cheng Cheng, Liang Ren, Chenglu Zhang, 2012. Textural properties and surface chemistry of lotus stalk-derived activated carbons prepared using different phosphorus oxyacids: Adsorption of trimethoprim. *Journal of Hazardous Materials*, 235–236, pp. 367-375.

Hai Yang, Taicheng An, Guiying Li, Weihua Song, William J. Cooper, Haiying Luo, Xindong Guo, 2010. Photocatalytic degradation kinetics and mechanism of environmental pharmaceuticals in aqueous suspension of TiO_2: A case of β-blockers. *Journal of Hazardous Materials*, 179(1–3), pp. 834-839.

Hey, G., Ledin, A., la Cour Jansen, J., Hörsing, M., Antoniou, M., Spiliotopoulou, A., Andersen, H. R., 2012. Application of chemical oxidation for removal of pharmaceuticals in wastewater effluents. *Book of Abstracts: Iwa Regional Conference on Wastewater Purification & Reuse*.

Hyun-Hee Cho, Haiou Huang, and Kellogg Schwab, 2011. Effects of Solution Chemistry on the Adsorption of Ibuprofen and Triclosan onto Carbon Nanotubes. *Langmuir*, 27(21), pp. 12960-12967.

I. Cabrita, B. Ruiz, A.S. Mestre, I.M. Fonseca, A.P. Carvalho, C.O. Ania, 2010. Removal of an analgesic using activated carbons prepared from urban and industrial residues. *Chemical Engineering Journal*, 163(3), pp. 249-255.

Ignasi Sirés, Enric Brillas, 2012. Remediation of water pollution caused by pharmaceutical residues based on electrochemical separation and degradation technologies: A review. *Environment International*, 40, pp. 212-229.

Ilho Kim, Naoyuki Yamashita, Hiroaki Tanaka, 2009. Performance of UV and UV/H_2O_2 processes for the removal of pharmaceuticals detected in secondary effluent of a sewage treatment plant in Japan. *Journal of Hazardous Materials*, 166(2–3), pp. 1134-1140.

Isabel Villaescusa, Núria Fiol, Jordi Poch, Antonio Bianchi, Carla Bazzicalupi, 2011. Mechanism of paracetamol removal by vegetable wastes: The contribution of π–π interactions, hydrogen bonding and hydrophobic effect. *Desalination*, 270(1–3), pp. 135-142.

J. Lindsay Oaks, Martin Gilbert, Munir Z. Virani, Richard T. Watson, Carol U. Meteyer, Bruce A. Rideout, H. L. Shivaprasad, Shakeel Ahmed, Muhammad Jamshed Iqbal Chaudhry, Muhammad Arshad, Shahid Mahmood, Ahmad Ali & Aleem Ahmed Khan, 2004. Diclofenac residues as the cause of vulture population decline in Pakistan. *Nature*, 427, pp. 630–633.

Jia-Qian Jiang, Z. Zhou, V.K. Sharma, 2013. Occurrence, transportation, monitoring and treatment of emerging micro-pollutants in waste water — A review from global views. *Microchemical Journal*, 110, pp. 292-300.

José Rivera-Utrilla, Manuel Sánchez-Polo, María Ángeles Ferro-García, Gonzalo Prados-Joya, Raúl Ocampo-Pérez, 2013. Pharmaceuticals as emerging contaminants and their removal from water. A review. *Chemosphere*, 93(7), pp. 1268-1287.

Juliane Hollender, Saskia G. Zimmermann, Stephan Koepke, Martin Krauss, Christa S. McArdell, Christoph Ort, Heinz Singer, Urs von Gunten, Hansruedi Siegrist, 2009. Elimination of Organic Micropollutants in a Municipal Wastewater Treatment Plant Upgraded with a Full-Scale Post-Ozonation Followed by Sand Filtration. *Environmental Science & Technology*, 43 (20), pp. 7862-7869.

Karen A. Kidd, Paul J. Blanchfield, Kenneth H. Mills, Vince P. Palace, Robert E. Evans, James M. Lazorchak, Robert W. Flick, 2007. Collapse of a fish population after exposure to a synthetic estrogen. *Proceedings of the National Academy of Science*s, 104(21), pp. 8897-8901.

Karin Lekkerkerker-Teunissen, Mark J. Benotti, Shane A. Snyder, Hans C. van Dijk, 2012. Transformation of atrazine, carbamazepine, diclofenac and sulfamethoxazole by low and medium pressure UV and UV/H_2O_2 treatment. *Separation and Purification Technology*, 96, pp. 33-43.

Karl Fent, Anna A. Weston, Daniel Caminada, 2006. Ecotoxicology of human pharmaceuticals. *Aquatic Toxicology*, 76(2), pp. 122-15.

Keun-Joo Choi, Sang-Goo Kim, Seung-Hyun Kim, 2008. Removal of antibiotics by coagulation and granular activated carbon filtration. *Journal of Hazardous Materials*, 151(1), pp. 38-43.

Khan, S. J., and J. E. Ongerth, 2005. Occurrence and removal of pharmaceuticals at an Australian sewage treatment plant. *Water*, 32(4), pp. 80-85.

Klaus Kümmerer, 2009. Antibiotics in the aquatic environment – A review – Part I. *Chemosphere*, 75(4), pp. 417-434.

Klaus Kümmerer, 2009. The presence of pharmaceuticals in the environment due to human use – present knowledge and future challenges. *Journal of Environmental Management*, 90(8), pp. 2354-2366.

Kümmerer, Klaus, 2009. Antibiotics in the aquatic environment – a review – part II. *Chemosphere*, 75(4), pp. 435-441.

L. Hernández-Leal, H. Temmink, G. Zeeman, C.J.N. Buisman, 2011. Removal of micropollutants from aerobically treated grey water via ozone and activated carbon. *Water Research*, 45(9), pp. 2887-2896.

L. Michelini, R. Reichel, W. Werner, R. Ghisi, S. Thiele-Bruhn, 2012. Sulfadiazine Uptake and Effects on Salix fragilis L. and Zea mays L. Plants. *Water, Air, & Soil Pollution*, 223(8), pp. 5243–5257.

L. Yang, Z. Chen, X. Liu, X. Zhai, J. Shen and Y. Han, 2009. Removal of Dimethylamine by Ozone Combined with Hydrogen Peroxide (O_3/H_2O_2). *International Conference on Energy and Environment Technology, Guilin, Guangxi*, pp. 691-694.

Liebig, M., Fernandez, Á. A., Blübaum-Gronau, E., Boxall, A., Brinke, M., Carbonell, G., Egeler, P., Fenner, K., Fernandez, C., Fink, G., Garric, J., Halling-Sørensen, B., Knacker, T., Krogh, K. A., Küster, A., Löffler, D., Cots, M. Á., Pope, L., Prasse, C., Römbke, J., Rönnefahrt, I., Schneider, M. K., Schweitzer, N., Tarazona, J. V., Ternes, T. A., Traunspurger, W., Wehrhan, A. and Duis, K., 2010. Environmental risk assessment of ivermectin: A case study. *Integrated Environmental Assessment and Management*, 6, pp. 567-587.

Lúcia H.M.L.M. Santos, A.N. Araújo, Adriano Fachini, A. Pena, C. Delerue-Matos, M.C.B.S.M. Montenegro, 2010. Ecotoxicological aspects related to the presence of pharmaceuticals in the aquatic environment. *Journal of Hazardous Materials*, 175(1–3), pp. 45-95.

Lucia Michelini, Franco Meggio, Rüdiger Reichel, Sören Thiele-Bruhn, Andrea Pitacco, Linda Scattolin, Lucio Montecchio, Sara Alberghin, iAndrea Squartini, Rossella Ghisi, 2015. Sulfadiazine uptake and effects in common hazel (Corylus avellana L.). *Environmental Science and Pollution Research*, 22(17), pp. 13362–13371.

M. Sánchez-Polo, J. Rivera-Utrilla, G. Prados-Joya, M.A. Ferro-García, I. Bautista-Toledo, 2008. Removal of pharmaceutical compounds, nitroimidazoles, from waters by using the ozone/carbon system. *Water Research*, 42, pp. 4163-4171.

Marc M. Huber, Silvio Canonica, Gun-Young Park, Urs von Gunten, 2003. Oxidation of Pharmaceuticals during Ozonation and Advanced Oxidation Processes. *Environmental Science & Technology,* 37(5), pp. 1016-1024.

Maria G. Antoniou, Gerly Hey, Sergio Rodríguez Vega, Aikaterini Spiliotopoulou, Jerker Fick, Mats Tysklind, Jes la Cour Jansen, Henrik Rasmus Andersen, 2013. Required ozone doses for removing pharmaceuticals from wastewater effluents. *Science of The Total Environment*, 456–457, pp. 42-49.

María Hijosa-Valsero, Guido Fink, Michael P. Schlüsener, Ricardo Sidrach-Cardona, Javier Martín-Villacorta, Thomas Ternes, Eloy Bécares, 2011. Removal of antibiotics from urban wastewater by constructed wetland optimization. *Chemosphere*, 83(5), pp. 713-719.

Marta Carballa, Francisco Omil, Juan M Lema, María Llompart, Carmen García-Jares, Isaac Rodríguez, Mariano Gómez, Thomas Ternes, 2004. Behavior of pharmaceuticals, cosmetics and hormones in a sewage treatment plant. *Water Research*, 38(12), pp. 2918-2926.

Mohammad Boshir Ahmed, John L. Zhou, Huu Hao Ngo, Wenshan Guo, Nikolaos S. Thomaidis, Jiang Xu, 2017. Progress in the biological and chemical treatment technologies for emerging contaminant removal from wastewater: A critical review. *Journal of Hazardous Materials*, 323(A), pp. 274-298.

N. De la Cruz, J. Giménez, S. Esplugas, D. Grandjean, L.F. de Alencastro, C. Pulgarín, 2012. Degradation of 32 emergent contaminants by UV and neutral photo-fenton in domestic wastewater effluent previously treated by activated sludge. *Water Research*, 46(6), pp. 1947-1957.

Norihide Nakada, Hiroyuki Shinohara, Ayako Murata, Kentaro Kiri, Satoshi Managaki, Nobuyuki Sato, Hideshige Takada, 2007. Removal of selected pharmaceuticals and personal care products (PPCPs) and endocrine-disrupting chemicals (EDCs) during sand filtration and ozonation at a municipal sewage treatment plant. *Water Research*, 41(19), pp. 4373-4382.

O.V. Enick, M.M. Moore, 2007. Assessing the assessments: Pharmaceuticals in the environment. *Environmental Impact Assessment Review*, 27(8), pp. 707-729.

P. Verlicchi, M. Al Aukidy, E. Zambello, 2012. Occurrence of pharmaceutical compounds in urban wastewater: Removal, mass load and environmental risk after a secondary treatment—A review. *Science of The Total Environment*, 429, pp. 123-155.

Paul Westerhoff, Yeomin Yoon, Shane Snyder, Eric Wert, 2005. Fate of Endocrine-Disruptor, Pharmaceutical, and Personal Care Product Chemicals during Simulated Drinking Water Treatment Processes. *Environmental Science & Technology*, 39(17), pp. 6649-6663.

Pedro N. Carvalho, José Luís Araújo, Ana P. Mucha, M. Clara P. Basto, C. Marisa R. Almeida, 2013. Potential of constructed wetlands microcosms for the removal of veterinary pharmaceuticals from livestock wastewater. *Bioresource Technology*, 134, pp. 412-416.

Pilon-Smits, Elizabeth, 2005. Phytoremediation. *Annual review of plant biology*, 56, pp. 15-39.

Qian Sui, Jun Huang, Shubo Deng, Gang Yu, Qing Fan, 2010. Occurrence and removal of pharmaceuticals, caffeine and DEET in wastewater treatment plants of Beijing, China. *Water Research*, 44(2), pp. 417-426.

R. Andreozzi, L. Campanella, B. Fraysse, J. Garric, A. Gonnella, R. Lo Giudice, R. Marotta, G. Pinto, A. Pollio, 2004. Effects of advanced oxidation processes (AOPs) on the toxicity of a mixture of pharmaceuticals. *Water Science and Technolog*y, 50(5), pp. 23-28.

R. Baccar, M. Sarrà, J. Bouzid, M. Feki, P. Blánquez, 2012. Removal of pharmaceutical compounds by activated carbon prepared from agricultural by-product. *Chemical Engineering Journal*, 211–212, pp. 310-317.

R. Triebskorn, H. Casper, V. Scheil, J. Schwaiger, 2007. Ultrastructural effects of pharmaceuticals (carbamazepine, clofibric acid, metoprolol, diclofenac) in rainbow trout (Oncorhynchus mykiss) and common carp (Cyprinus carpio). *Analytical and Bioanalytical Chemistry*, 387(4), pp. 1405–1416.

Richard H. Lindberg, Ulrika Olofsson, Per Rendahl, Magnus I. Johansson, Mats Tysklind, Barbro A. V. Andersson, 2006. Behavior of Fluoroquinolones and Trimethoprim during Mechanical, Chemical, and Active Sludge Treatment of Sewage Water and Digestion of Sludge. *Environmental Science & Technology*, 40(3), pp. 1042-1048.

S.A.C. Carabineiro, T. Thavorn-Amornsri, M.F.R. Pereira, J.L. Figueiredo, 2011. Adsorption of ciprofloxacin on surface-modified carbon materials. *Water Research*, 45(15), pp. 4583-4591.

S.H. Kim, H.K. Shon, H.H. Ngo, 2010. Adsorption characteristics of antibiotics trimethoprim on powdered and granular activated carbon. *Journal of Industrial and Engineering Chemistry*, 16(3), pp. 344-349.

Shane A. Snyder, Samer Adham, Adam M. Redding, Fred S. Cannon, James DeCarolis, Joan Oppenheimer, Eric C. Wert, Yeomin Yoon, 2007. Role of membranes and activated carbon in the removal of endocrine disruptors and pharmaceuticals. *Desalination*, 202(1–3), pp. 156-181.

Shishir Kumar Behera, Seok-Young Oh, Hung-Suck Park, 2010. Sorption of triclosan onto activated carbon, kaolinite and montmorillonite: Effects of pH, ionic strength, and humic acid. *Journal of Hazardous Materials*, 179(1–3), pp. 684-691.

Sridhar Susarla, Victor F. Medina, Steven C. McCutcheon, 2002. Phytoremediation: An ecological solution to organic chemical contamination. *Ecological Engineering*, 18(5), pp. 647-658.

Stephen R. Hughes, Paul Kay, Lee E. Brown, 2013. Global Synthesis and Critical Evaluation of Pharmaceutical Data Sets Collected from River Systems. *Environmental Science & Technology*, 47(2), pp. 661-677.

T. Brodin, J. Fick, M. Jonsson, J. Klaminder, 2013. Dilute Concentrations of a Psychiatric Drug Alter Behavior of Fish from Natural Populations. *Science*, 339(6121), pp. 814-815.

The McIlvaine Company. *Wastewater process flow diagram*, photograph, accessed 13 February 2018, <www.mcilvainecompany.com/generic%20applications/water/mncpl%20wastewater.htm>.

Thomas A. Ternes, Nadine Herrmann, Matthias Bonerz, Thomas Knacker, Hansruedi Siegrist, Adriano Joss, 2004. A rapid method to measure the solid–water distribution coefficient (K_d) for pharmaceuticals and musk fragrances in sewage sludge. *Water Research*, 38(19), pp. 4075-4084.

Tiphanie Deblonde, Carole Cossu-Leguille, Philippe Hartemann, 2011. Emerging pollutants in wastewater: A review of the literature. *International Journal of Hygiene and Environmental Health*, 214(6), pp. 442-448.

Tomáš Cajthaml, Zdena Křesinová, Kateřina Svobodová, Monika Möder, 2009. Biodegradation of endocrine-disrupting compounds and suppression of estrogenic activity by ligninolytic fungi. *Chemosphere*, 75(6), pp. 745-750.

Urs von Gunten, 2003. Ozonation of drinking water: Part II. Disinfection and by-product formation in presence of bromide, iodide or chlorine. *Water Research*, 37(7), pp. 1469-1487.

V. Lazarova, Ph. Savoye, 2004. Technical and sanitary aspects of wastewater disinfection by UV irradiation for landscape irrigation. *Water Science and Technology,* 50(2), pp. 203-209.

V. Matamoros, J.M. Bayona, D.B.a.S.P.r. Mira Petrovic, 2013. Removal of pharmaceutical compounds from wastewater and surface water by natural treatments. *Comprehensive Analytical Chemistry*, pp. 409–433.

Victor Kårelid, Gen Larsson, Berndt Björlenius, 2017. Pilot-scale removal of pharmaceuticals in municipal wastewater: Comparison of granular and powdered activated carbon treatment at three wastewater treatment plants. *Journal of Environmental Management*, 193, pp. 491-502.

Víctor Matamoros, Raquel Gutiérrez, Ivet Ferrer, Joan García, Josep M Bayona, 2015. Capability of microalgae-based wastewater treatment systems to remove emerging organic contaminants: A pilot-scale study. *Journal of Hazardous Materials*, 288, pp. 34-42. *Water Research*, 45(5), pp. 2155-2165.

Watkinson, A. J., Murby, E. J., & Costanzo, S. D., 2007. Removal of antibiotics in conventional and advanced wastewater treatment: implications for environmental discharge and wastewater recycling. *Water research*, 41(18), pp. 4164-4176.

Yasojima, M., Nakada, N., Komori, K., Suzuki, Y., & Tanaka, H., 2006. Occurrence of levofloxacin, clarithromycin and azithromycin in wastewater treatment plant in Japan. *Water science and technology*, 53(11), pp. 227-233.

Yeon Jung Jung, Wan Gi Kim, Yeojoon Yoon, Joon-Wun Kang, Young Min Hong, Hyun Wook Kim, 2012. Removal of amoxicillin by UV and UV/H_2O_2 processes, *Science of The Total Environment*, 420, pp. 160-167.

Yunlong Luo, Wenshan Guo, Huu Hao Ngo, Long Duc Nghiem, Faisal Ibney Hai, Jian Zhang, Shuang Liang, Xiaochang C. Wang, 2014. A review on the occurrence of micropollutants in the aquatic environment and their fate and removal during wastewater treatment. *Science of The Total Environment*, 473–474, pp. 619-641.

Zheyun Zhang, Hongtao Zhu, Xianghua Wen, Xiurong Si, 2012. Degradation behavior of 17α-ethinylestradiol by ozonation in the synthetic secondary effluent. *Journal of Environmental Sciences*, 24(2), pp. 228-233.

Zorita, Saioa, Lennart Mårtensson, and Lennart Mathiasson, 2009. Occurrence and removal of pharmaceuticals in a municipal sewage treatment system in the south of Sweden. *Science of the total environment*, 407(8), pp. 2760-2770.