UNIVERSIDADE FEDERAL DE MINAS GERAIS
Escola de Engenharia
Programa de Pós-graduação em Saneamento, Meio Ambiente e Recursos Hídricos

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ENVIRONMENTAL AND HUMAN HEALTH RISK ASSOCIATED WITH THE REMOVAL OF PHARMACEUTICALS FROM SEWAGE IN A HYBRID OSMOTIC MEMBRANE BIOREACTOR AND MEMBRANE DISTILLATION

Belo Horizonte

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["ENVIRONMENTAL AND HUMAN HEALTH RISK ASSOCIATED WITH THE REMOVAL OF PHARMACEUTICALS FROM SEWAGE IN A HYBRID OSMOTIC MEMBRANE BIOREACTOR AND MEMBRANE DISTILLATION "]

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RESUMO

Os fármacos vêm sendo cada vez mais detectados em efluentes brutos e tratados, águas superficiais e até mesmo em água potável, o que é de grande preocupação ambiental e de saúde pública. Esses micropoluentes são geralmente encontrados no ambiente aquático em concentrações na faixa de ng L^{-1} a μg L^{-1}, no entanto, podem causar efeitos adversos ao ecossistema mesmo em baixas concentrações. Para avaliar os impactos causados pelos micropoluentes no meio ambiente, a aplicação de testes ecotoxicológicos é fundamental. Esses testes, em geral, são análises laboratoriais que utilizam organismos vivos expostos por períodos de tempo estabelecidos, para quantificar ou qualificar o efeito tóxico de uma amostra. Desta forma, este trabalho teve como objetivo avaliar a toxicidade associada à remoção de fármacos de esgoto em um biorreator de membrana osmótico híbrido e destilação por membrana (BRMO-DM). Na primeira etapa foi avaliada a remoção de toxicidade pelo BRMO-DM para tratar esgoto sintético fortificado com sete fármacos: 17α-etinilestradiol, cetoprofeno, fenofibrato, fluconazol, loratadina, prednisona e betametasona, na concentração de 2 μg L^{-1} cada. Os fármacos escolhidos já foram detectados em águas superficiais, águas residuais brutas ou tratadas e até mesmo água potável em diversos locais do mundo. No monitoramento do biorreator foram realizadas análises físico-químicas semanalmente, seguindo o *Standard Methods for the Examination of Water and Wastewater* (APHA, 2017). Os testes de toxicidade aguda foram realizados com os organismos *Aliivibrio fischeri* e *Daphnia similis* e o teste de toxicidade crônica com *Raphidocelis subcapitata*. O BRMO-DM apresentou remoções de COD, P-PO_4^{3-} e N-NH_4^+ de 90.07, 99.99, 93.01%, respectivamente. O sobrenadante do biorreator apresentou toxicidade para todos os organismos, enquanto o destilado foi tóxico para *D. similis* e *R. subcapitata*, o que pode estar relacionado à presença de Mg^{2+} nessas amostras. Os resultados mostraram a importância da inclusão do parâmetro toxidade nos estudos que objetivam a avaliação dos solutos adequados para a solução osmótica. O esgoto sintético com a mistura de fármacos não foi tóxico para nenhum organismo avaliado, mostrando que a toxicidade desses fármacos pode estar relacionada a concentrações maiores e alertando para a importância de estudos aprofundados sobre o efeito dos fármacos. Desta forma, na segunda etapa do estudo foi feita uma revisão bibliográfica que aborda valores de toxicidade para fármacos e avalia se esses compostos representam um risco ao meio ambiente e à saúde humana. A plataforma *Scopus* foi selecionada como o principal banco de dados para a busca na literatura. Dos 140 artigos pesquisados, 39 fármacos de 9 classes terapêuticas foram selecionados para avaliação. Além disso, foi realizada a avaliação de risco humano e ambiental para cada fármaco, de acordo com a metodologia proposta pela *European Commission* (1996). A avaliação de risco com os dados da literatura mostrou que diclofenaco, naproxeno, eritromicina, roxitromicina e 17β-estradiol apresentaram alto risco agudo e crônico para o meio ambiente, enquanto o 17α-etinilestradiol apresentou alto risco à saúde humana. Isso mostra o potencial desses fármacos em causar efeitos adversos ao ecossistema e aos seres humanos e estabelece a prioridade de suas remoções por meio de tecnologias avançadas.

Palavras-chave: fármacos; testes ecotoxicológicos; biorreatores de membranas; avaliação de risco.

ABSTRACT

Pharmaceutically active compounds (PhACs) are increasingly being detected in raw and treated wastewater, surface water, and drinking water. PhACs are generally found in the aquatic environment in concentrations from ng L^{-1} to μg L^{-1}. However, these compounds can cause adverse effects to the ecosystem even at low concentrations and, to assess these impacts, the application of toxicity tests is essential. These tests, in general, are laboratory analyses that use living organisms exposed for established periods of time, to quantify or qualify the toxic effect of a sample. Thus, this work aimed to evaluate the toxicity removal associated to the pharmaceuticals from seweage in a hybrid osmotic membrane bioreactor and membrane distillation (AnOMBR-MD). In the first stage, the toxicity removal was evaluated by the AnOMBR-MD for treat synthetic sewage fortified with seven PhACs: 17α-ethinylestradiol, ketoprofen, fenofibrate, fluconazole, loratadine, prednisone and betamethasone, with a concentration of 2 μg L-1 each. The chosen PhACs have been detected in surface water, raw or treated wastewater and even drinking water in several locations around the world. In the bioreactor monitoring, physical-chemical analyses were performed weekly, following the Standard Methods for the Examination of Water and Wastewater (APHA, 2017). Acute toxicity tests were performed with *Aliivibrio fischeri* and *Daphnia similis* and the chronic toxicity test with *Raphidocelis subcapitata*. AnOMBR-MD presented removals of COD, P-PO_4^{3-} and N-NH_4^+ of 90.07, 99.99 and 93.01%, respectively. The mixed liquor was toxic to all organisms, while the distillate was toxic to *D. similis* and *R. subcapitata*, which may be related to the presence of Mg^{2+} in these samples. The results showed the importance of including the toxicity parameter in studies that aim to evaluate the appropriate solutes for the draw solution. The synthetic sewage with the mixture of PhACs was not toxic for any evaluated organism, showing that the toxicity of these micropollutants may be related to higher concentrations and alerting to the importance of in-depth studies on the effect of PhACs. Thus, in the second stage of the study, a literature review was carried out for addresses toxicity values for PhACs and assesses whether these compounds represent a risk to the environment and human health. The Scopus was selected as the central database for the literature search. Of the 140 articles surveyed, 39 PhACs from 9 therapeutic classes were selected for evaluation. Also, a human and environmental risk assessment was carried out for each PhAC, according to the methodology by the European Commission (1996). The risk assessment with data from literature showed that diclofenac, naproxen, erythromycin, roxithromycin, and 17β-estradiol presented a high acute and chronic risk to the environment, while 17α-ethinylestradiol presented a high risk to human health. This shows the potential of these PhACs to cause adverse effects to the ecosystem and humans and establishes the priority of their removal through advanced technologies.

Keywords: Pharmaceutically active compounds; ecotoxicological tests; membrane bioreactors; risk assessment.

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LIST OF ABBREVIATIONS, ACRONYMS AND SYMBOLS

ABNT – Associação brasileira de normas técnicas

AnOMBR-MD – Anaerobic osmotic membrane bioreactor with membrane distillation

AOP – Advanced oxidation process

BW – Body weight

COD – Chemical oxygen demand

DI – Daily input

DS – Draw solution

DW – Drinking water

DWGL – Drinking water guideline level

EC_{50} – Effect concentration

EGSB – Expanded granular sludge bed

FO – Forward osmosis

HI – Hazard index

HQ – Human health risk quotient

HQ_e – Hazard quotients

HQ_h – Human health risk

ILCR – Incremental lifetime carcinogenic risk

J_{FO} – Permeate flux in FO

J_{MD} – Permeate flux in MD

J_s – Reverse salt flux

LC_{50} – Letal concentration

MBRs – Membrane bioreactors

MD – Membrane distillation

MEC – Measured concentration

MF – Microfiltration membrane

Mg – Magnesium

ML – Mixed liquor

NOEC – No observed effect concentration

OEC – Observed effect concentration

OMBR – Osmotic membrane bioreactor

PhACs – Pharmaceutically active compounds

PNEC – Predicted non-effect concentration

RO – Reverse osmosis

RQ – Environmenral risk quotient

RWW – Raw wastewater

STPs – Sewage treatment plants

SW – Surface water

TDI – Tolerable daily intake

TrOC – Trace organis contaminants

TSS –Total suspended solids

TU – Toxic unit

TWW – Treated wastewater

UASB – Upflow Anaerobic Sludge Blanket

UF – Ultrafiltration membrane

VSS – Volatile suspendes solids

WWTPs – Wastewater treatment plants

$\Delta\pi$ – Osmotic pressure difference

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CHAPTER 1

INTRODUCTION

1.1 Background and justification

Pharmaceutically active compounds (PhACs) have been detected in the aquatic environment worldwide and attracted increasing attention due to their persistence and continuous discharge, which may cause adverse effects on the ecosystem (TIWARI et al., 2017). To assess the impacts caused by PhACs on the environment, the application of ecotoxicological tests is essential since these analyses use living organisms to quantify or qualify the toxic effect of a sample. Physical and chemical analyses for monitoring the water and wastewater cannot measure the impact caused by micropollutants on the ecosystem since only biological systems can detect toxic effects (CONNON et al., 2012). In this way, ecotoxicological tests have been carried out with several PhACs, showing high toxicity to aquatic organisms (WANG et al., 2020; CARBAJO et al., 2015; CHIFFRE et al., 2016). However, the toxicity data are still scarce for many PhACs, and when available, they are dispersed in the literature.

PhACs are generally found in the aquatic environment at concentration levels of ng L^{-1} to µg L^{-1}, however, studies show that these compounds can influence the ecosystem even at low concentrations, causing toxic effects such as mortality, reproduction inhibition, and growth inhibition (CALISTO AND ESTEVES, 2009). Also, PhACs can cause genotoxicity effects, like DNA damages and mutations in the aquatic organisms or their descendants, promoting changes in the aquatic ecosystem (OHE et al., 2004).

Concentrations of PhACs in aquatic matrices and the ecotoxicological data allow evaluating the hazard that these compounds represent for the environment through the risk assessment proposed by the European Commission (1996), classifying the risks as negligible, low, medium, or high. The human health risk can also be assessed through the concentrations of PhACs in drinking water. Risk assessments are essential since it allows the identification of the most dangerous compounds, whose removal from the aquatic environment must be prioritized (GUO et al., 2016).

The presence of PhACs and other pollutants with toxic effects in the environment occurs mainly due to the low removal efficiencies in the wastewater treatment plants (WWTPs), which shows the importance of advanced technologies to remove these contaminants (FOUREAUX et al., 2018).

In this context, several configurations of membrane bioreactors (MBRs) have been applied for the water and wastewater treatment, presenting satisfactory performance in the removal of PhACs and other pollutants (FARIA et al., 2020; LASTRE-ACOSTA et al., 2020; ASIF et al., 2020a; RICCI et al., 2021). MBRs integrate aerobic or anaerobic biological treatment with membrane separation processes such as microfiltration (MF), ultrafiltration (UF), nanofiltration (NF), membrane distillation (MD), forward osmosis (FO) or reverse osmosis (RO), such as shown in Figure 1.

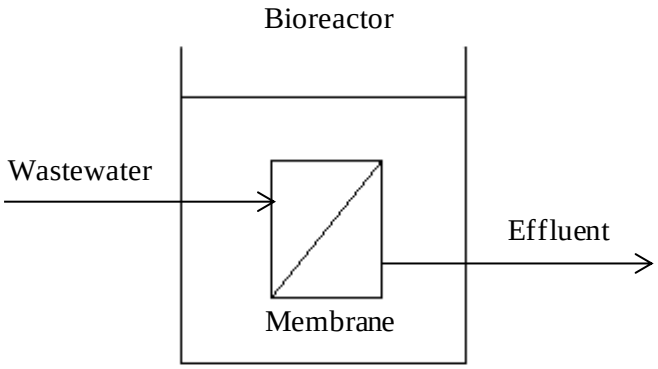

Figure 1 – MBR scheme

However, it is known that some advanced treatment systems can achieve high removals of pollutants but increase the treated effluent toxicity by the formation of toxic by-products or production of chemical oxidants (PRADO et al., 2017; OUARDA et al., 2018). Thus, it is essential to use processes that do not require chemical products to recover the concentrate in membrane separation processes. Despite the importance of ecotoxicological tests to predict adverse effects on aquatic environments, few studies have evaluated the toxicity of membrane bioreactors, mainly osmotic bioreactors, for treating wastewater with PhACs.

1.2 Objectives

1.2.1 General objective

This work aimed to evaluate the toxicity removal associated with the pharmaceuticals from sewage in an anaerobic hybrid osmotic membrane bioreactor - membrane distillation, and assess the environmental and human health risk of 39 selected PhACs.

1.2.2 Specific objective

- Verify the efficiency of a AnOMBR-MD in the treatment of sewage with PhACs;
- Analyze the removal of acute and chronic toxicity in a AnOMBR-MD;

- Evaluate the concentrations of the selected PhACs detected in raw and treated wastewater, surface water, and drinking water worldwide;
- Evaluate the ecotoxicological data of the selected PhACs, for different aquatic organisms;
- Assess acute and chronic environmental risk and human health risk for all selected PhACs.

1.3 Document structure

The present study was structured in 4 chapters. Chapter 1 contains a background related to the theme covered in this work, justifications, and general and specific objectives. Chapter 2 comprehends the evaluation of a membrane bioreactor in the removal of toxicity in sewage treatment. Chapter 3 presents a literature review that addresses the issue of PhACs in the aquatic environment and the risk related to them. Finally, chapters 4 contain final considerations.

CHAPTER 2

TOXICITY REMOVAL BY AN OSMOTIC MEMBRANE BIOREACTOR WITH MEMBRANE DISTILLATION

2.1 Introdution

The limitation of conventional treatment processes, such as UASB reactors, activated sludge, biological filters, or facultative ponds in the PhACs removal, can negatively impact the aquatic environment (TIWARE et al., 2016; COUTO, et al., 2019). Jelic et al. (2011) evaluated the removal of PhACs in a WWTP with activated sludge. Enalapril, naproxen, and ketoprofen had removals above 80%, however, carbamazepine removal was below 25%, diclofenac below 24%, and several antibiotics below 30%. Moya-Llamas et al. (2018) studied the efficiency of a UASB reactor for PhACs removal and observed removals of 84% and 77% for estrone and 17α-ethinylestradiol, respectively, while carbamazepine and diclofenac were more resistant, with removals of 48% and 61%. Incomplete PhACs removal can promote their release into the environment and, consequently, can cause toxic effects to aquatic organisms.

In contrast, membrane bioreactors (MBRs) have been showing high removal efficiencies for most of these micropollutants compared to conventional treatment systems (TIWARE et al., 2016). According to Judd and Judd (2006) membrane bioreactor is a water or wastewater treatment that combine the biological process with membrane technology. Currently, widely applied MBR use microfiltration (MF) or ultrafiltration (UF) membranes to retain biomass. MBRs that use UF/MF allows independence between the hydraulic retention time and the solids retention time, which allows operations with longer solids retention time, and consequently, a greater adaptation of the microorganisms to the substrates and a greater removal of recalcitrant compounds (PRASERTKULSAK et al., 2016). The digestion process in MBRs can be aerobic or anaerobic, which makes the treatment even more versatile. Aerobic digestion can achieve high removals of organic matter and other biodegradable compounds, on the other hand, MBRs with anaerobic digestion have advantages over aerobic digestion, such as low sludge production, methane production as a potential energy source, and low energy requirement, which is of great relevance (SHOW and LEE, 2017; MAHAT et al., 2018).

MBRs have several advantages about conventional treatments, such as the production of high-quality effluent, a high level of automation, and consequently the reduction in the labor demand, comparable capital costs, and reduced reactor size. On the other hand, some conditions may limit its application, such as not removing contaminants with smaller molar masses, energy demand in cases of aerobic MBRs and membrane fouling (JUDD and JUDD, 2006; GRANDCLÉMENT et al., 2017). It is important to emphasize that despite being a limiting

factor, studies have made significant progress in understanding the fouling mechanism and, consequently, the relief of its effects (JIANG, et al., 2017).

Despite the several advantages of membrane bioreactors, some PhACs are still resistant to this treatment process, especially those with highly hydrophilic characteristics (KAYA et al., 2016). This limitation can be overcome by developing other MBRs configurations, such as osmotic membrane bioreactors (OMBRs). In an OMBR, the biological aerobic or anaerobic reactor is associated with forward osmosis (FO) membrane. FO is a membrane separation process in which the driving force is the osmotic pressure gradient, which conducts water through the semipermeable membrane on the side of the feed solution, where the osmotic pressure is lower, to the draw solution (DS), which has high osmotic pressure (ZHAO et al. 2014). The result of FO is the concentration of the feed solution and the dilution of the draw solution. Thus, the DS must be reconcentrated. There are several solutes can be used, such as $MgCl_2$, $CaCl_2$, or NaCl (CATH et al., 2006; ARCANJO et al., 2020). Advantages of FO include lower energy consumption and greater water recovery than pressure-oriented processes, and less propensity to fouling (HOLLOWAY et al., 2015).

FO has been used for seawater desalination, wastewater treatment, and the food industry (CATH et al., 2006). Another possible application for FO is the removal of micropollutants. Valladares-Linares et al. (2011) used FO with reverse osmosis (RO) to treat wastewater with thirteen micropollutants, mostly PhACs, and found rejections greater than 89.1% for low molecular weight hydrophilic micropollutants and rejections above 99% for other compounds. Liu et al. (2016) used FO to treat wastewater with sulfamethoxazole, trimethoprim, norfloxacin, and roxithromycin, and 89% to 98% rejections were found for the four antibiotics. This way, OMBRs have low energy consumption, low fouling potential and high removal of contaminants and micropollutants, compared to the MBRs (ACHILLI et al., 2009).

The draw solution of OMBRs must be recovered by another process, such as membrane distillation (MD) or RO, to obtain the treated water. In MD the driving force is the temperature gradient, therefore, the vapor pressure is different at the two surfaces of the membrane. For this, hydrophobic membranes are used, allowing only vapor passage (BAKER, 2000). This process has several advantages when compared to other membrane separation processes, such as possibilities of using residual heat, low operating pressures and, consequently, lower costs, flux compatible with RO, high separation efficiency, low probability of fouling, dispenses extensive areas of membrane and can operate with concentrated saline solutions (BAKER, 2000).

In this context, MD has also shown effective of PhACs removal. For example, Han et al. (2017) reached a removal of 90% for ibuprofen using the MD process. Other PhACs such as carbamazepine, trimethoprim, bezafibrate, primidone, and acetaminophen were removed in values greater than 98% using MD (ASIF et al. 2019). Couto et al. (2018) evaluated MD in removing 25 PhACs and found removals greater than 99% for all of them. The process's high efficiency was mainly attributed to the low volatility of the compounds evaluated, which leads to their rejection by the hydrophobic membrane. Thus, the OMBRs integrated with MD is a promising technology for the treatment of effluents containing PhACs.

Therefore, the efficiency of removing PhACs in an OMBR-MD was evaluated by Ricci et al. (2021), with removals above 96.4% for 17α-ethinylestradiol, ketoprofen, fenofibrate, fluconazole, loratadine, prednisone, and betamethasone, in addition to removals of organic matter (97.1%), phosphorous (95%) and ammonium nitrogen (71%). Despite the high removals and micropollutants rejection, the toxicity removal for this MBR configuration has not been evaluated.

It is known that some treatment systems, such as advanced oxidative processes (AOP), for example, can achieve high removals of pollutants but increase the treated effluent toxicity by the formation of toxic by-products or production of chemical oxidants (PRADO et al., 2017; OUARDA et al., 2018). However, despite the importance of ecotoxicological tests to predict adverse effects on aquatic environments, few studies have evaluated the membrane bioreactors toxicity for treating wastewater with PhACs. Ouarda et al. (2018) and Prado et al. (2017) used MBRs combined with oxidative processes to treat wastewater with PhACs and showed significant toxicity removals for *Daphnia magna* in the permeate of MBRs, even with the persistence of some PhACs.

In contrast, studies evaluating other types of wastewater have shown that toxicity removals in MBRs may not be satisfactory. Reis et al. (2020) used an MBR-MF to treat leachate from sanitary landfill. After treatment by membrane bioreactor, there was a reduction in toxicity, which can be justified by removing the ammonia, degradation of organic matter, or retention of compounds by the MF, however, the permeate was still toxic. This shows that in addition to the PhACs, other compounds eventually not removed or generated during treatment may also promote toxicity to the treated sewage.

Hence, in this chapter, an anaerobic osmotic membrane bioreactor with membrane distillation (AnOMBR-MD) was evaluated to treat synthetic sewage with PhACs 17α-ethinylestradiol,

ketoprofen, fenofibrate, fluconazole, loratadine, prednisone, and betamethasone, focused on ecotoxicological studies to elucidate the mechanism of acute and chronic toxicity reduction in the system, using *Aliivibrio fischeri*, *Daphnia similis* and *Raphidocelis subcapitata* as indicators organism.

2.2 Materials and methods

2.2.1 Feed and draw solutions

Synthetic sewage used to feed the bioreactor simulates real domestic sewage. It was prepared according to the modified methodology of Mockaitis et al. (2014), as shown in the Table 1.

Table 1 - Composition of synthetic sewage.

Component	Concentration (mg L^{-1})
Meat extract	208
$CaCl_2$	2.68
KH_2PO_4	120
LAS (tensoative)	15
$MgCl_2$	1.53
NaCl	250
$NaHCO_3$	200
Oil	51
Starch	114
Sucrose	35

Physicochemical characterization of the synthetic sewage is presented in Table 2. Synthetic sewage was fortified with a mixture of seven PhACs: 17α-ethinylestradiol, ketoprofen, fenofibrate, fluconazole, loratadine, prednisone, and betamethasone, with a concentration of 2 μg L^{-1} each. The stipulated concentration is due to micropollutants' presence in concentrations in the order of μg L^{-1} and ng L^{-1} in the environment (CALISTO AND ESTEVES, 2009). The chosen PhACs have already been detected in surface water, raw or treated wastewater, and even drinking water (Table S1).

For the draw solution, $MgCl_2$ concentration of 1.25 mol L^{-1} was used as a solute and generated an osmotic pressure of 97.5 bar. $MgCl_2$ was pointed out by Arcanjo et al., (2020) as the ideal solute for this system, mainly due to the reduced reverse salt flux.

Table 2 - Physicochemical characterization of the synthetic sewage.

Parameter	Value
pH	8.29 ± 0.26
Conductivity (μS cm^{-1})	1183 ± 69
Alkalinity ($mgCaCO_3$ L^{-1})	165.16 ± 0
Volatile fatty acids (VFA) (mgHAc L^{-1})	46.66 ± 7.22
Chemical oxygen demand (COD) (mg L^{-1})	467.5 ± 130.1
Total suspended solids (TSS) (mg L^{-1})	100.3 ± 19.3
Volatile suspended solids (VSS) (mg L^{-1})	92.4 ± 19.23
$N\text{-}NH_4^+$ (mg L^{-1})	5.89 ± 2.46
$P\text{-}PO_4^{3-}$ (mg L^{-1})	35.97 ± 2.28

2.2.2 Experimental setup

Anaerobic osmotic membrane bioreactor with membrane distillation (AnOMBR-MD) was developed by Ricci et al. (2021). In this system, a hybrid module of FO-MD is submerged in an anaerobic bioreactor, as shown in Figure 2. Forward osmosis membranes are placed in the external faces of the module, where a heated draw solution (DS) circulates on the channel formed between FO and MD membranes. Inside the module are the hydrophobic distillation membranes, and a cooled distillate is circulated on the channel formed between them. In this way, the sewage goes through biological treatment and simultaneously by FO and MD separation processes. The feed tank and bioreactor were agitated continuously by mechanical and magnetic stirrers. A computer recorded the weight of DS and distillate for every 5 min. The conductivity of the distillate was also monitored daily by a conductivity meter.

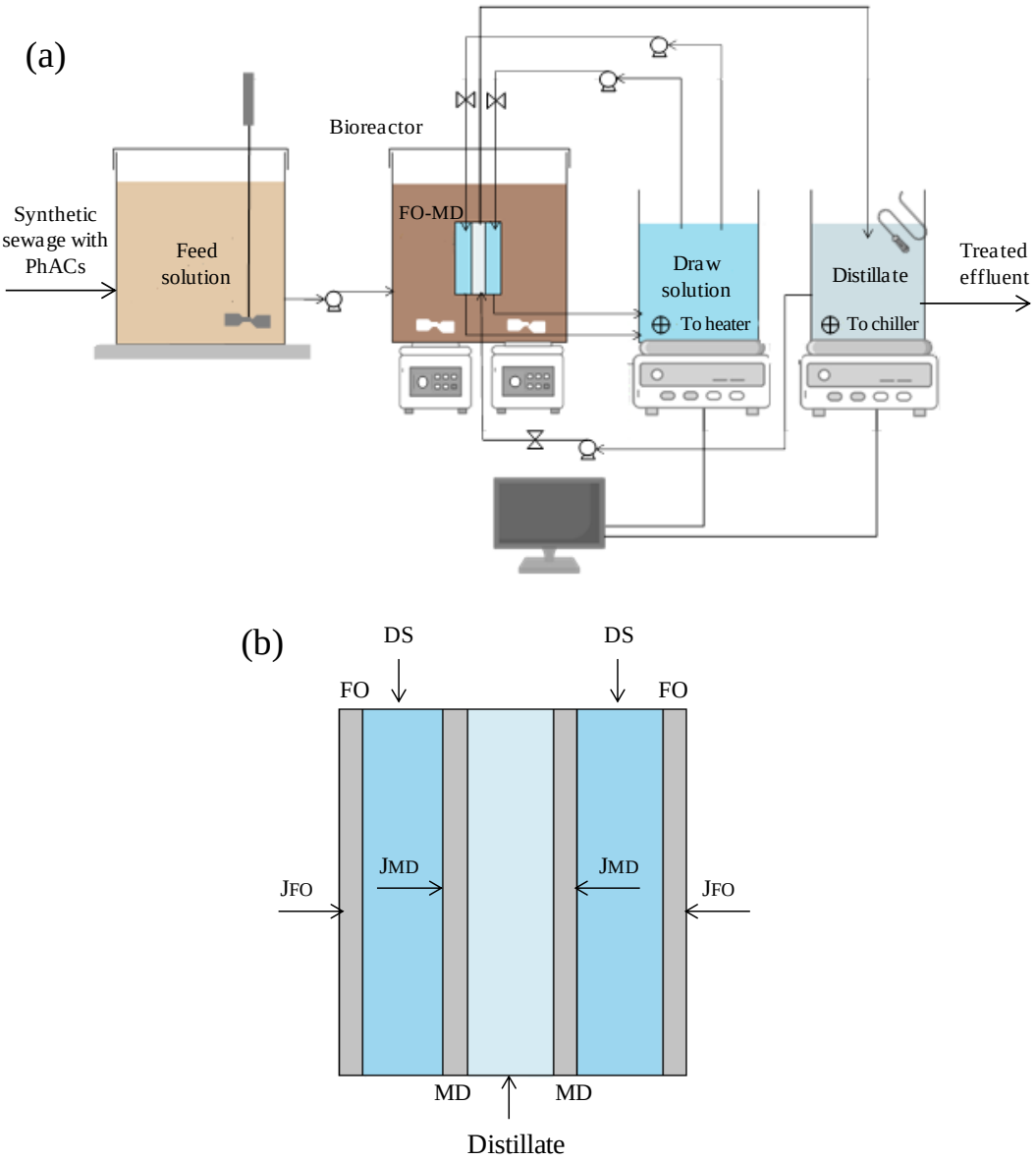

Figure 2 – Experimental setup of AnOMBR-MD (a) and FO-MD module scheme (b).

2.2.3 Operating conditions

Following the parameters used by Ricci et al. (2020), the system was inoculated with 10 g L^{-1} of volatile suspended solids (VSS). The operation started with 4 L of DS and 3 L of distillate (deionized water). The circulation rate and temperature for DS were setup in 75 L h^{-1} and 45 °C, respectively. For distillate, these values were 80 L h^{-1} and 25 °C. Synthetic sewage fortified with PhACs was added to the feed solution tank for every 2 days.

The AnOMBR-MD was operated under continuous flow for 32 days. With this operating time it is already possible to verify a stabilization in similar systems and satisfactory efficiencies removal to treat wastewater with PhACs (RICCI et al., 2020). For 5 days in a week, the temperature of each tank was recorded and samples from feed solution, mixed liquor (bioreactor

supernatant), DS and distillate were collected to measure pH and conductivity. Samples were also collected weekly for physico-chemical characterization and ecotoxicological tests.

2.2.4 Analytical methods

The physical-chemical analyses were performed following the methodologies of the Standard Methods for the Examination of Water and Wastewater (APHA, 2017), as shown in Table 3.

Table 3 - Analytical methods.

Parameter	Method
pH	4500-H^+
Conductivity	2510
Dissolved organic carbon (DOC)	5310 B
Alkalinity	2320 B
Total suspended solids (TSS)	2540 D
Volatile suspended solids (VSS)	2540 E
Total phosphorus (PO_4^{3-})	4500-P D
Ammoniacal nitrogen ($N-NH_4^+$)	4500-NH3 B e C
Volatile fatty acids (VFA)	5560
Hardness	2340

2.2.5 Permeate fluxes and removal efficiency

Permeate fluxes in MD (J_{MD}) and FO (J_{FO}) membranes, in kg m^{-2} h^{-1}, were calculated by Equation 1 and Equation 2:

$$J_{MD} = \frac{\Delta m_D}{\Delta t \times A_m} \quad \text{Eq. (1)}$$

$$J_{FO} = \frac{\Delta m_{DS}}{\Delta t \times A_m} + J_{MD} \quad \text{Eq. (2)}$$

where Δm_D and Δm_{DS} are the increase in distillate and DS weight, respectively, over a period, Δt, and Am is the membrane area.

The MD salt rejection ($R_{salt,MD}$) was calculated by Equation 3:

$$R_{salt,MD} = \frac{C_{MgCl_2,DS} - C_{MgCl_2,pMD}}{C_{MgCl_2,DS}} \times 100 \quad \text{Eq. (3)}$$

where $C_{MgCl2,DS}$ and $C_{MgCl2,pMD}$ are the draw solute concentration, $MgCl_2$, of the DS and MD permeate.

The overall removal efficiency of the AnOMBR-MD was calculated by Equation 4:

$$R_{AnOMBR-MD} = \frac{C_{FS} - C_{p,MD}}{C_{FS}} x\ 100 \qquad \text{Eq. (4)}$$

where C_{FS} is the contaminant concentration in the feed solution, and $C_{p,MD}$ is the contaminant concentration of the MD permeate.

2.2.6 Ecotoxicological tests

Ecotoxicological tests were carried out with three trophic levels for feed solution, mixed liquor, and distillate, according to the criteria established by Resolution CONAMA 430 (BRASIL, 2011). For the acute toxicity tests the bacteria *Aliivibrio fischeri* and the microcrustacean *Daphnia similis* were used, and for the chronic toxicity tests, the algae *Raphidocelis subcapitata*. Samples for toxicity tests were collected in the third week (W3), fourth week (W4) and fifth week (W5) of AnOMBR-MD operation.

To facilitate the approach of the results, effect values found in the toxicity tests were transformed into values of toxic unit (TU), as shown in Equation 5:

$$TU = \frac{100}{E(L)C_{50}} \qquad \text{Eq. (5)}$$

The results were classified as proposed by Persoone et al. (2003): class I (TU < 1) - slightly toxic; class II (1 < TU < 10) - toxic; class III (10 < TU <100) - very toxic; class IV (TU > 100) - highly toxic.

Toxicity removal (TR) of the FO-MD was calculated by Equation 6:

$$TR_{FO-MD} = \frac{TU_{ML} - TU_{DIST}}{TU_{ML}} x\ 100 \qquad \text{Eq. (6)}$$

where TU_{ML} is the toxic unit in mixed liquor and TU_{DIST} is is the toxic unit in distillate.

2.2.6.1 Acute toxicity tests with bacteria *Aliivibrio fischeri*

Acute toxicity tests with the luminescent marine bacteria *Aliivibrio fischeri* were carried out in the Biological Testing Laboratory of the Department of Sanitary and Environmental Engineering of the Federal University of Minas Gerais, using the MICROTOX® model 500 Analyzer (SDI) equipment, as shown in Figure 3. The tests were carried out following ABNT

NBR 15411-3: Ecotoxicologia Aquática – Determinação do efeito inibitório de amostras de água sobre a emissão de luz de *Vibrio Fischeri* (ABNT, 2006) and the protocol established by the software (MICROTOX® Omni Software, version 4.1) of MICROTOX®. Among the advantages of using the *A. fischeri* bacteria as an indicator organism can mention the short duration of the test and low volume requirement of samples and consumables. Besides, the bacteria's sensitivity can be compared to that of fish and the microcrustacean (PIVATO and GASPARI, 2006).

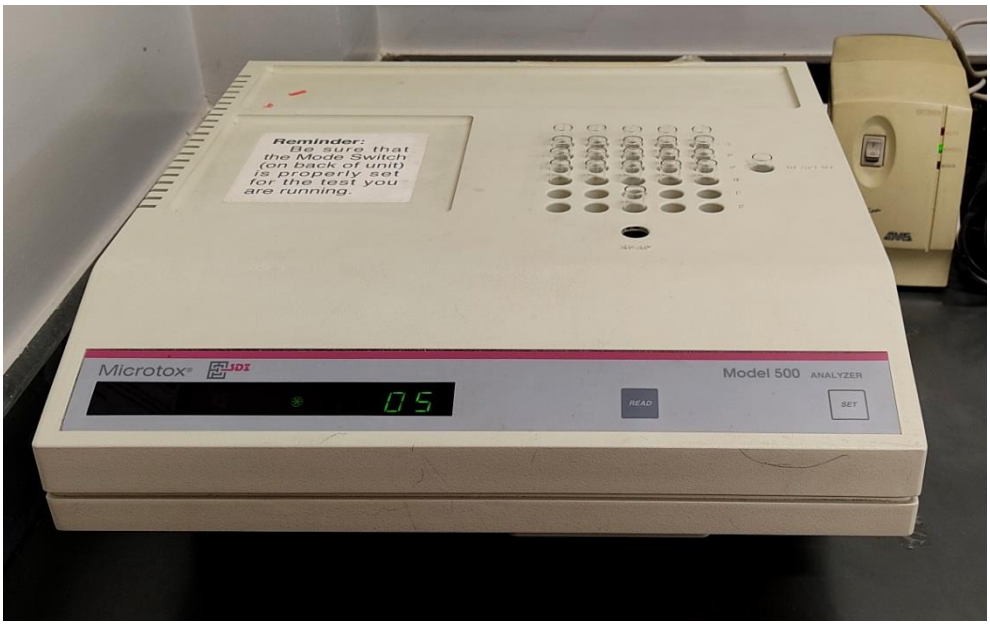

Figure 3 - MICROTOX® model 500 Analyzer (SDI) equipment.

The effect concentration (EC_{50}) was determined from the MICROTOX® 81.9% Basic Test for feed solution, mixed liquor, and distillate with 9 concentrations each (81.9%, 40.95%, 20.48%, 10.24%, 5.12%, 2.56%, 1.28%, 0.64% and 0.32% v/v). The luminescence measurement of the bacteria was carried out in 5, 15, and 30 minutes. The software makes a comparison of bacteria luminescence with samples and the control. The less light emitted, the greater the toxicity of the sample. Therefore, the relative toxicity of the sample is expressed as the percentage of inhibition compared to the control (BIAŁK-BIELIŃSKA et al., 2011).

To perform the tests, the pH of the samples was, when necessary, adjusted to values between 6.0 and 8.5 using HCl or NaOH, and the salinity was verified with an Instrutherm RTS-101ATC High Resolution Refractometer for Salinity. In samples with salinity below 20%, a NaCl (22%) solution was added for osmotic adjustment.

The bacteria used in the tests were kept at -22ºC, and according to NBR 15411-3 (ABNT, 2006), the sensitivity test was performed with each batch of bacteria, using the reference solution of zinc sulfate heptahydrate ($ZnSO_4$. $7H_2O$). According to standard, gamma effect should be between 0.6 and 1.8 in the control, and the inhibition effect between 20% and 80% for the reference solution.

2.2.6.2 Acute toxicity tests with microcrustacean *Daphnia similis*

Acute toxicity tests with the microcrustacean *Daphnia similis* were carried out in the Aquatic Ecotoxicology laboratory of the Federal University of Viçosa, according to ABNT NBR 12713: Ecotoxicologia Aquática – Toxicidade aguda – Método de ensaio com *Daphnia* spp (Crustacea, Cladocera) (ABNT, 2016). Microcrustaceans of the genus *Daphnia* have been widely used for effluent toxicity tests due to their high sensitivity to various substances, the precision of tests, and ease of cultivation in the laboratory (TKACZYK et al., 2021).

The organisms cultivated were kept in incubators with a temperature of 18 °C to 22 °C, and a photoperiod of 12 h to 16 h light, according to the recommendations of ABNT NBR 12713 (ABNT, 2016). The culture media consists of non-chlorinated natural water with a hardness corrected to approximately 44 mg $CaCO_3$ L^{-1} and pH between 7.0 and 7.6. Also, the organisms were feeding with a suspension of the microalgae *Pseudokirchneriella subcapitata*. The organism's sensitivity is evaluated periodically through bioassays using NaCl as a reference substance.

Toxicity tests were performed using concentrations of 100%, 50%, 25%, 12.5% and 6.2% (v/v) for the distillate and feed solution and 25%, 12.5%, 6.2%, 3.1%, 1.5% and 0.75% (v/v) for mixed liquor. These concentrations were determined from preliminary tests. Each concentration was evaluated in four replicates, containing five organisms aged between 6 and 24 hours (Figure 4). All tests contained a negative control with only the organisms and culture media, without the samples. The tests were static, lasting 48 hours, maintained at a temperature of 22 ± 2 ºC, with a photoperiod of 16 hours of light and without power.

At the end of the test, the number of survival organisms in the samples and control was counted and statistically analyzed using the Comprehensive Environmental Toxicity Information System (CETIS) software, with a significance level of 5%, which provides the values of LC_{50} (lethal concentration), as well as the confidence intervals.

Figure 4 - Acute toxicity tests with *Daphnia similis.*

2.2.6.3 Chronic toxicity tests with algae *Raphidocelis subcapitata*

Chronic toxicity tests with *Raphidocelis subcapitata* were carried out in the Aquatic Ecotoxicology laboratory of the Federal University of Viçosa, according to ABNT NBR 12648: Ecotoxicologia Aquática – Toxicidade crônica – Método de ensaio com algas (Chlorophyceae) (ABNT, 2011). Inhibition tests with algae are considered versatile, reliable, fast, and easily reproducible methods (HUARACHI-OLIVERA et al., 2019).

The following concentrations were used to perform the tests: 100%, 50%, 25%, 12.5% and 6.2% (v/v) for the distillate and feed solution and 100%, 50%, 25%, 12.5% and 6.2% and 3.1% (v/v) for mixed liquor. As a culture media, the L.C. Oligo was used, and for each sample concentration, three replicates were made in 40 mL glass tubes with 15 mL of the solution test, which consists of the L.C. Oligo, inoculum (3.14x106 cells per mL^{-1} of algae) and sample. The tubes were sealed with a cotton stopper and covered with aluminum foil. The tests were set up in aseptic conditions (laminar flow cabinet), and all materials used, including L.C. Oligo, were previously autoclaved. The tests were maintained on a shaking table, at a temperature between 23 °C and 27 °C, luminous intensity of 4500 Lux, and agitation of 100 rpm, for 72 h (Figure 5). Besides, the tubes were manually shaken once a day.

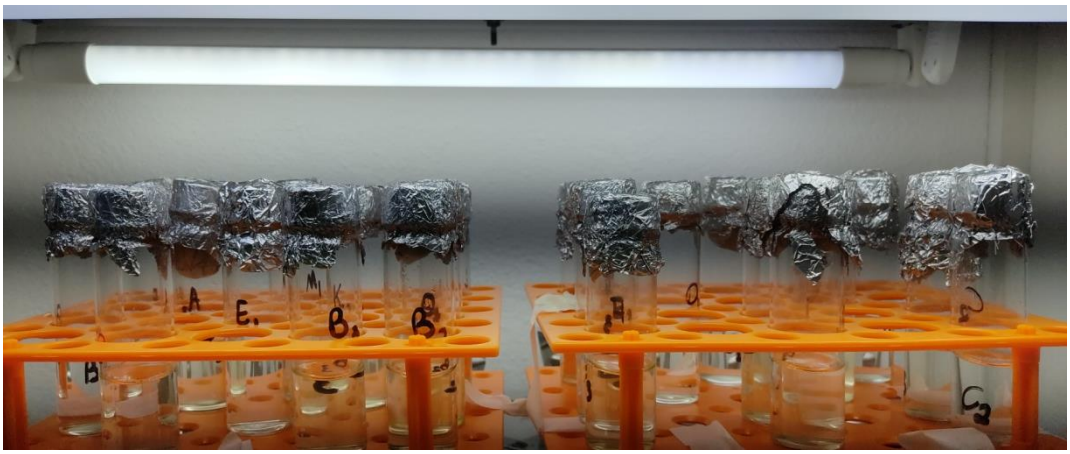

Figure 5 - Chronic toxicity tests with algae *Raphidocelis subcapitata.*

After the exposure period, cell density was estimated by spectrophotometry, in order to determine algae biomass with absorbance readings at 750nm. Thus, a regression curve was used to establish the values of cells per mL $^{-1}$ of algae as a function of absorbance. The algae biomass produced during the test for each sample was compared to the control, composed only by L.C. Oligo and the inoculum, using the Comprehensive Environmental Toxicity Information System (CETIS) software, with a significance level of 5%, which provides the IC values (inhibition concentration), as well as the confidence intervals.

2.3 Results and discussion

2.3.1 AnOMBR-MD permeate flux

Permeate flux in FO was about 2.83 kg m^{-2} h^{-1} at the beginning of AnOMBR-MD operation, and after 25 days, there was a stabilization trend, with average value of 0.597 kg m^{-2} h^{-1} (Figure 7). FO membrane fouling has contributed to the flux decline. Another reason for the decline in J_{FO} was salinity build-up in the bioreactor that lowered the FO driving force. The mixed liquor conductivity was about 1.12 mS cm^{-1} at the beginning of AnOMBR-MD operation, and at the end, it was about 5.24 mS cm^{-1}. Ion accumulation is influenced by the reverse salt flux (Js) and the dissolved compounds that enter the bioreactor and are retained by the FO membrane (JOHNSON et al., 2018). Beside to reducing the driving force, elevated ion concentration in the bulk sludge can cause osmotic stress for the bioreactor microorganisms, reducing their biological activity and, therefore, the overall performance in the AnOMBR-MD (JOHNSON et al., 2018).

A less sharp reduction in J_{MD} was observed. The initial J_{MD} was 1.61 kg m^{-2} h^{-1} and also there was a stabilization trend after 25 days, with average value of 0.551 kg m^{-2} h^{-1} (Figure 6). When

water vapor permeates the MD membrane, the $MgCl_2$ accumulates at the membrane surface, which can lead to pore blocking and flux decline (RAMEZANIANPOUR AND SIVAKUMAR, 2014). Also, with the temperature polarization, described as the reduction in the temperature difference across the membrane, the vapor pressure difference was reduced (MARTÍNEZ-DÍEZ and VÁZQUEZ-GONZÁLEZ, 1999).

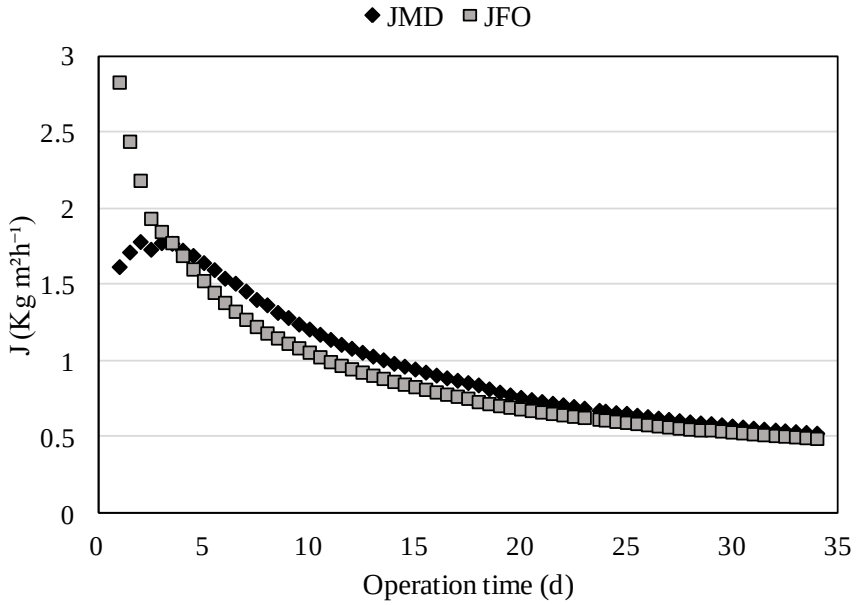

Figure 6 – Permeate flux in FO and MD membranes during AnOMBR-MD operation.

2.3.2 AnOMBR-MD removal efficiencies

Table 4 shows the average contaminant concentrations and removal efficiency in AnOMBR-MD operation. COD overall removal of 90.07% in the AnOMBR-MD was observed (Table 4). Furthermore, COD in ML was about 253.5 mg L^{-1}, suggesting that biodegradation was responsible for about 50% of the removal. Faria et al. (2020) used the same synthetic sewage with PhACs in an EGSB-MBR reactor and achieved 98% COD removal. Ricci et al. (2021) used an anaerobic OMBR-MD with NaCl as solute and achieved removals of 97.1%, with an average biodegradation efficiency of 77%.

Below-expected COD removals may be due to salinity build-up in the bioreactor. Zhao et al. (2018) evaluated the $MgCl_2$ reverse salt flux in anaerobic bioreactors and showed that the presence of Mg in the reactor could inhibit organisms' activity. According to the authors, although the influence was more significant in concentrations above 16 g L^{-1} of $MgCl_2$, this compound reduced the removal of COD even for low concentrations, including the

concentration found in the bioreactor of the present study (1.6 g L^{-1}). It was not possible to calculate the COD for the draw solution, due to the high interference of the chloride ion present in the sample.

Table 4 – Average contaminant concentration and removal efficiency in AnOMBR-MD operation.

Parameter	Feed solution	ML	DS	Distillate	RAnOMBR-MD (%)
Alkalinity (mg $CaCO_3$ L^{-1})	165.16 ± 0	696.4 ± 171.3	70 ± 38.8	22.6 ± 10.9	-
VFA (mgHAc L^{-1})	46.66 ± 7,22	416 ± 171.6	37.7 ± 13.5	24.1 ± 4	-
$N\text{-}NH_4^+$ (mg L^{-1})	5.89 ± 2.46	30.2 ± 8.6	18.1 ± 8.4	4.09 ± 2.2	93.01
$P\text{-}PO_4^{3-}$ (mg L^{-1})	35.97 ± 2.28	21.9 ± 4.5	0.04 ± 0.02	0.003 ± 4.4 x 10^{-19}	99.99
COD (mg L^{-1})	467.5 ± 130.1	253.56 ± 76.6	-	46.4 ± 21.1	90.07

In the anaerobic treatment, organic nitrogen is converted to its inorganic form ($N\text{-}NH_4^+$). Thus, nutrient accumulation in the bioreactor was expected (Figure 7a). Overall rejection of ammonia was 93.01%, and distillate presented an average $N\text{-}NH_4^+$ concentration of 4.09 mg L^{-1}. $N\text{-}NH_4^+$ removal was relatively low due to ammonia volatility, which can promote the passage of this compound through the MD membrane. However, removal was high considering other treatment systems (DIAS et al., 2017). Phosphorus removals were greater about to $N\text{-}NH_4^+$. The average $P\text{-}PO_4^{3-}$ concentration in the ML was 21.9 mg L^{-1} (Figure 7b), with concentrations in distillate below the method detection limit (0.003 mg L^{-1}). The overall removal was around 99.99%. Hence, several studies have been carried out to recover phosphorus in OMBRs (LUO et al., 2016; QIU et al., 2016; XIE et al., 2014).

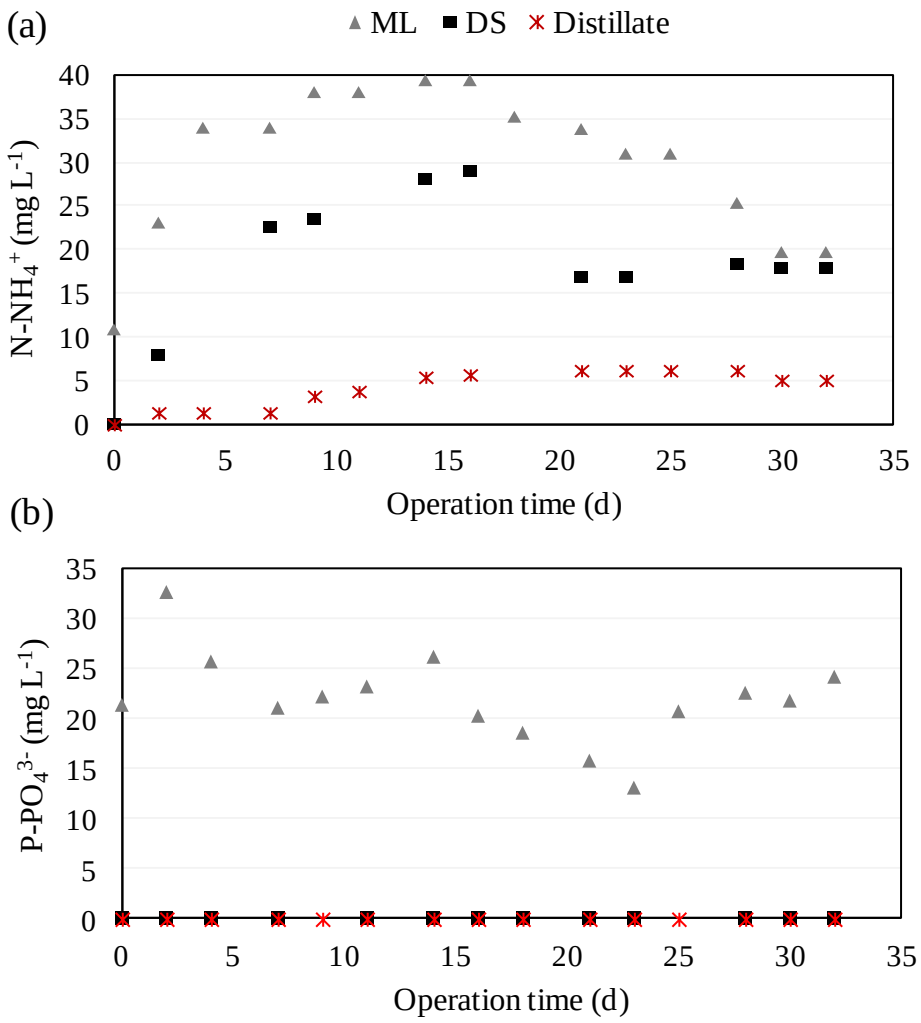

Figure 7 - N-NH_4^+ (a) and P-PO_4^{3-} (b) concentration during AnOMBR-MD operation.

Mixed liquor (ML) pH remained relatively constant at about 7.93 ± 0.24 and the same was observed for DS and distillate, with a pH of 6.85 ± 0.23 and 7.21 ± 0.58, respectively. The variation of ML pH was low, which can be explained by the high alkalinity (Table 4) that counteracted the pH-reducing effects of volatile fatty acids (VFA). The presence of VFA in their non-ionized form, at a pH below 6, can cause inhibition of methanogenic bactéria (WAINAINA, et al., 2019). Despite high VFA, above 416 mgHAc L^{-1} (Table 4), concentrations in ML, pH during the operation was between 6.9 and 8.2. Distillate pH at the beginning of the operation was around 6.4 and increased to around 7.8 at the end of the operation. This increase may be due to the dilution process that occurs with the water production.

MD salt rejections were greater than 99.8% making it suitable for DS reconcentration and water recovery processes in an AnOMBR. However, due to the high concentration of $MgCl_2$ in the

DS, the concentration of salts in the distillate was relatively high, in the range of 106.2 ± 26 mg L^{-1} of Mg^{2+} and 293.1 ± 34.7 mg L^{-1} of Cl^- (Figure 8).

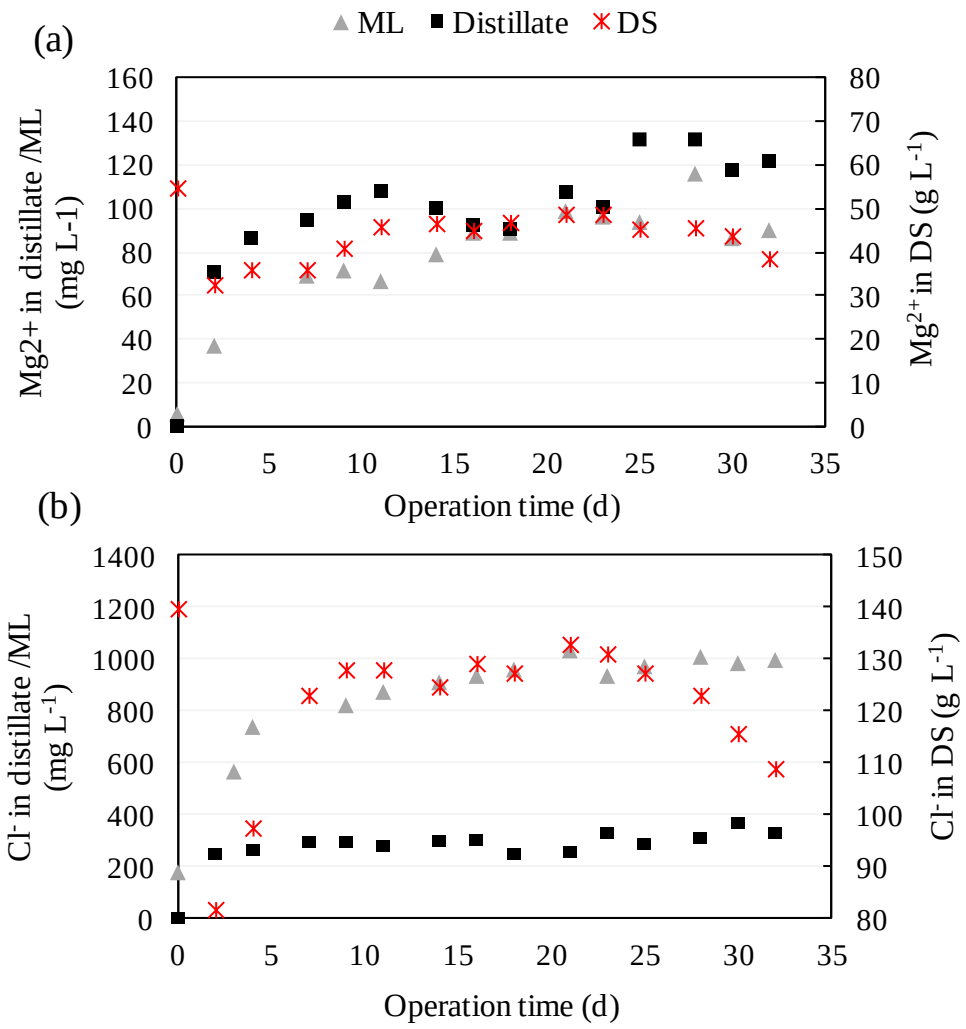

Figure 8 - Mg^{+2} (a) and Cl^- (b) concentrations during AnOMBR-MD operation.

2.3.3 Ecotoxicological assessment of the AnOMBR-MD

2.3.3.1 Acute toxicity tests with *Aliivibrio fischeri* and *Daphnia similis*

Acute toxicity tests with the bacteria *Aliivibrio fischeri* and the microcrustacean D*aphnia similis* were carried out for AnOMBR-MD samples collected in the third (W3), fourth (W4) and fifth (W5) weeks of operation. Table 5 shows the values of $E(L)C_{50}$, as well as the acute toxic unit (TUa) for these organisms.

In the feed solution, hormesis was verified for *A. fischeri* in 30 min of exposure, representing a positive response of the organism to the medium (CHAPMAN, 2002). The bacteria exposure to the feed solution caused an increase in luminescence emission, and this phenomenon may be related to a manifestation of the adaptive nature of organisms to overcome a specific imbalance

(CALABRESI, 2008). For *D. similis*, the feed solution did not present toxicity, with LC_{50} values greater than 100%. Some studies have been evaluated the toxicity in municipal sewage for *A. fischeri* and *D. similis* and detected toxic effects (WANG et al., 2003; HONGXIA, 2004), which indicates that other compounds that were not considered in this study may be present in the real sewage, promoting toxicity whose removal must be evaluated in WWTPs.

Table 5 - Acute effects for *A. fischeri* and *D. similis* in AnOMBR-MD samples.

Aliivibrio fischeri				
Sample	EC_{50} (%) 30 min	Confidence interval (%)	TUa	Classification
Feed solution	Hormesis*	-	-	-
Mixed liquor W3	94.6	24.91 - 359.2	1.06	Toxic
Mixed liquor W4	19.92	12.61 - 31.47	5.02	Toxic
Mixed liquor W5	76.4	37.76 - 154.8	1.31	Toxic
Distillate W4	>100	-	-	No toxic
Distillate W5	>100	-	-	No toxic
Daphnia similis				
Sample	LC_{50} (%)	Confidence interval (%)	TUa	Classification
Feed solution	>100**	-	-	No toxic
Mixed liquor W3	15.87	13.64 – 18.47	6.3	Toxic
Mixed liquor W4	3.18	2.14 - 4.71	31.45	Very toxic
Mixed liquor W5	17.68	15.19 - 20.57	5.66	Toxic
Distillate W4	30.55	25.71 - 36.31	3.27	Toxic

***** positive response of the organism to the medium.
****** no adverse effect even at the highest sample concentration (100%).

Besides, the results show that the mixture of the PhACs (17α-ethinylestradiol, ketoprofen, fenofibrate, fluconazole, loratadine, prednisone, and betamethasone) at 2 μg L^{-1} each, did not promote acute toxicity to the organisms, since the feed solution fortified with these micropollutants showed no toxicity. However, there is a need for further study regarding the toxicity of these single PhACs and the mixture between them, since the interaction of these compounds can cause synergistic or antagonistic effects. Few studies have evaluated the toxicity of these PhACs for *A. fischeri* and *D. similis*. Clubbs and Brooks (2007) found EC_{50} of 0.83 mg L^{-1} for *D. magna* evaluating the loratadine. 17α-ethinylestradiol toxicity has also been evaluated for *D. magna*, with an EC_{50} of 1.63 mg L^{-1} (FASS.SE, 2020), suggesting that these PhACs' toxicity can be related to higher concentrations. Table 6 shows the crustacean toxicity values found in the literature for these PhACs. No effect values were found for bacteria.

Table 6 - Crustacean toxicity values found in the literature for the seven PhACs.

Compound	Exposure time	Species	Toxicity assessment criteria	Value (mg L^{-1})	Reference
Betamethasone	21 d	*Daphnia magna*	NOEC (Parental survival)	17	Fass.se, 2020
Ketoprofen	6-8 d	*Ceriodaphnia dubia*	NOEC (Reproduction)	22.5	Watanabe et al., 2016
	21 d	*Daphnia magna*	NOEC (Reproduction)	9.15	Fass.se, 2020
Prednisone	24 h	*Brachionus calyciflorus*	LC50 (Mortality)	54.6	Dellagreca et al., 2002
Fluconazole	24 h	*Thamnocephalus platyurus*	LC50 (Immobilization)	100	Kim et al., 2009
Loratadine	48 h	*Daphnia magna*	EC50 (Immobilization)	0.83	Fass.se, 2020
17α-ethinylestradiol	-	*Ceriodaphnia dubia*	EC50 (Reproduction inhibition)	0.03	Iesce et al.,2019
	48 h	*Daphnia magna*	EC50 (Immobilization)	313	Cleuvers, 2005
	48 h	*Daphnia magna*	EC50	5.7	Safety Data Sheets, USP, 2019
	48 h	*Daphnia similis*	EC50 (Mortality)	1.63	Clubbs and Brooks, 2007
Fenofibrate	-	*Daphnia*	NOEC (Reproduction)	0.387	Vestel et al., 2016
	7 d	*Ceriodaphnia dubia*	EC50 (Growth inhibition)	0.76	Isidori et al., 2007
	-	*Ceriodaphnia dubia*	NOEC (Population growth inhitbition)	0.039	Orias et al., 2013
	7 d	*Ceriodaphnia dubia*	NOEC (Growth inhibition)	0.039	Isidori et al., 2007

Mixed liquor (ML) was considered toxic at 30 minutes of exposure to *A. fischeri* and *D. similis* in all samples, except for the four week of operation, in which ML was classified as very toxic for the microcrustacean. This shows that the phenomena that occur in the bioreactor, such as by-product formation and ion concentration due to FO rejection, promoted toxicity for the system. ML toxicity may be related to the accumulation of alkalinity, fatty acids, organic matter, ammonia, and other ions present in the bioreactor (Table 6). For *D. similis*, ABNT NBR 12713 establishes that the total hardness should be between 40 and 48 mg CaCO3 L^{-1} in ideal conditions for the organism, however, the average hardness concentration in ML was 370.5 mg CaCO3 L^{-1}, probably due to the reverse salt flux of $MgCl_2$, which may have caused toxicity to the microcrustacean, together with the accumulation of other ions. Table 7 shows the correlation values between the concentration of contaminants present in the bioreactor and the toxicity for *D. similis*, proving the influence of hardness on ML toxicity.

Table 7 – Correlation between toxic unit (TU) and concentration of contaminants in the ML for *D. similis.*

Parameters	R^2
$N\text{-}NH_4^+$ (mg L^{-1})	0.047
$P\text{-}PO_4^{3-}$ (mg L^{-1})	0.558

COD (mg L^{-1})	0.23
Hardness (mg $CaCO_3$ L^{-1})	0.992

For *A. fischeri*, ML was considered less toxic than for *D. similis*. Because it is a marine bacterium, the hardness values do not make the sample toxic to the organism, thus, the toxic effect of mixed liquor can be caused by other contaminants present in the bioreactor. Studies that evaluated toxicity in wastewater treatments show a significant positive correlation of the parameters alkalinity and ammoniacal nitrogen with *A. fischeri* toxicity (KALČÍKOVÁ et al., 2015; FILHO et al., 2017; COSTA et al., 2019).

A essential factor for *A. fischeri* is the exposure time of the organism. For the distillate and feed solution, the increase in toxicity did not occur or was not noticeable with increased exposure time (Figure 9). However, for ML, the longer the exposure time, the greater the toxic effect. This suggests that mixed liquor can be more still toxic in the long term and shows the importance of toxicity tests with longer exposure times.

The distillate was not considered toxic to *A. fischeri*, with effects above 100%. For *D. similis*, the distillate of the fourth week was classified as toxic, with a TUa value of 3.27 (Table 5). This shows the importance of carrying out tests with more than one trophic level since some organisms may be more sensitive to some contaminants. FO-MD membranes showed great nutrient rejections and relative removal of organic matter (Table 4), and these contaminants in the concentrations present in the distillate are not likely to cause toxicity since the feed solution was not toxic. However, the distillate's hardness was in the range of 419 mg CaCO3 L^{-1}, due to the high Mg concentration of DS and consequently the increase of this compound in the distillate, which may have promoted toxicity for *D. similis*, as occurred in the ML.

Hogan et al. (2013) evaluated the toxicity of $MgCl_2$, used as a solute for DS, for several freshwater species and showed that the compound can be toxic, especially at longer exposure times. This reinforces that the $MgCl_2$ concentration may have influenced the toxicity in the distillate. However, toxicity identification and evaluation must be carried out for the distillate to identify the actual toxicity-causing compounds and eliminate the risks of this effluent to the ecosystem.

Even with the distillate toxicity for *D. similis*, it is essential to emphasize FO-MD membranes' role in removing or reducing acute toxic effects. Mixed liquor was considered toxic to *A.*

fischeri, while the distillate did not present any toxicity. For *D. similis* there was an 89.6% removal of toxicity by membranes in the fourth week of operation.

Some studies have evaluated the toxicity removal in membrane bioreactors to treat other types of wastewater. Ouarda et al. (2018) used a combination of MBR and electro-oxidation to treat synthetic hospital wastewater fortified with four pharmaceuticals. In this study, after treatment by MBR alone, the effluent did not present toxicity for *D. magna* and *A. fischeri*. However, using electro-oxidation as a post-treatment of MBR, despite the high removal efficiencies for all PhACs, the effluent showed toxicity at 100% concentration, which may be related to the formation of by-products or chemical oxidants produced during electrolysis. Reis et al. (2020) used a MBR-NF to tretat landfill leachate and observed that the MBR effluent was still toxic to *A. fischeri*, which was totally eliminated in the NF effluent, highlighting the role of nanofiltration membrane.

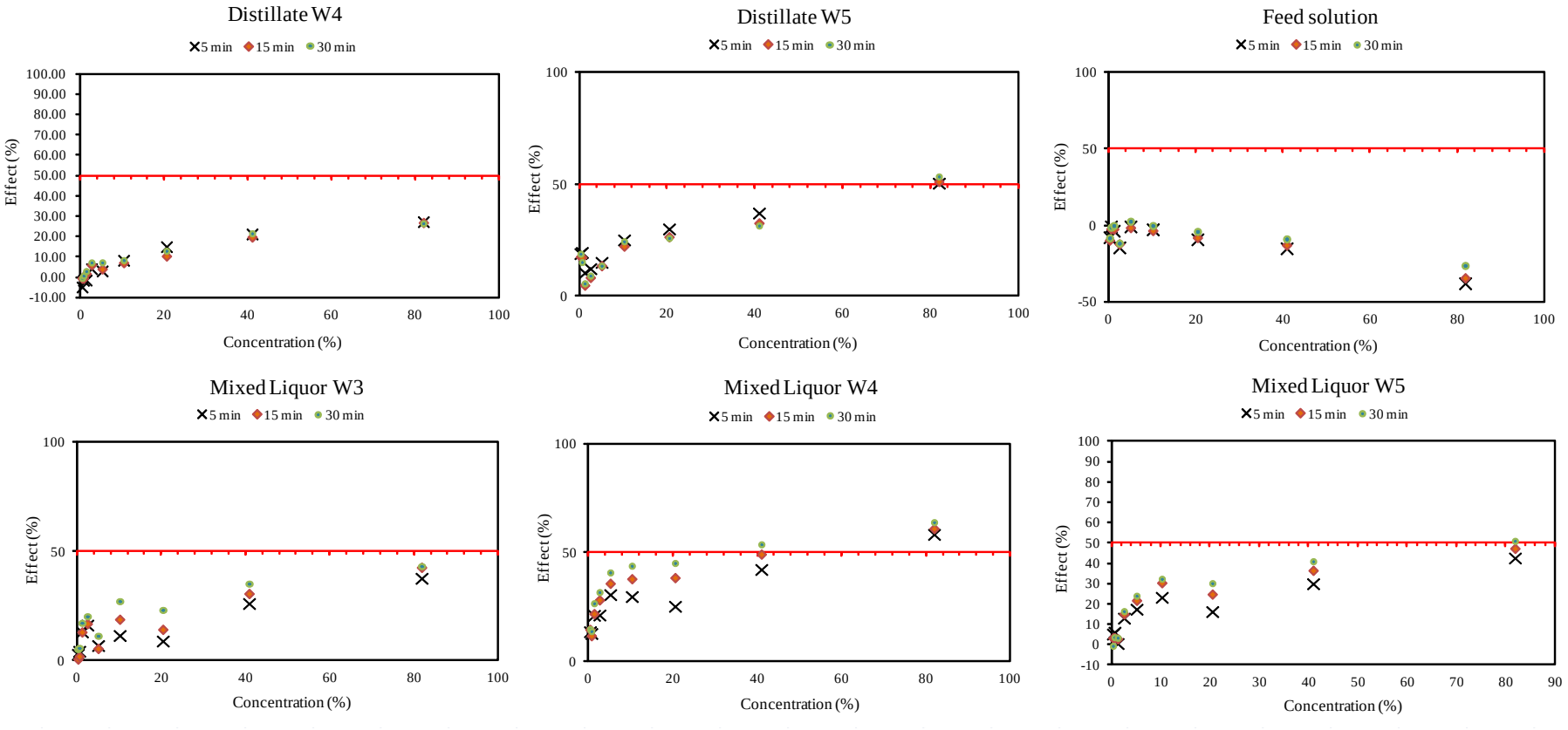

Figure 9 – Acute effects for *Aliivibrio fischeri* at 5, 15 and 30 minutes of exposure in distillate, feed solution and mixed liquor.

2.3.3.2 Chronic toxicity tests with algae *Raphidocelis subcapitata*

Chronic toxicity tests with *Raphidocelis subcapitata* were carried out for the distillate of the fourth week, and for the mixed liquor, the samples collected in the third, fourth and fifth week of operation were joined due to the low volume of sample. Table 8 shows the IC_{25} values and the chronic toxic unit (TUc) for this organism.

Table 8 – Chronic effects for *R. subcapitata* in AnOMBR-MD samples.

Sample	IC_{25} (%)	Confidence interval (%)	TUc	Classification
Feed solution	>100	-	-	No toxic
Mixed liquor W3+W4+W5	41.54	32.74 - 53.74	2.41	Toxic
Distillate W4	2.58	0.84 - 9.62	38.76	Very toxic

As in the acute toxicity tests, the feed solution did not present chronic toxicity to the algae. Table 9 shows that the algae toxicity values found in the literature for these PhACs are in the range of mg L^{-1}. Mixed liquor was considered toxic, with a TUc value of 2.41. However, the ML showed higher TU values for *D. similis*, showing that this organism was more sensitive to the sample than *A. fischeri* and *R. subcapitata*, even with the more extended exposure period for the algae. Andrade et al. (2011) evaluated the treatment of oil-field produced water containing several contaminants and attributed the effluent's toxicity for *R. subcapitata* to ammoniacal nitrogen, which may also be a possibility for the ML.

Table 9 - Algae toxicity values found in the literature for the seven PhACs.

Compound	**Exposure time**	**Species**	**Toxicity assessment criteria**	**Value (mg L^{-1})**	**Reference**
Betamethasone	72 h	*Selenastrum capricornutum*	NOEC (Growth rate and yield)	34	Fass.se, 2020
Ketoprofen	48 h	*Scenedesmus obliquus*	EC50 (Growth inhibition)	0.4	Wang et al. 2019
	96 h	*Pseudokirchneriella subcapitata*	EC50 (Mortality)	0.24	Mennillo et al., 2018
	72 h	*Pseudokirchneriella subcapitata*	EC50 (Growth inhibition)	0.03	Fass.se, 2020
	72 h	*Pseudokirchneriella subcapitata*	NOEC (Growth inhibition)	9.94	Watanabe et al., 2016
Prednisone	72h	-	EC50	31	Cayman Chemical Company, 2020
Fluconazole	72 h	*Pseudokirchneriella subcapitata*	NOEC (Growth inhibition)	3.06	Chen et al., 2014
Loratadine	-	*Pseudokirchneriella subcapitata*	EC50 (Growth inhibition)	2.15	Iesce et al.,2019
17α-ethinylestradiol	-	-	EC50 (ECOSAR)	0.1	Sanderson et al., 2004

Fenofibrate	3 d	*Pseudokirchneriella subcapitata*	NOEC (Population growth rate)	3.12	Isidori et al., 2007

The distillate was the most toxic sample for *R. subcapitata*, classified as very toxic. This shows the algae's sensitivity to the AnOMBR-MD effluent and suggests that longer exposure times can make the distillate even more toxic. Some studies evaluating the toxicity of metals show that hardness can positively influence toxicity in algae since calcium and magnesium cations can reduce the uptake of other compounds and reduce toxicity by absorption (PAQUET et al., 2019; DEFORESt et al., 2017). However, Gensemer et al. (2017) showed that tests using hardness values above 120 mg $CaCO_3$ L^{-1} cause an increase in chronic toxicity, inhibiting the growth of *R. subcapitata*. In this way, the high hardness of the distillate, due to the presence of Mg^{2+}, may be the reason for the toxicity. Furthermore, Van Dam et al. (2010) evaluated the toxicity of magnesium (Mg) compounds for the algae species *Chlorella sp*. and found an IC_{10} of 43 mg L^{-1} for Mg, while in the AnOMBR-MD distillate, the average Mg^{+2} concentration was 106.2 mg L^{-1}, higher than in the ML (73 mg L^{-1}). Therefore, despite the high salts rejection by MD, Mg^{+2} may have been toxic to *R. subcapitata* in distillate. This result shows the importance of considering the toxic effect in selection of DS solutes in bioreactors or other wastewater treatments.

2.4 Conclusion

In this chapter the performance of an AnOMBR-MD to treat synthetic sewage with seven PhACs was assessed with a focus on removing acute and chronic toxicity. The bioreactor showed great nutrient removals (99.99% removal of P-PO_4^{3-} and 93.01% removal of N-NH_4^+). However, the removal of organic matter was 90.07%, probably due to salinity build-up in the bioreactor, which shows the importance of assessing the chosen solute toxicity to microorganisms.

The feed solution fortified with a mixture of 17α-ethinylestradiol, ketoprofen, fenofibrate, fluconazole, loratadine, prednisone, and betamethasone at a concentration of 2 µg L^{-1} each, was not toxic for any of the evaluated organisms, showing that this concentration of PhACs mixed in the synthetic sewage did not cause adverse effects. In contrast, the ML showed acute toxicity for *A. fischeri* and *D. similis* and chronic toxicity for *R. subcapitata* in all evaluated samples, showing the accumulation of ammonia, alkalinity, and hardness in the bioreactor may cause toxic effects.

The distillate was not toxic to *A. fischeri* but promoted toxicity to *D. similis* and *R. subcapitata*, reinforcing the importance of ecotoxicological tests with more than one trophic level. The distillate's toxicity may have been caused by the high $MgCl_2$ concentration which can be toxic to these organisms. This warns of caution when using $MgCl_2$ as a solute in osmotic bioreactors. Despite the toxicity present in the distillate, FO and MD membranes' role in the removal of acute toxicity is highlighted. For *A. fischeri* there was complete removal of toxicity about mixed liquor, while for *D. similis* the removal was 89.6% in the fifth week of operation.

CHAPTER 3

PHARMACEUTICALS IN AQUATIC ENVIRONMENT AND RISK ASSESSMENT

3.1 Introduction

Pharmaceutically active compounds (PhACs) are chemical substances that provide essential elements in the prevention and treatment of diseases, infections or discomforts, and, for this reason, they are essential to ensure the health and the life quality of the population (PHOON et al., 2020). However, the overuse of PhACs has been of concern in several countries (MORGAN, 2006; ABRAHAM, 2010; BUSFIELD, 2015).

These PhACs can reach the wastewater treatment plants (WWTPs) through excretions released by the human body, in domestic sewage, and through irregularly disposition (BOTTONI et al., 2010). However, many treatments currently used in WWTPs are not effective for the complete removal of micropollutants, including PhACs, which is demonstrated by the presence of several pharmaceutical compounds in treated wastewater, surface water and even drinking water (DAUGHTON and TERNES, 1999; KAUSHIK and THOMAS, 2019; REIS et al., 2019). In addition to the launch of domestic sewage containing PhACs, there is also the release of effluents from industries, hospitals and clinics, and livestock activities, contributing to the presence of PhACs in aquatic environments (FOUREAUX et al., 2018). It shows the importance of advanced technologies for micropollutants removal in the WWTPs (FOUREAUX et al., 2018).

In this context, membrane bioreactors (MBR) have been applied for the wastewater treatment showing satisfactory results of PhACs removal (TIWARE et al., 2017). MBR integrate biological treatment with membrane separation processes for the treatment of water or wastewater (JUDD and JUDD, 2006) and can have different configurations to promote high removal of contaminants, such as aerobic or anaerobic biological treatment, separation processes by microfiltration, ultrafiltration, nanofiltration, membrane distillation, osmosis and can also include other configurations such as variation in sludge granulometry and integration with oxidative processes (RICCI et al., 2020; FARIA et al., 2020; LASTRE-ACOSTA et al., 2020; MONTEOLIVA-GARCÍA et al., 2020; ASIF et al., 2020b; YAO et al., 2020).

PhACs are generally found in the aquatic environment at concentration levels of ng L^{-1} to µg L^{-1}, however, studies show that some these compounds can influence the ecosystem even at low concentrations (CALISTO and ESTEVES, 2009). To assess the impacts caused by

micropollutants on the environment, the application of ecotoxicological tests is essential, since they can detect toxic effects on the ecosystem. These tests, in general, are laboratory analyses that use living organisms exposed for established periods of time, to quantify the toxic effect of a sample using different concentrations, or to assess whether a sample is toxic, at a specified concentration. Genotoxicity has also been increasingly used to assess the effects of micropollutants on the aquatic environment. These tests are performed directly on the organism's cells to assess DNA damage, in this way, it can identify sublethal effects not reported in other analyzes. Considering the variety of pharmaceuticals identified in the aquatic environment and the importance of these essays, ecotoxicological studies are still precarious for many PhACs (WANG et al., 2020; SWIACKA et al., 2019).

The values of pharmaceutical concentrations in the aquatic environment and the toxicity data related to them, for different organisms, are fundamental to measure the risks of these compounds. Environmental and human health risks are determined using risk quotients, which is possible to assess if a pollutant poses a danger to aquatic organisms or humans if it is ingested. Thus, the risk assessment of PhACs allows the identification of the most dangerous compounds, whose removal from the aquatic environment must be prioritized (GUO et al., 2016).

Thus, in this review, PhACs from different therapeutic classes were selected for the analysis of their concentrations in the aquatic environment in different locations around the world. The pharmaceuticals toxicity to several aquatic organisms was also reported in this review, as well as the genotoxicity. Scopus was selected as databases for searching literature and, to find the articles of interest, the keywords used were: pharmaceuticals in water or wastewater treatment plants, pharmaceuticals in drinking water, pharmaceuticals in surface water, aquatic ecotoxicology, pharmaceuticals ecotoxicity, and environmental risk assessment. From the 140 researched articles, PhACs of 9 therapeutic classes were selected for evaluation. Finally, using PhACs concentration and toxicity, human and environmental risk assessment was also carried out. It is essential to highlight that the toxicity data are scarce for many PhACs, and when available, they are dispersed in the literature. This review provides data consolidation and promotes identifying PhACs that require greater attention due to the risk offered to the environment and human health.

3.2 Occurrence of PhACs in aquatic environment

The occurrence of PhACs has been demonstrated in aquatic ecosystems worldwide. In addition to surface and groundwater, studies document such compounds also in raw and treated

wastewater and drinking water (MEZZELANI et al., 2018). The concentration of PhACs in the aquatic environment depends on pharmaceutical consumption patterns, level of socio-economic development, population lifestyle, climatic conditions and treatment technologies (SEGURA et al., 2015; AUS DER BEEK et al., 2016). Table S1 summarizes the occurrence of pharmaceuticals of different therapeutic classes in raw wastewater (RWW), treated wastewater (TWW), surface water (SW), and drinking water (DW), worldwide.

The therapeutic classes most detected in aquatic environments according to literature data are antibiotics, followed by anti-inflammatory and psychiatrics (Table S1). Carbamazepine, ibuprofen, diclofenac, sulfamethoxazole and trimethoprim, respectively, were the most reported PhACs. In contrast, fexofenadine, loratadine, fluoxetine and fenofibrate were less detected among the evaluated pharmaceuticals. Antibiotics and anti-inflammatories are of concern due to the high and growing consumption in the world (HUNGIN and KEAN, 2001; VAN BOECKEL et al., 2014; BUSFIELD, 2015; CRYER et al., 2016; PHOON et al., 2020). Studies have already confirmed the relationship between the consumption rate and the presence of some PhACs in the environment (CAMACHO-MUÑOZ et al. 2014; NANNOU et al. 2020). These compounds are detected in treated wastewater and even drinking water in various locations around the world, indicating that they are not completely removed in the various technologies for the water and wastewater treatment. Furthermore, there is a concern about traces of antibiotics in the environment even at low concentrations since these compounds have the potential to increase resistance among natural populations of bacteria, which can have negative impacts on public health (PHOON et al., 2020; KAIRIGO et al., 2020).

The increasing use of psychiatrics also has been contributed to a greater presence of these compounds in the environment (ABRAHAM, 2010). Carbamazepine is one of the most studied pharmaceuticals for being very persistent, which can be observed in studies that show the low removal of this PhAC in the wastewater treatments, mainly in conventional treatment systems, such as activated sludge (PETROVIC et al., 2006; HUERTA-FONTELA et al., 2010; OOSTERHUIS et al., 2013; WU et al., 2015; YANG et al., 2017; RIVERA-JAIMES et al., 2018; KUMAR et al., 2019).

Seasonal occurrence of PhACs in the aquatic environment indicating that in some cases their concentrations vary about the periods of the year, due to consumption patterns, dilution effect and water temperature (CAO et al., 2020). Papageorgiou et al. (2016) observed that in raw wastewater analgesic and anti-inflammatories presented higher concentrations in summer and

autumn, while the antibiotics were higher in winter, and lipid regulators, psychiatric, antihistamines, and beta-blockers do not have any significant seasonal variation in their concentration levels. Moreno-González et al. (2014) also observed a higher concentration of anti-inflammatories in water bodies in the autumn period, however, antibiotics were higher in the spring. Evidence shows that higher concentrations of PhACs in surface water can occur in colder seasons, due to the higher consumption of some pharmaceuticals and lower removals in treatment plants in these periods of the year (YU et al., 2013; KIBUYE et al., 2019; KIBUYE et al., 2020). In contrast, dilution factors due to the increased rainfall in the winter period might lead to low concentrations of the pharmaceuticals in determined regions (PAPAGEORGIOU et al. 2016). This indicates that the influence of seasonality on the concentration of PhACs depends on several factors and variables, which cannot yet be fully defined.

Temperature is an important parameter that influences the compounds biodegradation and sorption processes, therefore, it can also influence the concentration of PhACs in the environment. The sorption of some compounds may increase at lower temperatures, while biodegradation decreases (LACEY et al., 2012). This can influence both WWTPs and natural processes that occur in surface water. In addition to these factors, from the literature data, it was evident that there is a considerable variation in the PhACs concentrations according to the aquatic matrix and therapeutic class. Thus, a more detailed analysis was made for these cases.

3.2.1 PhAC's concentration by aquatic matrix and therapeutic class

PhACs concentrations were analyzed for each aquatic matrix in different locations around the world (Table S1). According to the database, drinking water has the lowest concentration of PhACs, with an average of 10 ng L^{-1} followed by surface water with an average equal to 1544 ng L^{-1}. Raw wastewater has the highest concentration with an average equal to 56970 ng L^{-1} and finally, treated wastewater has an average of 3271 ng L^{-1} (Figure 10).

The lower concentration of PhACs in drinking water is justified, since in addition to the dilution and the natural removal processes that occur in water bodies, there is still removal in water treatment plants. However, even low concentrations of pharmaceuticals compounds in drinking water can be dangerous when daily and long-term ingestion of these micropollutants occurs (WEE et al., 2020). The highest concentrations of PhACs reported in drinking water were 6323 ng L^{-1} for prednisone, 2620 ng L^{-1} for betamethasone and 561 ng L^{-1} for ketoprofen, which shows low removal efficiencies at water treatment plants in Brazil (REIS et al., 2019).

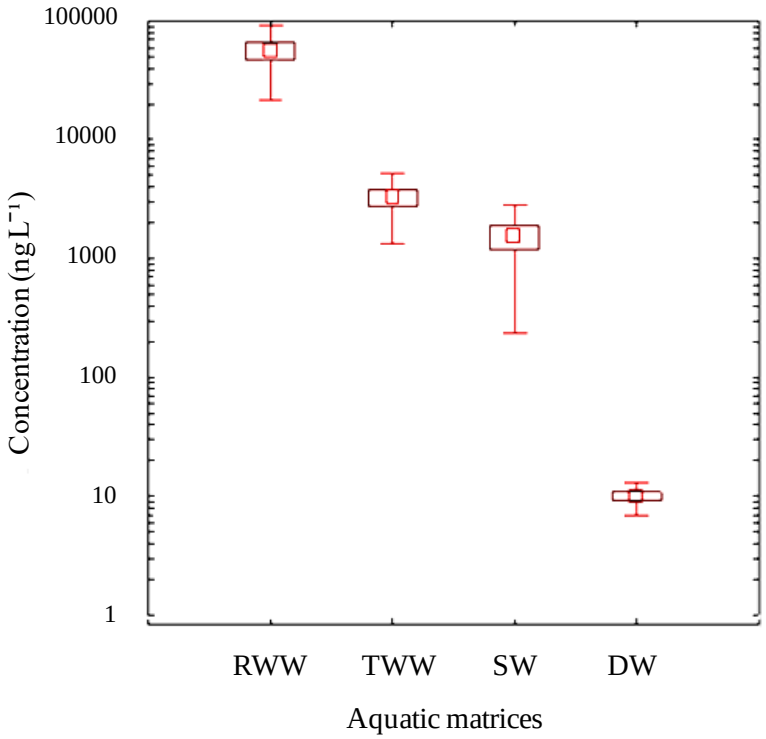

Figure 10 – Concentrations of PhACs by raw wastewater (RWW), treated wastewater (TWW), surface water (SW) and drinking water (DW).

Although the treated wastewater has lower average concentrations than the raw wastewater according to the studies evaluated (Figure 10), it is already known that most of the PhACs are not completely removed after treatments. This is even more evident when the analysis by therapeutic class is performed (Figure 11). Antibiotics, beta-blockers, hormones and psychiatric drugs concentrations in treated wastewater are very close to or even higher than in raw wastewater, indicating low or negative removals. Negative values of removal efficiencies are observed in several studies (GUERRA et al., 2014; KOSMA et al., 2014; SUBEDI and KANNAN, 2015; WU et al., 2015; PAPAGEORGIOU et al., 2016; WANG et al., 2018), where the concentrations or mass loads are higher in the WWTP effluent than in the influent, showing that the treatment of wastewater can increase the availability of PhACs in the environment. This can occur due to measurement uncertainties, interference from sample collection, pharmaceutical compounds released from the adsorbed phase, release of endogenous compounds during cell lysis, or the formation of metabolites during treatment (JOSS et al., 2005; GÖBEL et al., 2005; KOSMA et al., 2014; EVGENIDOU et al., 2015; WANG et al., 2018).

It is important to note that the evaluation of PhACs in aquatic ecosystems must consider not only parent drugs, but also their metabolites and the transformation by-products that can be generated during wastewater treatment (GARCÍA-GALÁN et al., 2016). Some treatments by advanced oxidation processes (AOPs), for example, can degrade pharmaceuticals compounds but generate even more toxic by-products, as reported in several studies (GARCÍA-GALÁN et al., 2016; BERETSOU et al., 2020; PRETALI et al., 2020).

Also, in other cases, some pharmaceutical compounds are detected in effluents, but not in influents, which may be due to the complex matrices analyzed, which make it impossible or cause interference in the detection method of PhACs or the time difference between the collection of the influent and effluent samples (KOSMA et al., 2014). In addition to negative removals, low PhACs removal occurs as a result of WWTP's inefficiency. Conventional treatment processes, such as UASB reactors, activated sludge, biological filters, or ponds are intended to treat biodegradable organic compounds and can reduce nutrients and pathogenic organisms and, eventually, remove some PhACs by biodegradation or adsorption of these micropollutants in the sludge (CASTIGLIONI et al., 2005; JELIC et al., 2011; TIWARE et al., 2017; COUTO, et al., 2019).

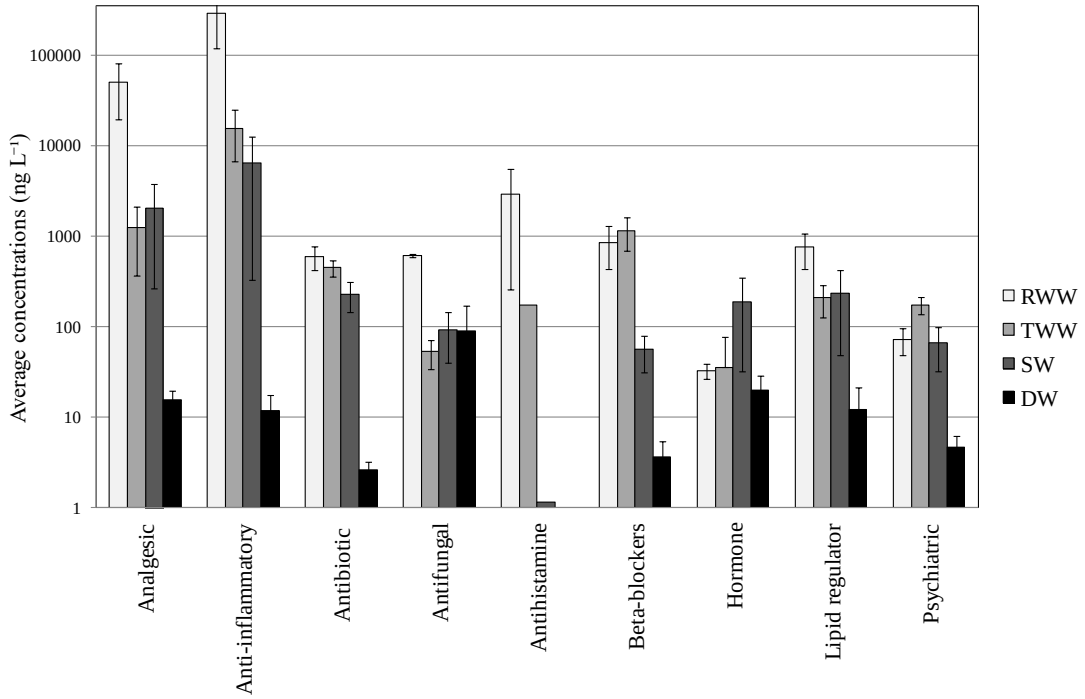

Figure 11 – Average concentration and standard error of PhACs in different aquatic matrix by therapeutic class.

Reduction of PhACs concentration in wastewater treatment plants is a measure of environmental protection and human health, since a barrier is created so that these micropollutants do not reach watercourses and drinking water. However, even tertiary treatment can have low removal of some pharmaceuticals. Rivera-Jaimes et al. (2018) evaluated the removal of PhACs in a full-scale WWTP, with conventional activated sludge treatment after aerobic and anaerobic digestion and a tertiary treatment based on UV oxidation. According to this study, the treatment did not remove PhACs such as gemfibrozil and carbamazepine and obtained low removals for others, such as trimethoprim (<4%), indomethacin (<19%) and atenolol (<44%).

3.3 Membrane bioreactors to PhAC's removal

Membrane bioreactors (MBR) have shown promise in removing PhACs. This technology integrate biological treatment with membrane separation processes for treating water or wastewater (JUDD and JUDD, 2006). Commonly applied processes use microfiltration (MF) or ultrafiltration (UF) membranes to retain the biomass, resulting in a clarified and purified product. The MBRs using UF/MF allows independence between the hydraulic retention time and the solid retention time, which promotes operations with longer solid retention times, and consequently, a greater adaptation of the microorganisms to the substrates and greater removal of recalcitrant compounds (PRASERTKULSAK et al., 2016). Membrane's fouling in these systems can be a limiting factor, however, studies have been to substantial progress in understanding the fouling mechanism for reducing its effects (JIANG, et al., 2017; BAGHERI and MIRBAGUERI, 2018; BAGHERI et al., 2019).

Regarding PhACs removal, MBR systems have high removal efficiencies for most of these micropollutants when compared to conventional treatments (TIWARE et al., 2016). However, some PhACs are still resistant to membrane bioreactors treatment processes, especially those that have highly hydrophilic characteristics, which limits their adsorption to sludge (LASTRE-ACOSTA et al., 2020). This limitation has been overcome by the development of other MBR configurations and schemes. Table 10 summarizes the removal of PhACs in some recently studied membrane bioreactor configurations.

Ricci et al. (2021), evaluated an anaerobic bioreactor combined with a hybrid module of forward osmosis (FO) and membrane distillation (MD) for the treatment of municipal wastewater fortified with betamethasone, ketoprofen, ethinylestradiol, fenofibrate, fluconazole, loratadine and prednisone, in the concentration of 2 $\mu g\ L^{-1}$ each. The overall removal efficiency

values were between 96.4% and 99.98% at the end of the monitoring. In this study, the removal for each PhAC varied due, mainly, to its characteristics, such as biodegradability, molecular weight, hydrophobicity, volatility and charge (RICCI et al., 2021). Faria et al. (2020) evaluated the removal of the same PhACs with an expanded granular sludge bed reactor with UF membrane and also verified the influence of the factors cited by Ricci et al. (2021) on the PhACs removal. In this study, prednisone, loratadine and fenofibrate were removed mainly by abiotic factors, while ethinylestradiol and betamethasone by biotic factors.

Table 10 – Removal of PhACs by different MBR configurations.

MBR scheme	Membane	Feed	PhACs removal (%)	Reference
Osmotic membrane bioreactor integrated with membrane distillation	FO membrane: flat-sheet composed of cellulose triacetate with an embedded polyester screen support and 157 cm² of surface areaMD membrane: flat-sheet composed of polytetrafluoroethylene in a non-woven polypropylene with an average pore size of 0.2 µm and 157 cm² of surface area	Municipal wastewater fortified with pharmaceuticals	96.4 - 99.98	Ricci et al., 2021
Expanded granular sludge bed reactor with ultrafiltration membrane	UF membrane: hollow-fiber composed of polyvinylidene fluoride, with a nominal pore size of 0.04 µm, surface with nonionic and hydrophilic properties and 45 cm² of filtration area	Synthetic sewage fortified with pharmaceuticals	84 - 98	Faria et al., 2020
Moving bed biofilm reactor with membrane bioreactor	UF membrane: hollow-fiber with a nominal pore size of 0.04 µm and 9700 cm² of surface area	Municipal wastewater fortified with pharmaceuticals	81.36 - 100	Monteoliva-García et al., 2020
Enzymatic membrane bioreactor with nanofiltration	NF membrane: flat-sheet with a polyamide based active layerwith and a surface area of 40 cm²	Synthetic wastewater fortified with pharmaceuticals	90 - 99	Asif et al., 2020a
Submerged forward osmotic membrane bioreactor	FO membrane: flat-sheet composed of cellulose triacetate with embedded polyester screen support and 50 cm²	Synthetic wastewater fortified with pharmaceuticals	88.20 - 94.45	Yao et al., 2020
Powdered activated carbon - Membrane bioreactor	Ceramic membrane: average pore size of 0.1 µm and an effective surface area of 425 cm²	Synthetic wastewater fortified with pharmaceuticals	86 - 99.9	Asif et al., 2020b
Pre-denitrification membrane bioreactor	UF membrane: flat-sheet composed of polyvinylidene fluoride with a average pore size of 0.1 µm	Synthetic wastewater fortified with pharmaceuticals	80	Matsubara et al., 2020

Another MBR scheme was evaluated by Monteoliva-García et al. (2020) who tested a moving bed biofilm reactor-membrane bioreactor (MBBR-MBR) for removal of carbamazepine,

ciprofloxacin and ibuprofen in the concentrations of 100, 10 and 100 μg L^{-1}, respectively, added to the municipal wastewater. The MBBR-MBR system promoted removals of 81.36 for carbamazepine, 99.20 for ciprofloxacin and 100% for ibuprofen, while the isolated MBR process had removals of 72.34, 93.90 and 100% for the same PhACs. According to Monteoliva-García et al. (2020) the main factor in the removal of PhACs was biodegradability, since in this system the contact area between microorganisms and the effluent increases. It shows that the moving bed biofilm is a configuration option that increases the efficiency of the MBR and can be used for the removal of biodegradable pharmaceuticals.

Besides Monteoliva-García et al. (2020), the removal of carbamazepine was also evaluated by Yao et al., (2020). In this study, a submerged forward osmotic membrane bioreactor (FOMBR) was used, in which the removals varied between 88.20-94.45% and were attributed to membrane rejection and biodegradation. The high removal of carbamazepine in MBR systems shows the efficiency and importance of applying these technologies, since this PhAC is very persistent and has low removal in conventional treatment systems and may not be removed even with tertiary treatments (OOSTERHUIS et al., 2013; WU et al., 2015; RIVERA-JAIMES et al., 2018; PETROVIC et al., 2006; YANG et al., 2017; HUERTA-FONTELA et al., 2010; KUMAR et al., 2019).

Asif et al. (2020b) also showed an increase in the efficiency of MBR when combined with other technologies, using an anoxic-aerobic ceramic MBR with powdered activated carbon (PAC) system to remove micropollutants, including PhACs. The addition of PAC increased the removal efficiency for all micropollutants, which ranged between 86 and 99.9%, while the MBR alone removed between 60 and 99%. Matsubara et al. (2020) also used anoxic-aerobic condition combined with the separation process by ultrafiltration. The study showed an 80% removal of amoxylin, for a hydraulic retention time of 40 h.

In addition, an important factor in an MBR is the efficiency of membrane rejection, which can occur through the mechanisms of size exclusion, charge repulsion and adsorption (SIMON et al., 2013). Asif et al. (2020a) evaluated the removal of 29 trace organic contaminants (TrOC), including several PhACs, using an enzymatic membrane bioreactors (EMBR) with nanofiltration (NF). The study showed that TrOC removal in the enzymatic bioreactor ranged between 10-99%, while in the NF-EMBR system it was 90-99%, demonstrating the significant contribution of the NF membrane to the overall removal.

3.4 PhAC's toxicity to aquatic organisms

The toxicity of PhACs to aquatic organisms is increasingly addressed in the literature, since ecotoxicological tests have the potential to evaluate the effect of pollutants at different trophic levels, at determined concentrations. Table 11 shows several acute and chronic ecotoxicological data for the PhACs selected in this review, for different aquatic organisms, exposure times, and evaluation criteria.

Ecotoxicological tests can be categorized into two types: acute toxicity and chronic toxicity. Acute toxicity tests are short-term assays that provide quicker responses to the effects of a sample on aquatic organisms exposed to generally lethal concentrations. On the other hand, chronic toxicity tests correspond to assessments of effects for longer periods and can include the entire life cycle of an organism exposed to sub-lethal concentrations. Some substances do not cause acute effects for certain organisms, but in longer exposure times, chronic effects can be detected. So acute and chronic tests must be carried out jointly and complementarily. (CONNON et al., 2012).

In addition, there are the avoidance tests, which have been increasingly used in ecotoxicological studies. These tests consider that the effects of contaminants on organisms can be spatially avoided since many organisms have the ability to escape when detecting changes in the environment. Thus, the effects of contaminants may not affect the organisms, however, their migration may promote the extinction of species, causing an imbalance in the ecosystem (MOREIRA-SANTOS et al., 2019). Avoidance tests are generally performed with fish, which can move freely in compartments, with different concentrations of contaminants, choosing the most favorable environment, which allows measuring the spatial avoidance of organisms (ARAUJO et al., 2016; JACOB et al., 2021).

According to Connon et al. (2012), the effects observed in aquatic organisms in ecotoxicological tests can be mortality or immobility, avoidance, changes in biological functions, such as reproduction, egg development, growth, and maturation. The results of these tests are usually expressed in average effective concentration (EC_{50}): sample concentration that causes an acute effect on 50% of the organisms; average lethal concentration (LC_{50}): sample concentration that causes mortality of 50% of the organisms; no observed effect concentration (NOEC): higher concentration of sample that does not cause a statistically significant deleterious effect on organisms; and observed effect concentration (OEC): lower concentration of sample that causes a statistically significant deleterious effect on organisms (Connon et al., 2012). Effects can be classified as low concern (>100 mg L^{-1}), moderate concern (1-100 mg

L^{-1}) and high concern (<1 mg L^{-1}) for acute aquatic toxicity, and low concern (>10 mg L^{-1}), moderate concern (0.1 -10 mg L^{-1}) and high concern (<0.1 mg L^{-1}) for chronic toxicity (EUROPEAN COMMISSION, 1996).

Several species of aquatic organisms have been used for ecotoxicological assays and the main groups used are microalgae, microcrustaceans, bacteria, and fish. The choice of the organism should be based mainly on its representativeness, availability, sensitivity, easiness in the standardization of the tests, and easiness in the cultivation (Connon et al., 2012). It is known that the presence of recalcitrant compounds in water bodies, such as pharmaceuticals, can promote toxicity to several aquatic species, causing changes in the biological structure and even the death of these organisms. In this sense, studies have been developed to assess the toxicity of PhACs in the aquatic environment and the impacts of these micropollutants on the ecosystem.

Wang et al. (2020) assessed the toxicity of three anti-inflammatory drugs for the green algae species *Scenedesmus obliquus* and showed that ketoprofen was the most toxic among them, with EC_{50} (Growth inhibition) value of 0.4 mg L^{-1} in an exposure time of 48 hours. Diclofenac, also in the anti-inflammatory group, had an EC_{50} (Immobility) for *Daphnia magna* of 0.22 mg L^{-1} (FERRARI et al., 2003). Several antibiotics are also reported as toxic, for different aquatic organisms, with $E(L)C_{50}$ values less than 1 mg L^{-1} or NOECs below 0.1 mg L^{-1} (EGUCHI et al., 2004; ROBINSON et al. 2005; ISIDORI et al. 2005; ANDO et al., 2007; YANG et al., 2008; BIAŁK-BIELIŃSKA et al., 2011; CARBAJO et al., 2015).

Despite the evidence of anti-inflammatories and antibiotics in the literature due to their higher occurrences in environment, other classes of PhACs such as hormones, antihistamines and psychiatrics should also be highlighted, due to their toxic potential. Loratadine had EC_{50} (Immobility) and NOEC (Growth inhibition) of 0.83 mg L^{-1} and 0.053 mg L^{-1}, for *D. magna* and *Pseudokirchneriella subcapitata*, respectively (FASS.SE, 2020). Fluoxetine was also considered toxic for *D. magna*, with EC_{50} (Immobility) of 6.4 mg L^{-1} and for *Oryzias latipes* with NOEC (Locomotion) of 0.01 mg L^{-1} (CHRISTENSEN et al., 2007; CHIFFRE et al., 2016). Likewise, 17-β estradiol, from the group of hormones, showed NOEC of 0.286 μg L^{-1} for fish *O. latipes* (SEKI et al., 2004). In the case of hormones, toxicity values are generally high for organisms that have an endocrine system when endocrine disruption is the evaluation criterion. These natural or synthetic hormones excreted by the body and found in surface water can induce, for example, the increase in levels of vitellogenin in male fish. In this

way, the vitellogenins concentration can also be used as a biomarker for chronic toxicity tests (ROSE et al., 2002).

In contrast, some pharmaceuticals may not promote acute effects, but have chronic effects for determined organisms. This is the case of fluconazole, from the anti-fungal group, which have an low acute toxic effect for the crustacean *Thamnocephalus platyurus* with EC_{50} (Immobility) of 100 mg L^{-1} in 24 h of exposure (KIM et al., 2009), but obtained a NOEC (Growth inhibition) of 3.06 mg L^{-1} for the algae *P. subcapitata* with 72 h of exposure. This shows that chronic toxicity tests are of fundamental importance to detect possible toxicities not found in shorter exposure times and that different organisms may have different sensitivities when exposed to the same contaminant.

The difference in sensitivity between organisms tested with the same PhAC can also be seen in other studies. Cleuvers (2003) evaluated ibuprofen toxicity and found an EC_{50} of 315 mg L^{-1}, 22 mg L^{-1}, and 108 mg L^{-1}, for *Desmodesmus subspicatus*, *Lemna minor*, and *D. magna*, respectively, showing that *L. minor* was more sensitive to this pharmaceuticals, compared to other organisms. Brun et al. (2006) and Cleuvers (2004) used naproxen and found EC_{50} (Luminescence inhibition) equal to 0.451 mg L^{-1} for *Aliivibrio fischeri*, and EC_{50} (Immobility) of 166.3 mg L^{-1} for *D. m*agna. Thus, the ecotoxicological tests should be performed with more than one trophic level, for assessing the real impacts on the aquatic ecosystem.

In this sense, the pharmaceuticals can have different toxic effects for the same organism, depending on the formulation used in the toxicity tests (generic, similar, and reference). This is due to the excipients present in each formulation. Excipients are used to provide to the drugs the rate of release and absorption, stability, volume, texture, and color (WASAN, 2001). Jacob et al., (2016) studied the toxicity of 10 PhACs in the three formulations for *A. fischeri* and observed that the toxicity was related to the excipients and not necessarily to the active ingredients.

Another important factor when assessing the toxicity of PhACs is the interaction between them in the aquatic environment. PhACs interation can cause synergistic and antagonistic effects, causing an increase or reduction in toxicity. There are mathematical models that simulate the effects of mixing between PhACs, such as concentration addition (CA) and independent action (IA). These models are important tools, since it is not possible to test the effects for all possible mixture combinations of PhACs, due to a large number of them in the environment. However, they cannot predict all the phenomena of the interaction between the compounds. Thus, the

ecotoxicological tests of the mixtures and not only of individual contaminants more accurately represents what occurs in natural ecosystem (JACOB et al., 2020). Therefore, several studies show that the mixture of PhACs, and also other compounds, can be more or less toxic than the single-pharmaceuticals (DI NICA et al., 2017; DI POI et al., 2018; WIECZERZAK et al., 2018; BAEK et al., 2019).

Table 11 – Toxicity of PhACs to aquatic organisms

Compound	Exposure time	Species	Organism	Toxicity assessment criteria	Value (mg L^{-1})	Reference
Paracetamol	-	*Daphnia magna*	Crustacean	EC50	50	Henschel et al. 1997
	30 min	*Aliivibrio fischeri*	Bacteria	EC50 (Luminescence inhibition)	650	Henschel et al. 1997
	-	*Brachydanio rerio*	Fish	EC50 (Mortality)	378	Henschel et al. 1997
	21 d	*Daphnia magna*	Crustacean	NOEC (Reproduction)	1	Fass.se 2020
	-	*Pimephales promelas*	Fish	NOEC (Survival)	0.46	Fass.se 2020
Codeine	-	-	Algae	EC50 (ECOSAR)	23	Sanderson et al., 2004
	-	-	Crustacean	EC50 (ECOSAR)	16	Sanderson et al., 2004
	-	-	Fish	EC50 (ECOSAR)	238	Sanderson et al., 2004
Morphine	-	-	Algae	EC50 (ECOSAR)	39	Sanderson et al., 2004
	-	-	Crustacean	EC50 (ECOSAR)	32	Sanderson et al., 2004
	-	-	Fish	EC50 (ECOSAR)	257	Sanderson et al., 2004
Acetaminophen	48 h	*Daphnia magna*	Crustacean	LC50	20.1	Han et al., 2010
		-	Crustacean	EC50 (ECOSAR)	41	Sanderson et al., 2004
		-	Fish	EC50 (ECOSAR)	258	Sanderson et al., 2004
	10 d	*Mytilus galloprovincialis*	Mussel	NOEC (Feeding rate)	0.403	Solé et al., 2010
	72 h	*Selenastrum capricornutum*	Algae	NOEC (Algal cells survival)	0.032	Brun et al., 2006
	7 d	*Ceriodaphnia dubia*	Crustacean	NOEC (Offspring survival)	0.032	Brun et al., 2006
Propyphenazone	-	-	Algae	EC50 (ECOSAR)	1	Sanderson et al., 2004
	-	-	Crustacean	EC50 (ECOSAR)	3.5	Sanderson et al., 2004
	-	-	Fish	EC50 (ECOSAR)	0.8	Sanderson et al., 2004
Betamethasone	-	-	Algae	EC50 (ECOSAR)	41	Sanderson et al., 2004
	-	-	Crustacean	EC50 (ECOSAR)	32	Sanderson et al., 2004
	-	-	Fish	EC50 (ECOSAR)	37	Sanderson et al., 2004
	72 h	*Selenastrum capricornutum*	Algae	NOEC (Growth rate and yield)	34	Fass.se, 2020
	21 d	*Daphnia magna*	Crustacean	NOEC (Parental survival)	17	Fass.se, 2020
	32 d	*Pimephales promelas*	Fish	NOEC (Mean dry weight)	0.052	Fass.se, 2020
Ketoprofen	48 h	*Scenedesmus obliquus*	Alga	EC50 (Growth inhibition)	0.4	Wang et al. (2020)

Continuation

Compound	Exposure time	Species	Organism	Toxicity assessment criteria	Value (mg L^{-1})	Reference
	96 h	*Pseudokirchneriella subcapitata*	Algae	EC50 (Mortality)	0.24	Mennillo et al., 2018
	72 h	*Pseudokirchneriella subcapitata*	Algae	EC50 (Growth inhibition)	0.03	Fass.se, 2020
	96 h	*Danio rerio*	Fish	LC50 (Mortality)	632	Prášková et al., 2011
	72 h	*Pseudokirchneriella subcapitata*	Algae	NOEC (Growth inhibition)	9.94	Watanabe et al., 2016
	6-8 d	*Ceriodaphnia dubia*	Crustacean	NOEC (Reproduction)	22.5	Watanabe et al., 2016
	9 d	*Danio rerio*	Fish	NOEC (Hatch, mortality, growth)	6.25	Watanabe et al., 2016
	21 d	*Daphnia magna*	Crustacean	NOEC (Reproduction)	9.15	Fass.se, 2020
	28 d	*Danio Rerio*	Fish	NOEC (Mortality)	0.093	Fass.se, 2020
Ibuprofen	3 d	*Desmodesmus subspicatus*	Algae	EC50	315	Cleuvers, 2003
	3 d	*Desmodesmus subspicatus*	Algae	EC50	342.2	Cleuvers, 2004
	7 d	*Lemna minor*	Lemnoideae	EC50	22	Cleuvers, 2003
	48 h	*Daphnia magna*	Crustacean	EC50	31	Fass.se, 2020
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobility)	108	Cleuvers, 2003
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobility)	101.2	Cleuvers, 2004
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobility)	51.4	Han et al., 2010
	48 h	*Moina macrocopa*	Crustacean	EC50 (Immobility)	72.6	Han et al., 2010
	14 d	*Daphnia magna*	Crustacean	EC50 (Reproduction)	13.4	Heckmann et al., 2007
	96 h	*Oryzias latipes*	Fish	LC50	89	Fass.se, 2020
	48 h	*Daphnia magna*	Crustacean	LC50	132.6	Han et al., 2010
	24 h	*Thamnocephalus platyurus*	Crustacean	LC50 (Immobility)	19.59	Kim et al., 2009
	14 d	*Daphnia magna*	Crustacean	NOEC (Survival)	20	Heckmann et al., 2007
	21 d	*Daphnia magna*	Crustacean	NOEC (Reproduction)	20	Han et al., 2010
	3 d	*Desmodesmus subspicatus*	Algae	NOEC	30	Fass.se, 2020
	7-8 d	*Moina macrocopa*	Crustacean	NOEC (Reproduction)	25	Han et al., 2010
	21 d	*Daphnia magna*	Crustacean	NOEC (Survival)	33.3	Han et al., 2010

Compound	Exposure time	Species	Organism	Toxicity assessment criteria	Value (mg L^{-1})	Reference
Diclofenac	21 d	*Danio rerio*	Fish	NOEC (Growth)	0.2659	Constantine et al., 2020
	48 h	*Daphnia magna*	Crustacean	LC50 (Mortality)	80.1	Han et al., 2010
	96 h	*Danio rerio*	Fish	LC50 (Mortality)	0.082	Fass.se, 2020
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobility)	22.43	Ferrari et al., 2003
	48 h	*Ceriodaphnia dubia*	Crustacean	EC50 (Immobility)	0.0227	Ferrari et al., 2003
	3 d	*Desmodesmus subspicatus*	Algae	EC50	72	Cleuvers, 2003
	7 d	*Lemna minor*	Lemnoideae	EC50	7.5	Cleuvers, 2003
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobility)	68	Cleuvers, 2003
	96 h	*Pseudokirchneriella subcapitata*	Algae	NOEC (Growth rate)	10	Ferrari et al., 2003
	7 d	*Ceriodaphnia dubia*	Crustacean	NOEC (Reproduction)	1	Ferrari et al., 2003
	95 d	*Oncorhynchus mykiss*	Fish	NOEC (Histopathological alterations in gills)	0.369	Fass.se, 2020
	10 d	*Danio rerio*	Fish	NOEC (Development)	4	Ferrari et al., 2003
	34 d	*Danio rerio*	Fish	NOEC (Survival)	0.32	Fass.se, 2020
	21 d	*Daphnia magna*	Crustacean	NOEC (Reproduction)	10	Han et al., 2010
Naproxen	7 d	*Lemna minor*	Lemnoideae	EC50	24.2	Cleuvers, 2003
	48 h	*Daphnia magna*	Crustacean	EC50	174	Cleuvers, 2003
	3 d	*Desmodesmus subspicatus*	Algae	EC50 (Growth inhibition)	625.5	Cleuvers, 2004
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobility)	166.3	Cleuvers, 2004
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobility)	59.44	DellaGreca et al., 2003
	48 h	*Ceriodaphnia dubia*	Crustacean	EC50 (Mortality)	66.37	Isidori et al., 2005
	15 min	*Aliivibrio fischeri*	Bacteria	EC50 (Luminescence inhibition)	0.451	Brun et al., 2006
	24 h	*Brachionus calyciflorus*	Rotifers	LC50 (Mortality)	62.48	Isidori et al., 2005
	24 h	*Thamnocephalus platyurus*	Crustacean	LC50 (Mortality)	84.09	Isidori et al., 2005
	21 d	*Daphnia magna*	Crustacean	NOEC (Survival, reprodution, growth)	0.15	Fass.se, 2020
	7 d	*Ceriodaphnia dubia*	Crustacean	NOEC (Living offspring)	0.032	Brun et al., 2006
	32 d	*Pimephales promelas*	Fish	NOEC (Hatch, survival, growth)	1	Fass.se, 2020

Compound	Exposure time	Species	Organism	Toxicity assessment criteria	Value (mg L^{-1})	Reference
		Pseudokirchneriella subcapitata	Algae	NOEC (Average growth rate)	6.2	Fass.se, 2020
Prednisone	72h	-	Alga	EC50	31	Cayman Chemical Company, 2020
	24 h	*Brachionus calyciflorus*	Crustacean	LC50 (Mortality)	54.6	Dellagreca et al., 2002
	-	-	Crustacean	NOEC (ECOSAR)	2.48	Gouveia et al., 2019
Indomethacin	-	-	Algae	EC50 (ECOSAR)	18	Sanderson et al., 2004
	-	-	Crustacean	EC50 (ECOSAR)	26	Sanderson et al., 2004
	-	-	Fish	EC50 (ECOSAR)	3.9	Sanderson et al., 2004
	24 h	*Thamnocephalus platyurus*	Crustacean	LC50 (Immobility)	16.14	Kim et al., 2009
	24 h	*Oryzias latipes*	Fish	LC50	81.92	Kim et al., 2009
	48 h	*Daphnia magna*	Crustacean	EC50 (Mortality and behavior)	22.38	Gheorghe et al., 2016
	15 min	*Aliivibrio fischeri*	Bacteria	EC50 (Luminescence inhibition)	7.94	Gheorghe et al., 2016
	48 h	*Daphnia magna*	Crustacean	NOEC	0.43	Gheorghe et al., 2016
	96 h	*Cyprinus carpio*	Fish	NOEC (Mortality and behavior)	0.85	Gheorghe et al., 2016
Amoxicillin	5 m	*Aliivibrio fischeri*	Bacteria	EC50 (Luminescence inhibition)	1320	Park e Choi, 2008
	48 h	*Danio rerio*	Fish	EC50 (Mortality)	132.4	Oliveira et al., 2013
	-	*Selenastrum capricornutum*	Algae	NOEC (Growth inhibition)	250	Lützhøft et al., 1999
	96 h	*Isochrysis galbana*	Algae	NOEC (Growth inhibition)	250	De Orte et al., 2013
Ciprofloxacin	24 h	*Microcystis aeruginosa*	Cyanobacteria	EC50	0.017	Robinson et al. 2005
	-	*Selenastrum capricornutum*	Algae	EC50	2.97	Halling-Sørensen, 2000
	28 d	*Daphnia magna*	Crustacean	EC50 (Reprodution)	14.4	Zaleska-Radziwill et al., 2011
	7 d	*Lemna minor*	Lemnoideae	EC50 (Growth inhibition)	3.75	Martins et al., 2012
	30 min	*Aliivibrio fischeri*	Bacteria	EC50 (Luminescence inhibition)	11.5	Martins et al., 2012
	96 h	*Pseudokirchneriella subcapitata*	Algae	EC50 (Growth inhibition)	4.83	Martins et al., 2012
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobility)	65.3	Martins et al., 2012
	96 h	*Pseudokirchneriella subcapitata*	Algae	NOEC (Growth inhibition)	1.09	Martins et al., 2012

Compound	Exposure time	Species	Organism	Toxicity assessment criteria	Value (mg L^{-1})	Reference
	28 d	*Daphnia magna*	Crustacean	NOEC (Reprodution)	0.156	Zaleska-Radziwill, et al., 2011
	28 d	*Danio rerio*	Fish	NOEC (Juvenile growth)	0.78	Zaleska-Radziwill, et al., 2011
	28 d	*Lebistes reticulatus*	Fish	NOEC (Juvenile growth)	0.78	Zaleska-Radziwill, et al., 2011
Trimethoprim	48 h	*Daphnia magna*	Crustacean	EC50	92	Park e Choi, 2008
	48 h	*Daphnia magna*	Crustacean	EC50	123	Halling-Sørensen, 2000
	-	*Selenastrum capricornutum*	Algae	EC50	110	Halling-Sørensen, 2000
	-	*Microcystis aeruginosa*	Cyanobacteria	EC50	112	Välitalo et al., 2017
	-	*Pseudokirchneriella subcapitata*	Algae	EC50	84	Välitalo et al., 2017
	-	*Pseudokirchneriella subcapitata*	Algae	EC50 (Growth inhibition)	80.3	Eguchi et al., 2004
	-	*Pseudokirchneriella subcapitata*	Algae	NOEC (Growth inhibition)	25.5	Eguchi et al., 2004
	72 h	*Danio rerio*	Fish	NOEC	100	Halling-Sørensen, 2000
	6 d	*Synechococcus leopoliensis*	Cyanobacteria	NOEC (Growth rate)	13	Ando et al., 2007
	7 d	*Lemna minor*	Lemnoideae	NOEC (Growth inhibition)	6.25	De Liguoro et al., 2012
Erythromycin	-	*Pseudokirchneriella subcapitata*	Algae	EC50 (Growth inhibition)	0.0366	Eguchi et al., 2004
	72 h	*Pseudokirchneriella subcapitata*	Algae	EC50 (Population growth rate)	0.35	González-Pleiter et al., 2013
	72 h	*Anabaena sp.*	Cyanobacteria	EC50 (Population growth rate)	0.022	González-Pleiter et al., 2013
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobility)	22.45	Isidori et al., 2005
	24 h	*Thamnocephalus platyurus*	Crustacean	LC50 (Immobility)	100	Kim et al., 2009
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobility)	207.83	Ji et al., 2012
	7 d	*Moina macrocopa*	Crustacean	NOEC (Mortality)	50	Ji et al., 2012
	-	*Pseudokirchneriella subcapitata*	Microalga	NOEC (Growth inhibition)	0.0103	Eguchi et al., 2004
	6 d	*Synechococcus leopoliensis*	Cyanobacteria	NOEC (Growth rate)	0.002	Ando et al., 2007

Continuation

Compound	Exposure time	Species	Organism	Toxicity assessment criteria	Value (mg L^{-1})	Reference
Roxithromycin	72 h	*Anabaena flos-aquae*	Algae	EC50 (Growth rate)	0.211	Fass.se, 2020
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobility)	100	Fass.se, 2020
	96 h	*Danio rerio*	Fish	LC50 (Lethality)	100	Fass.se, 2020
	72 h	*Anabaena flos-aquae*	Algae	NOEC (Growth rate)	0.0646	Fass.se, 2020
	72 h	*Pseudokirchneriella subcapitata*	Algae	NOEC (Growth inhibition)	0.01	Yang et al., 2008
Sulfamethoxazale	-	*Lemna minor*	Lemnoideae	EC50 (Growth inhibition)	0.21	Białk-Bielińska et al., 2011
	48 h	*Pseudokirchneriella subcapitata*	Algae	EC50	0.52	Isidori et al., 2005
	48 h	*Daphnia magna*	Crustacean	EC50	123.1	Park e Choi, 2008
	24 h	*Scenedesmus vacuolatus*	Algae	EC50 (Reproduction inhibition)	1.54	Białk-Bielińska et al., 2011
	72 h	*Raphidocelis subcapitata*	Algae	EC50 (Growth inhibition)	98	Fass.se, 2020
	7 d	*Lemna minor*	Lemnoideae	EC50 (Growth)	215	Fass.se, 2020
	72 h	*Raphidocelis subcapitata*	Algae	NOEC	32	Fass.se, 2020
	7 d	*Lemna minor*	Lemnoideae	NOEC	53.5	Fass.se, 2020
	48 h	*Daphnia magna*	Crustacean	NOEC (Immobilization)	100	Fass.se, 2020
Sulfadiazine	-	*Lemna minor*	Lemnoideae	EC50 (Growth inhibition)	2.22	Białk-Bielińska et al., 2011
	24 h	*Scenedesmus vacuolatus*	Algae	EC50 (Reproduction inhibition)	0.07	Białk-Bielińska et al., 2011
	-	*Selenastrum capricornutum*	Algae	EC50 (Growth inhibition)	7.8	Lützhøft et al., 1999
	15 min	*Aliivibrio fischeri*	Bacteria	EC50 (Luminescence inhibition)	67.61	Wei et al., 2018
	21 d	*Daphnia magna*	Crustacean	NOEC (Survival)	50	Forfait-Dubuc et al., 2012
Ofloxacin	-	*Pseudomonas putida*	Bacteria	EC50	0.11	Carbajo et al., 2015
	24 h	*Lemna minor*	Lemnoideae	EC50	0.126	Robinson et al., 2005
	48 h	*Ceriodaphnia dubia*	Crustacean	EC50	3.13	Isidori et al., 2005
	96 h	*Pseudokirchneriella subcapitata*	Algae	EC50 (Growth inhibition)	4.74	Ferrari et al., 2004
	48 h	*Daphnia magna*	Crustacean	EC50 (Mortality)	76.58	Ferrari et al., 2004

Continuation

	96 h	*Pseudokirchneriella subcapitata*	Algae	NOEC (Growth inhibition)	2.5	Ferrari et al., 2004
Compound	**Exposure time**	**Species**	**Organism**	**Toxicity assessment criteria**	**Value (mg L^{-1})**	**Reference**
	7 d	*Ceriodaphnia dubia*	Crustacean	NOEC (Reproduction)	10	Ferrari et al., 2004
	10 d	*Danio rerio*	Fish	NOEC (Mortality)	16	Ferrari et al., 2004
Norfloxacin	6 d	*Anabaena cylindrica*	Cyanobacteria	EC50	0.053	Eguchi et al., 2004
	72 h	*Selenastrum capricornutum*	Algae	EC50	16.6	Eguchi et al., 2004
	96 h	*Chlorella vulgaris*	Algae	EC50	58.6	Xiong et al., 2017b
		Pseudokirchneriella subcapitata	Algae	EC50	16.6	Eguchi et al., 2004
		Pseudokirchneriella subcapitata	Algae	NOEC	4.01	Eguchi et al., 2004
	6 d	*Synechococcus leopoliensis*	Cyanobacteria	NOEC (Growth rate)	0.16	Ando et al., 2007
Fluconazole	24 h	*Thamnocephalus platyurus*	Crustacean	LC50 (Immobilization)	100	Kim et al., 2009
	96 h	*Oryzias latipes*	Fish	LC50 (Mortality)	100	Kim et al., 2010
	72 h	*Pseudokirchneriella subcapitata*	Algae	NOEC (Growth inhibition)	3.06	Chen et al., 2016
	7 d	*Lemna minor*	Aquatic plant	NOEC (Growth rate)	0.3	Richter et al., 2016
Miconazole	24 h	*Daphnia magna*	Crustacean	EC50 (Reproduction)	0.3	Furuhagen et al., 2014
Thiabendazole	48 h	*Daphnia magna*	Crustacean	EC50 (Immobilization)	0.55	Martín-de-Lucía et al., 2019
	5 min	*Aliivibrio fischeri*	Bacteria	EC50 (Luminescence inhibition)	29.64	Oh et al., 2006
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobilization)	0.8436	Oh et al., 2006
Loratadine	48 h	*Daphnia magna*	Crustacean	EC50 (Immobilization)	0.83	Fass.se, 2020
	-	*Pseudokirchneriella subcapitata*	Algae	EC50 (Growth inhibition)	2.15	Iesce et al.,2019
	-	*Ceriodaphnia dubia*	Crustacean	EC50 (Reproduction inhibition)	0.03	Iesce et al.,2019
	-	*Brachionus calyciflorus*	Rotifer	EC50 (Reproduction inhibition)	0.05	Iesce et al.,2019
	-	-	Fish	EC50 (ECOSAR)	0.02	Sanderson et al., 2004
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobilization)	3.1	Fass.se, 2020
	21 d	*Daphnia magna*	Crustacean	NOEC (Reproduction)	0.078	Fass.se, 2020
	72 h	*Pseudokirchneriella subcapitata*	Algae	NOEC (Growth inhibition)	0.053	Fass.se, 2020

Continuation

	28 d	*Lepomis macrochirus*	Fish	NOEC (Hatch, mortality, growth)	0.084	Fass.se, 2020
Compound	**Exposure time**	**Species**	**Organism**	**Toxicity assessment criteria**	**Value (mg L^{-1})**	**Reference**
Fexofenadine	48 h	*Daphnia magna*	Crustacean	EC50 (Immobilization)	780	Fass.se, 2020
	72 h	*Desmodesmus subspicatus*	Algae	NOEC	25	Fass.se, 2020
Atenolol	48 h	*Ceriodaphnia dubia*	Crustacean	EC50 (Immobilization)	33.4	Fraysse and Garric, 2005
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobilization)	313	Cleuvers, 2005
	-	*Desmodesmus subspicatus*	Algae	EC50 (Growth inhibition)	620	Cleuvers, 2005
	72 h	*Pseudokirchneriella subcapitata*	Algae	NOEC (Growth rate, yield, biomass integral)	128.8	Küster et al., 2010
	21 d	*Daphnia magna*	Crustacean	NOEC (Reproduction)	8.872	Küster et al., 2010
	21 d	*Pimephales promelas*	Fish	NOEC (Reproduction)	10	Winter et al., 2008
Metoprolol	3 d	*Desmodesmus subspicatus*	Algae	EC50 (Growth inhibition)	7.3	Cleuvers, 2003
	48 h	*Ceriodaphnia dubia*	Crustacean	EC50 (Immobilization)	45.3	Fraysse and Garric, 2005
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobilization)	120	Fass.se, 2020
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobilization)	438	Cleuvers, 2005
	72 h	*Pseudokirchneriella subcapitata*	Algae	NOEC (Growth inhibition)	7.5	Fass.se, 2020
	96 h	*Oncorhynchus mykiss*	Trout	NOEC	32	Fass.se, 2020
Propanolol	3 d	*Desmodesmus subspicatus*	Algae	EC50	5.8	Cleuvers, 2003
	7 d	*Lemna minor*	Lemnoideae	EC50	114	Cleuvers, 2003
	48 h	*Daphnia magna*	Crustacean	EC50	7.5	Cleuvers, 2003
	48 h	*Ceriodaphnia dubia*	Crustacean	EC50 (Immobilization)	1.4	Fraysse and Garric, 2005
	24 h	*Oryzias latipes*	Fish	LC50	11.4	Kim et al., 2009
	24 h	*Thamnocephalus platyurus*	Crustacean	LC50 (Immobility)	10.31	Kim et al., 2009
	48 h	*Pseudokirchneriella subcapitata*	Algae	NOEC (Growth inhibition)	1.25	Liu et al., 2009
	48 h	*Brachionus calyciflorus*	Rotifer	NOEC (Reproduction)	5	Liu et al., 2009
	-	*Hyalella azteca*	Crustacean	NOEC (Reproduction)	0.001	Huggett et al., 2002
	-	*Ceriodaphnia dubia*	Crustacean	NOEC (Reproduction)	0.125	Huggett et al., 2002
17α-ethinylestradiol	96 h	*Oncorhynchus mykiss*	Fish	LC50	1.6	Safety Data Sheets, 2019

Continuation

	48 h	*Daphnia magna*	Crustacean	EC50	5.7	Safety Data Sheets, 2019
Compound	**Exposure time**	**Species**	**Organism**	**Toxicity assessment criteria**	**Value (mg L^{-1})**	**Reference**
	48 h	*Daphnia similis*	Crustacean	EC50 (Mortality)	1.63	Clubbs and Brooks, 2007
	21 d	*Fundulus heteroclitus*	Fish	NOEC (Mortality)	0.5	Castro et al., 2014
	-	*Daphnia*	Crustacean	NOEC (Reproduction)	0.387	Vestel et al., 2016
	-	-	Algae	-	0.054	Vestel et al., 2016
	21 d	*Daphnia magna*	Crustacean	NOEC (Reproduction)	0.729	Fass.se, 2020
17β-estradiol	8 d	*Danio rerio*	Fish	EC50 (Vitellogenin concentration)	0.0000412	Rose et al., 2002
	8 d	*Danio rerio*	Fish	NOEC (Vitellogenin concentration)	0.0000129	Rose et al., 2002
	Full Life-cycle	*Oryzias latipes*	Fish	NOEC	0.000286	Seki et al., 2004
Bezafibrate	48 h	*Daphnia magna*	Crustacean	LC50	30.3	Han et al., 2006
	-	-	Algae	EC50 (ECOSAR)	18	Sanderson et al., 2004
	-	-	Fish	EC50 (ECOSAR)	5.3	Sanderson et al., 2004
	24 h	*Daphnia magna*	Crustacean	EC50 (Immobility)	100.08	Isidori et al., 2009
	24 h	*Thamnocephalus platyurus*	Crustacean	EC50 (Mortality)	39.69	Isidori et al., 2009
	7 d	*Ceriodaphnia dubia*	Crustacean	NOEC (Growth inhibition)	0.023	Isidori et al., 2009
	48 h	*Brachionus calyciflorus*	Rotifers	NOEC (Growth inhibition)	0.156	Isidori et al., 2009
Simvastatin	96 h	*Dunaliella tertiolecta*	Algae	EC50 (Growth)	22.8	De Lorenzo and Fleming, 2008
	96 h	*Fundulus heteroclitus*	Fish	LC50	2.68	Key et al., 2009
	96 h	*Fundulus heteroclitus*	Fish	NOEC	1.25	Key et al., 2009
Fenofibrate		-	Algae	EC50 (ECOSAR)	0.1	Sanderson et al., 2004
	7 d	*Ceriodaphnia dubia*	Crustacean	EC50 (Growth inhibition)	0.76	Isidori et al., 2009
	24 h	*Poeciliopsis lucida*	Fish	EC50 (Cytotoxicity)	3.25	Laville et al., 2004
	3 d	*Pseudokirchneriella subcapitata*	Algae	NOEC (Population growth rate)	3.12	Isidori et al., 2009
	-	*Ceriodaphnia dubia*	Crustacean	NOEC (Population growth inhitbition)	0.039	Orias and Perrodin et al., 2013
	7 d	*Ceriodaphnia dubia*	Crustacean	NOEC (Growth inhibition)	0.039	Isidori et al., 2009
	7 d	*Pimephales promelas*	Fish	NOEC (Morphology)	0.025	Nallani, 2011

Continuation

Compound	Exposure time	Species	Organism	Toxicity assessment criteria	Value (mg L^{-1})	Reference
Fluoxetine	96 h	*Dunaliella tertiolecta*	Algae	EC50 (Growth)	0.1698	De Lorenzo and Fleming, 2008
	24 h	*Brachionus koreanus*	Rotifer	LC50 (growth, reactive oxygen species, glutathione levels, and antioxidant enzymatic activities)	1.56	Byeon et al., 2020
	72 h	*Oryzias latipes*	Fish	LC50 (Mortality)	0.84	Chiffre et al., 2016
	72 h	*Skeletonema pseudocostatum*	Algae	EC50 (Growth inhibition)	0.016	Petersen et al., 2014
	48 h	*Pseudokirchneriella subcapitata*	Algae	EC50 (Growth rate)	0.027	Christensen et al., 2007
	48 h	*Daphnia magna*	Crustacean	EC50 (Immobility)	6.4	Christensen et al., 2007
	72 h	*Oryzias latipes*	Fish	NOEC (Locomotion)	0.01	Chiffre et al., 2014
	7 d	*Carcinus maenas*	Crab	NOEC (Locomotor behaviour)	0.01	Mesquita et al., 2011
	7 d	*Pimephales promelas*	Fish	NOEC (Growth)	0.118	Stanley et al., 2007
	21 d	*Daphnia magna*	Crustacean	NOEC (Reproduction)	0.17	Stanley et al., 2007
	24 h	*Brachionus koreanus*	Rotifer	NOEC (growth, reactive oxygen species, glutathione levels, and antioxidant enzymatic activities)	1	Byeon et al., 2020
Diazepam	96 h	*Gambusia holbrooki*	Fish	LC50 (Mortality)	12.7	Sanderson et al., 2004
	48 h	*Artemia parthenogenetica*	Crustacean	LC50 (Mortality)	12.2	Nunes et al., 2005
	96 h	*Tetraselmis chuii*	Algae	LC50 (Growth inhibition)	16.5	Nunes et al., 2005
	72 h	*Pseudokirchneriella subcapitata*	Algae	NOEC (Reproduction)	1.387	Jacob, 2017
Oxazepam	72 h	*Oryzias latipes*	Fish	LC50 (Mortality)	10	Chiffre et al., 2014
	72 h	*Oryzias latipes*	Fish	NOEC	0.01	Chiffre et al., 2014
Carbamazepine	48 h	*Daphnia magna*	Crustacean	LC50	111	Han et al., 2006
	3 d	*Desmodesmus subspicatus*	Algae	EC50	74	Cleuvers, 2003
	7 d	*Lemna minor*	Lemnoideae	EC50	25.5	Cleuvers, 2003
	48 h	*Ceriodaphnia dubia*	Crustacean	EC50 (Immobility)	77.7	Ferrari et al., 2003
	24 h	*Oryzias latipes*	Fish	LC50	45.87	Kim et al., 2009
	7 d	*Ceriodaphnia dubia*	Crustacean	NOEC (Reproduction)	0.025	Ferrari et al., 2003
	10 d	*Danio rerio*	Fish	NOEC (Development)	25	Ferrari et al., 2003

	48 h	*Brachionus calyciflorus*	Rotifers	NOEC (Reproduction)	0.377	Ferrari et al., 2003

3.4.1 Genotoxicity of PhACs to aquatic organisms

Toxicity can be evaluated for several criteria, and genotoxicity has been highlighted in current studies. Genotoxicity refers to the damage and stresses caused to DNA or genetic information of organisms when exposed to chemical agents or contaminants (BARCELÓ et al., 2020). These DNA damages can cause mutagenic effects in organisms or their descendants, promoting changes in the aquatic ecosystem (OHE et al., 2004). Although genotoxicity is still little explored compared to other toxicity criteria, it is considered a reliable endpoint to assess PhAC's toxicity (AGUIRRE-MARTÍNEZ et al., 2013; MARANHO et al., 2014).

Anti-cancer drugs present in water bodies have been studied for acting on the structures and functions of DNA, directly or indirectly affecting cells (PARRELLA et al, 2015; FONSECA et al., 2017). To evaluate the effect of these PhACs on aquatic organisms, genotoxicity assays are essential. Parrella et al. (2015) submitted the crustaceans D. *magna* and *Ceriodaphnia dubia* to six anti-neoplastic drugs (5-fluorouracil, capecitabine, cisplatin, doxorubicin, etoposide, and imatinib) for 24 h. In this study, all single PhACs induced an increase in DNA damage, in concentrations between 0.01 e 120 μg L^{-1}, considered high environmental concern (EUROPEAN COMMISSION, 1996). Similarly, the ragworm *Nereis diversicolor* was also exposed to the PhAC cisplatin for 14 days and, in this case, according to genotoxicity assay, expressed as a percentage of DNA tail, no changes in DNA damage were observed in concentrations of 0.1, 10 and 100 *n*g L^{-1} (FONSECA et al., 2017), unlike Parrella et al., (2015) which observed DNA damage of *D. magna* exposed to cisplatin, in the concentration of 10 *n*g L^{-1}. This shows that some organisms may be more sensitive to breaks in DNA when exposed to this type of pharmaceutical.

In addition to anti-neoplastic drugs, other therapeutic classes have also been evaluated for genotoxicity to aquatic organisms. Losartan, used extensively for the hypertension treatment, caused a significant increase in primary DNA damage after 48 h of exposure, at a concentration of 3 μg L^{-1}, for brown *mussel Perna perna* (CORTEZ et al., 2018). A similar result was found by Fontes et al. (2018) with diclofenac, which caused DNA damage to *P. perna* at a concentration of 2 μg L^{-1}, in 48 h of exposure.

Orozco-Hernández et al. (2019) used *Cyprinus carpio* for the genotoxicity assays of the amoxicillin. Two methods were used to determine genotoxicity: the single-cell gel electrophoresis or comet assay and the micronuclei test (ÇAVAS and ERGENE-GOZÜKARA et al., 2005). Fish were exposed to concentrations of 0.039 μg L^{-1} and 1.67 μg L^{-1} at 12, 24, 48,

72, and 96 h. In both tests, there was a significant increase in DNA damage compared to the control, in the two concentrations. Islas-Flores et al. (2016) also evaluated genotoxicity cause by ibuprofen (17.6 mg L^{-1}) and diclofenac (7.1 mg L^{-1}) in *C. carpio*. A significant increase in DNA damage was found at all exposure times for both the single PhACs and the mixture. This increase was greater when *C. carpio* was exposed to ibuprofen, compared to diclofenac alone, while the mixture induced an even greater increase in DNA damage (ISLAS-FLORES et al., 2017). In that same study, the LC_{50} was evaluated with values of 175.6 mg L^{-1} for ibuprofen and 70.98 mg L^{-1} for diclofenate, which represent a low and moderate environmental concern. With these results, it is evident that genotoxicity tests are of great relevance since can detect sublethal effects of a great impact on aquatic organisms.

The psychiatric drug fluoxetine also caused an increase in DNA damage at a concentration of 3 μg L^{-1} for fish *Argyrosomus regius* (DUARTE et al., 2020). In a study carried out by Aguirre-Martínez et al. (2015), carbamazepine, also from the psychiatric group, was highlighted for its high DNA damage to *Corbicula fluminea*, even at the lowest tested concentration, 0.1 μg L^{-1}, with an exposure time of 21 days. This fact is worrying due to the concentrations of carbamazepine found in water bodies, which can reach 0.699 μg L^{-1} (Table S1), promoting high risks to the organisms exposed to this PhAC.

The genotoxicity of PhACs should be more explored in the literature, mainly for their complexity. A PhAC may, for example, not damage the DNA of determined cells but be harmful to the functions of others. Novak et al. (2021) assessed *Danio rerio* exposure to the anti-cancer drug imatinib at concentrations of 0.01, 1 and 100 μg L^{-1}. The results showed no significant increase in DNA damage in gills, liver and gonads, while in blood cells a significant increase in DNA strand breaks was observed at a concentration of 1 μg L^{-1}.

3.5 Environmental and human health risk assessment of PhACs

Environmental risk assessment is essential to determine whether pollutants present in water bodies represent a danger to aquatic organisms and humans. Thus, values of pharmaceutical concentrations in the aquatic environment and the toxicity data related to them, for different organisms, are fundamental to measure the risks of these compounds. In this context, the risk values for the PhACs selected in this review were calculated to classify the risk they represent globally.

For assess the acute and chronic environmental risks, measured from the risk quotient (RQ), the maximum concentration of each PhAC in surface water, raw and treated wastewater using the database (Table S1) were used. The RQ values were obtained through the quotient between the average concentrations of PhACs by PNEC. For the calculation of the PNEC, acute or chronic toxicities for each pharmaceutical were considered (Table 2), as well as a correction factor, which follows the criteria: 10 for NOECs from at least three species representing three trophic levels; 50 for NOECs from species representing two trophic levels; 100 for NOECs from only one trophic level; and 1000 for one $E(L)C_{50}$ from each of three trophic levels (EUROPEAN COMMISSION, 1996). For risk calculations, the $E(L)C_{50}$ or NOEC values that presented greater toxicity for the organisms found in the literature were considered. Thus, the most critical risk situation can be determined for the aquatic environment.

Human health risk, measured from the hazard quotient (HQ), was calculated using the average concentrations of PhACs in drinking water divided by DWEL. DWEL considers acceptable daily intake for each PhAC, body weight (70 kg), the relative contribution of water exposure (equal to 1) and the daily water intake (2 L d^{-1}). For both environmental and human risk assessment, the following classification was used: for $R(H)Q > 1$, the risk is high; when $0.1 \leq R(H)Q \leq 1$, the risk was considered medium; for $0.01 \leq R(H)Q < 0.1$ the risk is low; and if $R(H)Q < 0.01$ the risk is negligible (EUROPEAN COMMISSION, 1996; COUTO et al., 2020).

Figure 12 shows the acute (a) and chronic (b) risks calculated for the selected PhACs. For acute risks, ketoprofen, diclofenac, naproxen, erythromycin, roxithromycin, sulfamethoxazale, sulfadiazine, ofloxacin, and 17β-estradiol were classified as high risk for all aquatic matrices. For chronic risks, acetaminophen, diclofenac, naproxen, erythromycin, roxithromycin, 17β-estradiol and bezafibrate presented high risks for all matrices. In a study by Li et al. (2021) the PhACs diclofenac and 17β-estradiol were also classified as high risk and considered as prioritize since may pose a great risk in the aquatic environment. Naproxen and ofloxacin were classified as high acute risk and were among the first in the lists of pharmaceutical compounds to be prioritized, due to the dangers they can pose to the aquatic environment (JI et al., 2015; GUO et al., 2016; GUO et al., 2021). Erythromycin has also been among the top 10 in the ranking of compounds that deserve greater attention due to risks, in a study carried out in the Mediterranean rivers (LLORENS et al., 2020). In contrast, ketoprofen has been classified as low or negligible risk in some studies (GHEORGHE et al., 2016; VYMAZAL et al., 2017).

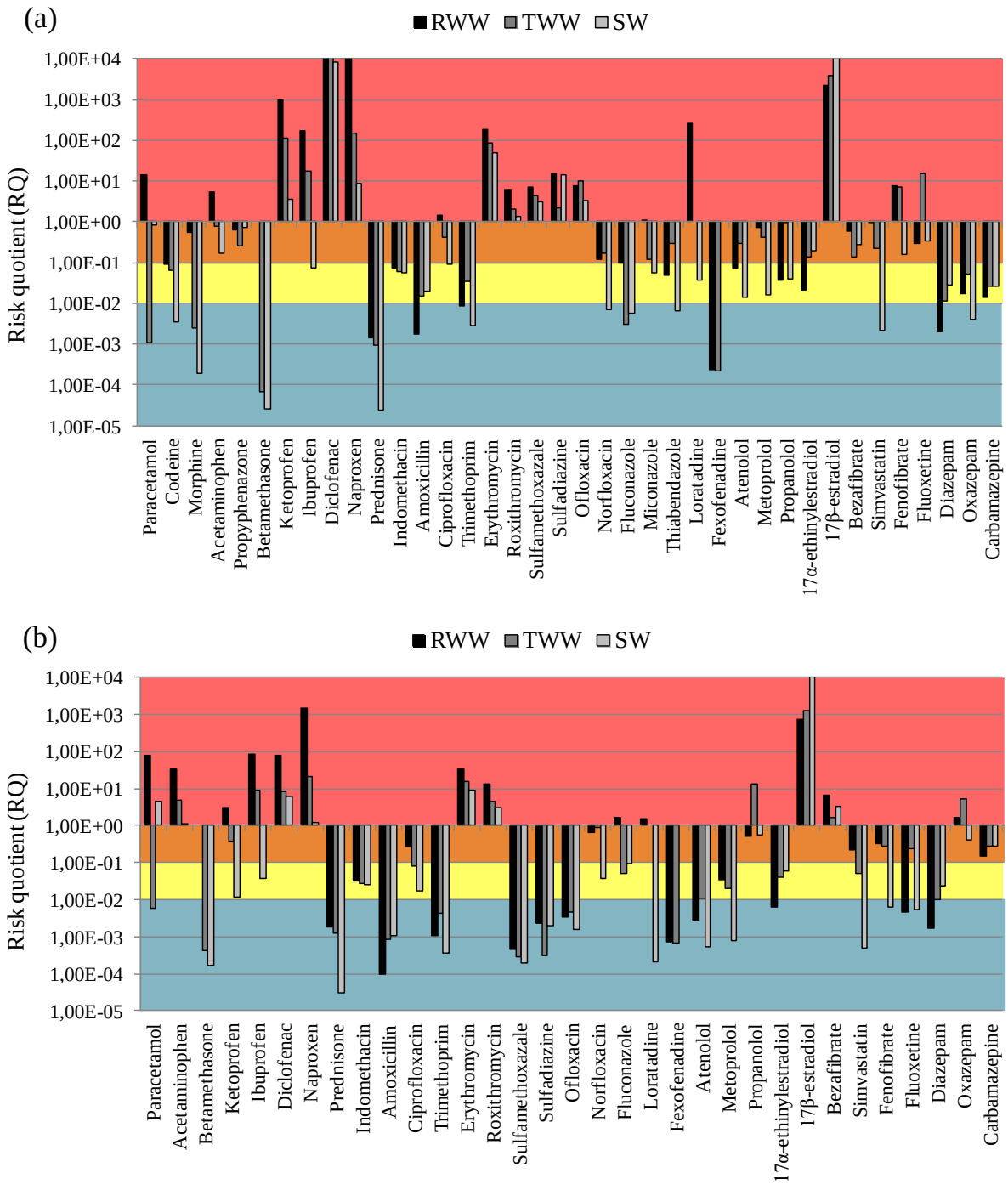

Figure 12 – Environmental risk acute (a) and chronic (b) for selected PhACs (Red area – High risk; Orange area – Medium risk; Yellow area – Low risk; Blue area – Negligible risk).

Some PhACs did not present high acute risk but were classified as high chronic risk, such as propanolol, bezafibrate and oxazepam, which indicates that the risk is associated with longer periods of exposure. In contrast, ketoprofen, sulfamethoxazale, sulfadiazine, ofloxacin, loratadine, fenofibrate and fluoxetine had a high acute risk for certain matrices but did not present a high chronic risk, which may be related to the difference in organisms sensitivity or

the criteria evaluated for acute and chronic toxicity in literature data. Ketoprofen for example, had a high acute risk, that was calculated from the toxicity value for the organism *P. subcapitata*, while the chronic risk, calculated from the toxicity for the organism *D. rerio*, was low. Calculating acute risk also for the organism *D. rerio*, with LC_{50} of 632 mg L^{-1} for ketoprofen (Table 10), the acute risk would be classified as negligible for all matrices. However, it is important to calculate the risks considering the most critical cases, that is, the organisms most sensitive to PhACs.

In general, the highest risks were determined for raw wastewater, which was expected, since the highest concentrations of PhACs are in this matrix. However, risk assessment reinforced the importance of not only reducing or eliminating micropollutants but also the toxicity related to them. For 17β-estradiol, for example, low concentrations were found in all aquatic matrices, however, the hormone presented high acute and chronic risks for surface water, raw and treated wastewater, due to its high toxic potential. Du et al. (2020) also evaluated the risks of 17β-estradiol in surface water and treated wastewater and showed that the hormone presented a high risk for the aquatic environment in several locations around the world. In contrast, for some PhACs such as ofloxacin, 17β-estradiol and oxazepam, the risk for treated wastewater was greater than for raw wastewater. From this it is evident that in some cases the wastewater treatments do not reduce the risks related to PhACs and may even increase them, which may be due, for example, to the formation of toxic by-products in treatment plants (GARCÍA-GALÁN et al., 2016).

Finally, only 17α-ethinylestradiol was classified as a high risk for human health and 17β-estradiol presented a medium risk, while other PhACs presented negligible risk (Figure 13). Even at low concentrations in drinking water, these hormones can promote high risks to human health, since these compounds are endocrine disruptors, and can cause immune effects, metabolic effects, reproductive abnormalities, behavioral changes, diabetes, obesity, cardiovascular diseases, neurological disorders, disrupted fetal development and growth, and a wide variety of cancers (WEE and ARIS, 2017). However, studies that evaluate the effects of endocrine disruptors on human health still have some gaps, since it must be evaluated in the long term and can have interference by several variables (KIYAMA and WADA-KIYAMA, 2015). Anyway, it is essential that these compounds are not present in drinking water due to their attributed risks.

To represent the interaction of PhACs in the environment, the cumulative risks were estimated for studies that reported the presence of several PhACs in surface waters of certain locations (Table S1). The risk of the mixture was calculated from the hazard índex (HI), which represents the sum of the risks found for each PhAC in the evaluated locations (US EPA, 2000). The acute or chronic HI in different places of the world, like Egypt, Canada, Portugal, Spain, India, Mexico, and Brazil were considered high, while isolated compounds had low or negligible risks (Figure 14). However, despite showing that the risk of the mixture is usually greater than the risks of isolated PhACs, this model does not yet represent what actually occurs in the environment. For the HI calculation only reported PhACs were considered, however, other PhACs and compounds such as pesticides, metals, endocrine disruptors and several classes of pollutants may be present in surface waters (DI POI et al., 2018).

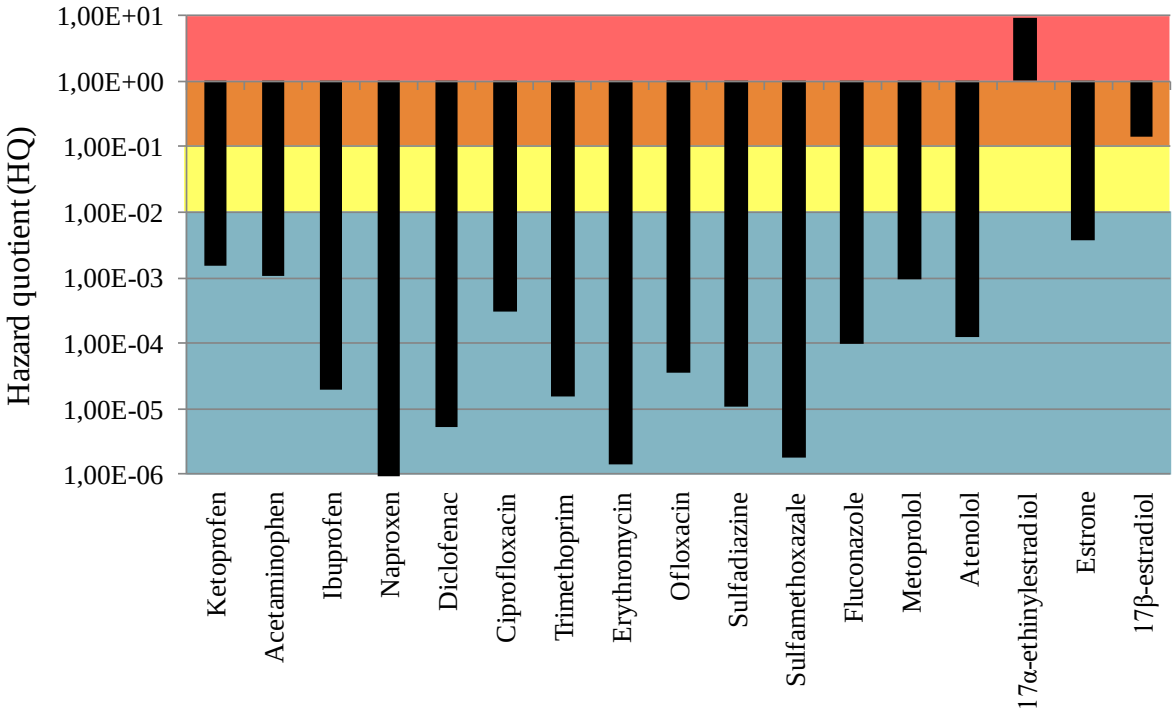

Figure 13 – Human health risk for selected PhACs (Red area – High risk; Orange area – Medium risk; Yellow area – Low risk; Blue area – Negligible risk).

Erythromycin contributes considerably to a high HI in Egypt, Canada, and Spain. Studies show that the removal of erythromycin in the wastewater treatment systems used in these countries was low or did not occur (Petrovic et al., 2006; Guerra et al., 2014; Abdallah et al., 2019), which is indicative that the removal of this PhAC should be prioritized in these places. In Portugal, India, Mexico, and Brazil, the PhACs ketoprofen and diclofenac were the main contributors for the HI classified as high. These PhACs are widely detected in these countries' water bodies

(Palma et al., 2020; Sharma et al., 2019; Rivera-Jaimes et al., 2018; Reis et al., 2019), which is aggravated by the high and increasing consumption of anti-inflammatories in the world (PHOON et al., 2020). Among the countries evaluated, only China did not show high HI, which may be related to investments in the environmental sector and the wastewater treatment systems adopted in the country. According to Qu et al., (2019), China possesses the world's largest municipal wastewater infrastructure and the world's largest research team in the water and wastewater treatment.

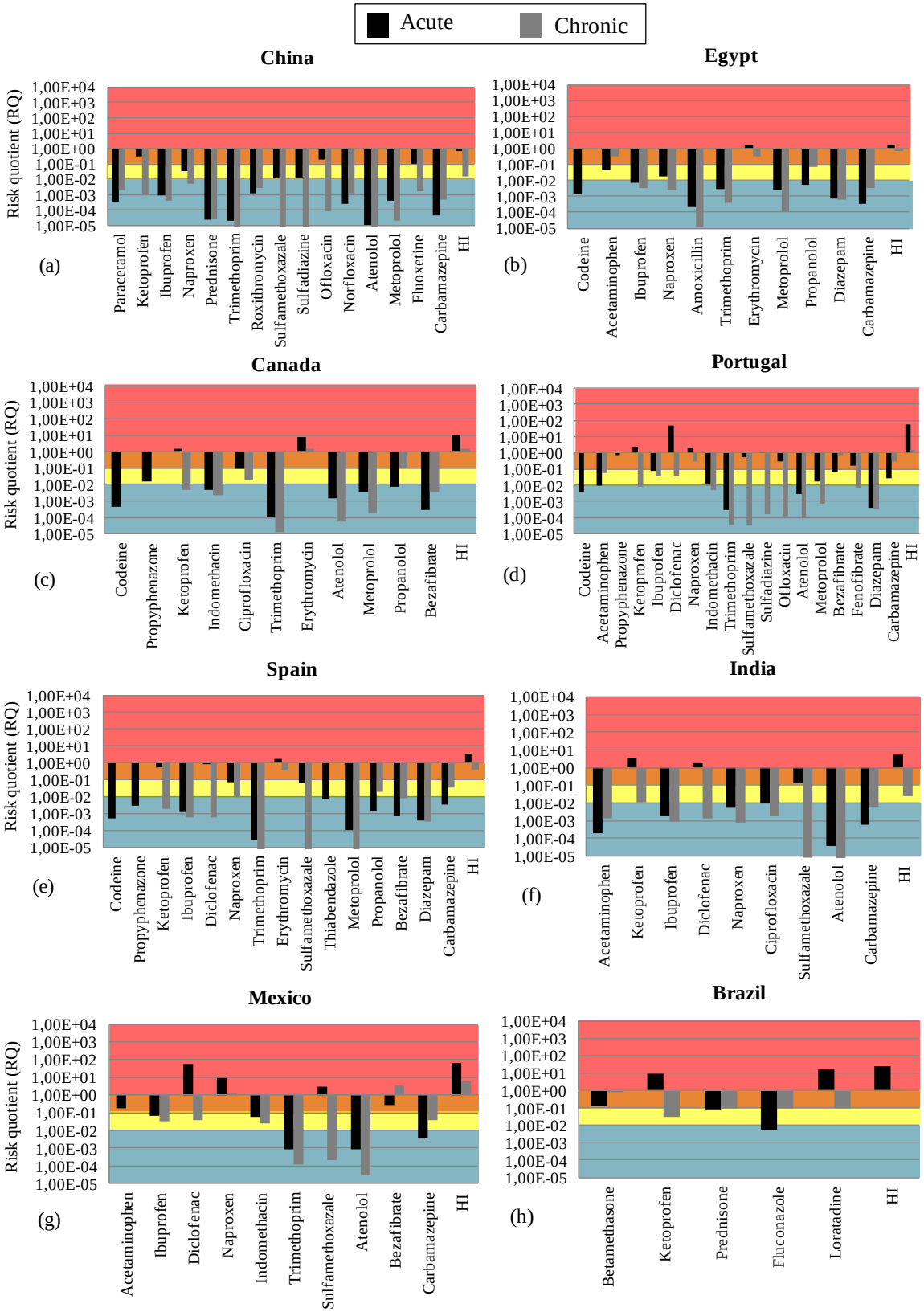

Figure 14 – Hazard index (HI) for selected PhACs in surface water from China (a), Egypt (b), Canada (c), Portugal (d), Spain (e), India (f), Mexico (g) and Brasil (h). (Red area – High risk; Orange area – Medium risk; Yellow area – Low risk; Blue area – Negligible risk)

3.6 Conclusion

PhACs are present in raw wastewater, treated wastewater, surface water and drinking water worldwide. Knowing concentrations of these compounds in the aquatic matrices as well as the toxicity related to them is essential to measure environmental and human health risks. The concentrations of PhACs in the aquatic matrices can be relatively low, in the range of ng L^{-1} and ug L^{-1}, however, even in low concentrations these micropollutants can be toxic to aquatic organisms, causing several adverse effects to the ecosystem and promoting high environmental risks. Several PhACs were classified as a high environmental risk, however, in the environment there is the interaction of PhACs with several compounds that were not considered, thus, the risks can be even greater.

The risk assessment showed that diclofenac, naproxen, erythromycin, roxithromycin, and 17β-estradiol presented a high acute and chronic risk to the environment, while 17α-ethinylestradiol presented a high risk to human health. For hazard index, erythromycin contributes considerably to a high risk in Egypt, Canada, and Spain, while in Portugal, India, Mexico, and Brazil, the PhACs ketoprofen and diclofenac were the main contributors for the HI classified as high.

This shows the potential of these PhACs to cause adverse effects to the ecosystem and humans and establishes the priority of their removal. Thus, for environmental risk reduction, the use of efficient technologies to remove micropollutants and toxicity is essential. In this sense, membrane bioreactors have been efficient in removing PhACs, with removals reported in the literature in the range of 81.36-100%. In addition to assessing the removal of PhACs in treated wastewater, ecotoxicological tests are essential to assess whether adverse effects on aquatic organisms have also been eliminated by treatment.

CHAPTER 4

FINAL CONSIDERATIONS

In this study an anaerobic osmotic membrane bioreactor with membrane distillation was evaluated to treat municipal sewage with 7 PhACs, achieving overall removal efficiency for

COD, $P\text{-}PO_4^{3-}$ and $N\text{-}NH_4^{+}$ of 90.07, 99.99, 93.01%, respectively. Toxicity removal for *A. fischeri* was complete in the distillate, while for *D. similis* it was 89.6%. In contrast, there was no removal of chronic toxicity for *R. subcapitata,* which may be due to the presence of magnesium in the distillate, since the compound can be toxic to this organism. This shows the importance of toxicity studies for the solute choice in osmotic bioreactors.

The feed solution fortified with a mixture of seven PhACs at a concentration of 2 μg L^{-1} each, was not toxic for any of the evaluated organisms, showing that this concentration of PhACs mixed in the synthetic sewage did not cause adverse effects. However, a more detailed approach is needed regarding PhACs toxicity and concentrations that can cause adverse effects on aquatic organisms. Therefore, a more in-depth study was carried out regarding the toxicity of the micropollutants used in the membrane bioreactor and also of other PhACs, in order to assess the risks of these compounds to aquatic organisms.

For this, was carried out a lirerature review thah evaluated 39 PhACs from 8 different therapeutic classes. The selected PhACs are found in the aquatic environment with an average concentration of 10 ng L^{-1} for drinking water, 1,544 ng L^{-1} for surface water, 5,6970 ng L^{-1} for raw wastewater, and 3,271 ng L^{-1} for treated wastewater. The study showed that even in concentrations range ng L^{-1} and μg L^{-1} some these micropollutants can be toxic to aquatic organisms, causing several adverse effects on the ecosystem, like reproduction inhibition, immobilization, luminescence inhibition, growth inhibition, and even mortality.

Thus, the PhACs diclofenac, naproxen, erythromycin, roxithromycin, and 17β-estradiol presented a high acute and chronic risk to the environment and 17α-ethinylestradiol presented a high risk to human health. This shows the potential of these PhACs to cause adverse effects on the ecosystem and humans and determines the priority of their removal through advanced technologies.

To represent the interaction of PhACs in the environment, the cumulative risks were also estimated. The acute or chronic risk of the mixture in different places like Egypt, Canada, Portugal, Spain, India, Mexico, and Brazil were considered high, while isolated compounds had low or negligible risks. However, in the environment, there is the interaction of PhACs with several compounds that were not considered, therefore, the risks can be even greater.

Despite the mixture of PhACs (17α-ethinylestradiol, ketoprofen, fenofibrate, fluconazole, loratadine, prednisone, and betamethasone) at a concentration of 2 ug L^{-1} used in the first chapter was not toxic for any organism evaluated, the review in the second chapter showed that

ketoprofen and 17α-ethinylestradiol presented a high acute or chronic environmental risk. Specifically in Brazil, ketoprofen and loratadine were also at high risk. This shows that although the mixture used in chapter 1 was not toxic under the conditions tested, it does not guarantee that these PhACs are free from environmental risks, in other concentrations and for different organisms.

The review also showed that wastewater treatment plants can be a distribution source of PhACs to the environment since conventional technologies do not entirely remove these compounds. Therefore, membrane bioreactors have been efficient in removing PhACs, with removals reported in the literature range of 81.36-100%.

In this study, the importance of ecotoxicological tests was shown to measure the risk of PhACs in the environment and to evaluate the wastewater treatment in the removal of toxicity, since even with satisfactory efficiencies for removal of physical-chemical parameters and even micropollutants, the effluent can be still toxic to aquatic organisms and cause disturbances in the aquatic environment. It is essential to highlight the need to include toxicity studies in selecting solutes and their respective concentrations for the draw solution of osmotic bioreactors. Operations with a lower concentration of $MgCl_2$ could reduce the impact caused by this compound.

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SUPPLEMENTARY MATERIAL

Table S1 – Occurrence of PhACs in raw wastewater, treated wastewater, surface water, and drinking water, worldwide

Therapeutic class	Compound	Concentration (ng/L)	Environment - Contry	Reference
Analgesic	Paracetamol	18.73	Surface water - China	Xu et al. (2019)
		136	Surface water - China	Yang et al. (2017)
		250	Surface water - Portugal	Santos et al. (2013)
		402.7	Surface water - Spain	Robles-Molina et al (2014)
		1289	Surface water - Spain	Boleda et al. (2013)
		42000	Surface water - Brazil	Veras et al (2019)
		3.6	Drinking water - Holland	Houtman et al. (2014)
		18	Drinking water - Spain	Boleda et al. (2013)
		1350	Raw wastewater - China	Yang et al. (2017)
		1996	Raw wastewater - Greece	Papageorgiou et al. (2016)
		25935.1	Raw wastewater - Portugal	Pereira et al. (2015)
		130000	Raw wastewater - Brazil	Américo et al. (2012)
		700000	Raw wastewater - Sweden	Daouk et al. (2016)
		17.3	Treated wastewater - China	Yang et al. (2017)
		26.9	Treated wastewater - Portugal	Pereira et al. (2015)
		55	Treated wastewater - Greece	Papageorgiou et al. (2016)
	Codeine	7.3	Surface water - Canada	Petrović et al. (2014)
		7.8	Surface water - Spain	Moreno-González et al. (2014)
		21	Surface water - Egypt	Abdallah et al. (2018)
		26.7	Surface water - Spain	Boleda et al. (2007)
		40.4	Surface water - Spain	Robles-Molina et al (2014)
		56.12	Surface water - Portugal	Palma et al. (2020)
		119.7	Raw wastewater - Spain	Boleda et al. (2007)
		195	Raw wastewater - Spain	Gallardo-Altamirano et al. (2018)

Continuation

		753	Raw wastewater - New Zealand	Kumar et al. (2018) a
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
		940	Raw wastewater - Canada	Guerra et al. (2014)
		1500	Raw wastewater - Sweden	Daouk et al. (2016)
		104	Treated wastewater - New Zealand	Kumar et al. (2018) a
		146	Treated wastewater - Spain	Gallardo-Altamirano et al. (2018)
		260	Treated wastewater - Canada	Guerra et al. (2014)
		397	Treated wastewater - Spain	Boleda et al. (2007)
		466	Treated wastewater - Egypt	Abdallah et al. (2018)
		492	Treated wastewater - USA	Scott et al. (2018)
		1017	Treated wastewater - Canada	Petrović et al. (2014)
	Morphine	0.3	Surface water - England	Krizman-Matasic et al. (2018)
		6.3	Surface water - Spain	Boleda et al. (2007)
		41.6	Raw wastewater - China	Du et al. (2019)
		96.7	Raw wastewater - Spain	Boleda et al. (2007)
		223	Raw wastewater - New Zealand	Kumar et al. (2019) a
		445	Raw wastewater - Croatia	Krizman-Matasic et al. (2018)
		18000	Raw wastewater - Sweden	Daouk et al. (2016)
		< 25	Treated wastewater - Australia	Busetti et al. (2009)
		81.1	Treated wastewater - Spain	Boleda et al. (2007)
		590	Treated wastewater - USA	Scott et al. (2018)
	Acetaminophen	4.17	Surface water - India	Sharma et al. (2016)
		96.5	Surface water - Spain	López-Serna et al. (2012)
		173.91	Surface water - Portugal	Palma et al. (2020)
		954	Surface water - Egypt	Abdallah et al. (2018)
		3422	Surface water - Mexico	Rivera-Jaimes et al. (2018)
		1.92	Drinking water - India	Sharma et al. (2016)
		3	Drinking water - Taiwan	Yang et al. (2014)
		6.4	Drinking water - China	Lin et al. (2016)
		12.8	Drinking water - Spain	Boleda et al. (2011)

Continuation		28	Drinking water - USA	Wang et al. (2011)
		30.03	Drinking water - China	Jiang et al. (2019)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
		11600	Raw wastewater - Mexico	Rivera-Jaimes et al. (2018)
		49037	Raw wastewater - New Zealand	Kumar et al. (2019) b
		92000	Raw wastewater - Canada	Guerra et al. (2014)
		110942	Raw wastewater - Spain	Gallardo-Altamirano et al. (2018)
		1234	Treated wastewater - Spain	Gallardo-Altamirano et al. (2018)
		2200	Treated wastewater - Canada	Guerra et al. (2014)
		15947	Treated wastewater - Egypt	Abdallah et al. (2018)
	Propyphenazone	2.26	Surface water - Spain	Moreno-González et al. (2014)
		3.42	Surface water - Spain	López-Serna et al. (2012)
		12	Surface water - Netherlands	De Jongh et al. (2012)
		12.5	Surface water - Canada	Petrović et al. (2014)
		43	Surface water - Germany	Ternes et al. (2001)
		568	Surface water - Portugal	Palma et al. (2020)
		6.4	Raw wastewater - Spain	Gallardo-Altamirano et al. (2018)
		120	Raw wastewater - Germany	Ternes et al. (2001)
		500	Raw wastewater - Spain	Petrovic et al. (2006)
		5.2	Treated wastewater - Spain	Gallardo-Altamirano et al. (2018)
		13.5	Treated wastewater - Canada	Petrović et al. (2014)
		47	Treated wastewater - Spain	Campos-Mañas et al. (2017)
		180	Treated wastewater - Germany	Ternes et al. (2001)
		200	Treated wastewater - Spain	Petrovic et al. (2006)
Anti-inflammatory	Betamethasone	0.3	Surface water - Italy	Speltini et al. (2018)
		0.83	Surface water - China	Gong et al. (2019)
		7.2	Surface water - China	Shen et al. (2020)
		4109	Surface water - Brazil	Reis et al. (2019)
		2620	Drinking water - Brazil	Reis et al. (2019)
		20	Raw wastewater - Spain	Herrero et al. (2012)

Continuation

		34	Raw wastewater - Spain	Veiga-Gómez et al. (2017)
		62	Raw wastewater - Canada	Guerra et al. (2014)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
	Ketoprofen	2.2	Treated wastewater - Italy	Speltini et al. (2018)
		< 10	Treated wastewater - Spain	Herrero et al. (2012)
		< 16	Treated wastewater - Canada	Guerra et al. (2014)
		56.9	Treated wastewater - USA	Scott et al. (2018)
		9.05	Surface water - China	Xu et al. (2019)
		17	Surface water - Spain	Moreno-González et al. (2014)
		45	Surface water - Serbia	Petrović et al. (2014)
		68.92	Surface water - Portugal	Palma et al. (2020)
		107	Surface water - India	Sharma et al. (2016)
		298	Surface water - Brazil	Reis et al. (2019)
		0.6	Drinking water - Holland	Houtman et al. (2014)
		8	Drinking water - Finland	Vieno et al. (2005)
		16	Drinking water - Poland	Caban et al. (2015)
		16	Drinking water - Serbia	Petrović et al. (2014)
		23.4	Drinking water - India	Sharma et al. (2016)
		31.67	Drinking water - China	Jiang et al. (2019)
		561	Drinking water - Brazil	Reis et al. (2019)
		80	Raw wastewater - Canada	Lee et al. (2005)
		230	Raw wastewater - Spain	Petrovic et al. (2006)
		281	Raw wastewater - Greece	Papageorgiou et al. (2016)
		1288	Raw wastewater - Spain	Gallardo-Altamirano et al. (2018)
		28400	Raw wastewater - South Africa	Zunngo et al. (2016)
		50	Treated wastewater - Canada	Lee et al. (2005)
		59.4	Treated wastewater - Greece	Papageorgiou et al. (2016)
		200	Treated wastewater - Spain	Petrovic et al. (2006)
		247	Treated wastewater - Serbia	Petrović et al. (2014)
		415	Treated wastewater - Spain	Campos-Mañas et al. (2017)

Continuation

		737	Treated wastewater - Spain	Gallardo-Altamirano et al. (2018)
		3500	Treated water - South Africa	Zunngo et al. (2016)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
	Ibuprofen	11.38	Surface water - China	Xu et al. (2019)
		17.1	Surface water - Spain	Moreno-González et al. (2014)
		22.85	Surface water - India	Sharma et al. (2016)
		83.4	Surface water - China	Yang et al. (2017)
		91	Surface water - Egypt	Abdallah et al. (2018)
		836	Surface wastewater - Mexico	Rivera-Jaimes et al. (2018)
		1020.46	Surface water - Portugal	Palma et al. (2020)
		0.33	Drinking water - Canada	Kleywegt et al. (2011)
		3.4	Drinking water - Canada	Yu et al. (2007)
		6	Drinking water - Japan	Simazaki et al. (2015)
		8.36	Drinking water - China	Jiang et al. (2019)
		8.5	Drinking water - Finland	Vieno et al. (2005)
		10	Drinking water - Taiwan	Yang et al. (2014)
		30.95	Drinking water - India	Sharma et al. (2016)
		72.8	Drinking water - USA	Wang et al. (2011)
		202	Drinking water - Spain	Boleda et al. (2011)
		155	Raw wastewater - China	Yang et al. (2017)
		540	Raw wastewater - Spain	Petrovic et al. (2006)
		1983	Raw wastewater - Mexico	Rivera-Jaimes et al. (2018)
		3451.2	Raw wastewater - Portugal	Pereira et al. (2015)
		6770	Raw wastewater - Canada	Lee et al. (2005)
		8600	Raw wastewater - Canada	Guerra et al. (2014)
		20000	Raw wastewater - Spain	Gallardo-Altamirano et al. (2018)
		2325000	Raw wastewater - Brazil	Américo et al. (2012)
		43.9	Treated wastewater - China	Yang et al. (2017)
		247.9	Treated wastewater - Portugal	Pereira et al. (2015)
		270	Treated wastewater - Spain	Petrovic et al. (2006)

Continuation

		310	Treated wastewater - Canada	Lee et al. (2005)
		510	Treated wastewater - Canada	Guerra et al. (2014)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
		1638	Treated wastewater - Spain	Gallardo-Altamirano et al. (2018)
		6702	Treated wastewater - Egypt	Abdallah et al. (2018)
		20130	Treated wastewater - Canada	Petrović et al. (2014)
		233000	Treated wastewater - Brazil	Américo et al. (2012)
	Diclofenac	12.8	Surface water - China	Yang et al. (2017)
		17.4	Surface water - Spain	López-Serna et al. (2012)
		20	Surface water - Spain	Moreno-González et al. (2014)
		41.3	Surface water - India	Sharma et al. (2016)
		1152.57	Surface water - Portugal	Palma et al. (2020)
		1209	Surface water - Mexico	Rivera-Jaimes et al. (2018)
		193000	Surface water - Brazil	Veras et al (2019)
		0.0495	Drinking water - Malaysia	Mohd Nasir et al. (2019)
		1.56	Drinking water - India	Sharma et al. (2016)
		4	Drinking water - Holland	Houtman et al. (2014)
		12	Drinking water - Sweden	Tröger et al. (2018)
		16	Drinking water- Japan	Simazaki et al. (2015)
		31.7	Raw wastewater - China	Yang et al. (2017)
		125.2	Raw wastewater - Portugal	Pereira et al. (2015)
		170	Raw wastewater - Canada	Lee et al. (2005)
		250	Raw wastewater - Spain	Petrovic et al. (2006)
		833	Raw wastewater - Greece	Papageorgiou et al. (2016)
		1080	Raw wastewater - Spain	Osorio et al. (2014)
		1093	Raw wastewater - Spain	Gallardo-Altamirano et al. (2018)
		1310	Raw wastewater - Bavaria	Sun et al. (2008)
		2363	Raw wastewater - Mexico	Rivera-Jaimes et al. (2018)
		2471000	Raw wastewater - Brazil	Américo et al. (2012)
		39	Treated wastewater - China	Yang et al. (2017)

Continuation

		89.9	Treated wastewater - Portugal	Pereira et al. (2015)
		110	Treated wastewater - Canada	Lee et al. (2005)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
	Naproxen	320	Treated wastewater - Spain	Petrovic et al. (2006)
		684	Treated wastewater - Greece	Papageorgiou et al. (2016)
		720	Treated wastewater - Spain	Osorio et al. (2014)
		1266	Treated wastewater - Spain	Gallardo-Altamirano et al. (2018)
		1338	Treated wastewater - Canada	Petrović et al. (2014)
		1600	Treated wastewater - Bavaria	Sun et al. (2008)
		2030	Treated wastewater - Mexico	Rivera-Jaimes et al. (2018)
		273000	Treated wastewater - Brazil	Américo et al. (2012)
		2.62	Surface water - India	Sharma et al. (2016)
		8	Surface water - Egypt	Abdallah et al. (2018)
		15.88	Surface water - China	Xu et al. (2019)
		31.9	Surface water - Spain	Moreno-González et al. (2014)
		978.77	Surface water - Portugal	Palma et al. (2020)
		3990	Surface water - Mexico	Rivera-Jaimes et al. (2018)
		0.3	Drinking water - Holland	Houtman et al. (2014)
		2.37	Drinking water - India	Sharma et al. (2016)
		<3	Drinking water - Nigeria	Ebele et al. (2020)
		90.5	Drinking water - Spain	Boleda et al. (2011)
		648	Raw wastewater - Greece	Papageorgiou et al. (2016)
		2600	Raw wastewater - Mexico	Rivera-Jaimes et al. (2018)
		2760	Raw wastewater - Canada	Lee et al. (2005)
		7264	Raw wastewater - Spain	Gallardo-Altamirano et al. (2018)
		4603000	Raw wastewater - Brazil	Américo et al. (2012)
		89	Treated wastewater - Egypt	Abdallah et al. (2018)
		208	Treated wastewater - Canada	Petrović et al. (2014)
		260	Treated wastewater - Mexico	Rivera-Jaimes et al. (2018)
		577	Treated wastewater - Spain	Campos-Mañas et al. (2017)

Continuation

		820	Treated wastewater - Canada	Lee et al. (2005)
		938	Treated wastewater - Spain	Gallardo-Altamirano et al. (2018)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
	Prednisone	70000	Treated wastewater - Brazil	Américo et al. (2012)
		0.44	Surface water - China	Gong et al. (2019)
		0.74	Surface water - China	Xu et al. (2019)
		2444	Surface water - Brazil	Reis et al. (2019)
		6323	Drinking water - Brazil	Reis et al. (2019)
		8.5	Raw wastewater - China	Liu et al. (2011)
		< 28	Raw wastewater - Canada	Guerra et al. (2014)
		45	Raw wastewater - Spain	Herrero et al. (2012)
		<10	Treated wastewater - Spain	Herrero et al. (2012)
		30	Treated wastewater - Spain	Gómez-Canela et al. (2014)
		< 60	Treated wastewater - Canada	Guerra et al. (2014)
		200	Treated wastewater - USA	Scott et al. (2018)
	Indomethacin	19.5	Surface water - Canada	Petrović et al. (2014)
		42.32	Surface water - Portugal	Palma et al. (2020)
		212	Surface water - Mexico	Rivera-Jaimes et al. (2018)
		27.9	Raw wastewater - Spain	Gallardo-Altamirano et al. (2018)
		280	Raw wastewater - Canada	Lee et al. (2005)
		283	Raw wastewater - Mexico	Rivera-Jaimes et al. (2018)
		< 5	Treated wastewater - Australia	Busetti et al. (2009)
		5.2	Treated wastewater - Spain	Gallardo-Altamirano et al. (2018)
		57	Treated wastewater - Spain	Campos-Mañas et al. (2017)
		180	Treated wastewater - Canada	Lee et al. (2005)
		228	Treated wastewater - Mexico	Rivera-Jaimes et al. (2018)
Antibiotic	Amoxicillin	8	Surface water - Brazil	Montagner et al. (2019)
		28	Surface water - Egypt	Abdallah et al. (2018)
		127.8	Surface water - Greece	Alygizakis et al. (2006)
		2720	Surface water - China	Yin et al. (2010)

Continuation

		0.001	Drinking water - Malaysia	Mohd Nasir et al. (2019)
		140	Raw wastewater - Germany	Savin et al. (2020)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
		328.1	Raw wastewater - Greece	Papageorgiou et al. (2019)
		26.6	Treated wastewater - Greece	Papageorgiou et al. (2019)
		258	Treated wastewater - Spain	Gros et al. (2013)
		1230	Treated wastewater - USA	Oppenheimer et al. (2011)
		2038	Treated wastewater - Egypt	Abdallah et al. (2018)
	Ciprofloxacin	3.91	Surface water - Portugal	Reis-Santos et al. (2018)
		28.8	Surface water - India	Sharma et al. (2016)
		30.5	Surface water - China	Yang et al. (2017)
		278	Surface water - Canada	Petrović et al. (2014)
		0.6669	Drinking water - Malaysia	Mohd Nasir et al. (2019)
		5	Drinking water - India	Sharma et al. (2016)
		64.5	Raw wastewater - China	Yang et al. (2017)
		147	Raw wastewater - Spain	Gros et al. (2013)
		406	Raw wastewater - Greece	Papageorgiou et al. (2016)
		600	Raw wastewater - Canada	Guerra et al. (2014)
		720	Raw wastewater - China	Li et al. (2009)
		4373.6	Raw wastewater - Portugal	Pereira et al. (2015)
		11.4	Treated wastewater - China	Yang et al. (2017)
		28.2	Treated wastewater - Canada	Petrović et al. (2014)
		73.3	Treated wastewater - China	Li et al. (2009)
		200	Treated wastewater - Canada	Guerra et al. (2014)
		445	Treated wastewater - Spain	Gros et al. (2013)
		499	Treated wastewater - Greece	Papageorgiou et al. (2016)
		825	Treated wastewater - Spain	Campos-Mañas et al. (2017)
		1224.7	Treated wastewater - Portugal	Pereira et al. (2015)
	Trimethoprim	1.63	Surface water - China	Xu et al. (2019)
		2.3	Surface water - Spain	Moreno-González et al. (2014)

Continuation		8.1	Surface water - Canada	Petrović et al. (2014)
		9.46	Surface water - Spain	López-Serna et al. (2012)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
		12	Surface water - United Kingdom	Ashton et al. (2004)
		21.89	Surface water - Portugal	Palma et al. (2020)
		27.4	Surface water - China	Yang et al. (2017)
		72	Surface water - Mexico	Rivera-Jaimes et al. (2018)
		230	Surface water - Egypt	Abdallah et al. (2018)
		<1	Drinking water - Nigeria	Ebele et al. (2020)
		1.7	Drinking water - USA	Wang et al. (2011)
		2.7	Drinking water - China	Lin et al. (2016)
		5.1	Drinking water - Holland	Houtman et al. (2014)
		13	Drinking water - Spain	Boleda et al. (2011)
		39	Raw wastewater - China	Yang et al. (2017)
		137	Raw wastewater - Spain	Veiga-Gómez et al. (2017)
		170	Raw wastewater - Greece	Papageorgiou et al. (2016)
		257	Raw wastewater - China	Wang et al. (2013)
		380	Raw wastewater - Spain	Petrovic et al. (2006)
		590	Raw wastewater - New Zealand	Kumar et al. (2019) b
		680	Raw wastewater - Mexico	Rivera-Jaimes et al. (2018)
		12.1	Treated wastewater - China	Yang et al. (2017)
		78.4	Treated wastewater - Greece	Papageorgiou et al. (2016)
		110	Treated wastewater - Spain	Petrovic et al. (2006)
		186	Treated wastewater - China	Wang et al. (2013)
		259	Treated wastewater - Canada	Petrović et al. (2014)
		338	Treated wastewater - Mexico	Rivera-Jaimes et al. (2018)
		380	Treated wastewater - New Zealand	Kumar et al. (2019) b
		449	Treated wastewater - Spain	Campos-Mañas et al. (2017)
		558	Treated wastewater - USA	Scott et al. (2018)
		2738	Treated wastewater - Egypt	Abdallah et al. (2018)

Continuation	Erythromycin	61	Surface water - Egypt	Abdallah et al. (2018)
		65.1	Surface water - Spain	Moreno-González et al. (2014)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
		292	Surface water - Canada	Petrović et al. (2014)
		645	Surface water - China	Yang et al. (2017)
		1770	Surface water - Croatia	Ivešić et al. (2017)
		0.03	Drinking water - Canada	Kleywegt et al. (2011)
		2	Drinking water - Spain	Boleda et al. (2011)
		2	Drinking water - Taiwan	Yang et al. (2014)
		58.6	Raw wastewater - South Africa	Faleye et al. (2019)
		92	Raw wastewater - Canada	Guerra et al. (2014)
		130	Raw wastewater - Spain	Petrovic et al. (2006)
		135	Raw wastewater - Greece	Papageorgiou et al. (2016)
		785.2	Raw wastewater - United Arab Emirates	Semerjian et al. (2017)
		6910	Raw wastewater - China	Yang et al. (2017)
		63.7	Treated wastewater - USA	Scott et al. (2018)
		96	Treated wastewater - Canada	Guerra et al. (2014)
		150	Treated wastewater - Spain	Petrovic et al. (2006)
		275	Treated wastewater - Egypt	Abdallah et al. (2018)
		319	Treated wastewater - Spain	Campos-Mañas et al. (2017)
		541.2	Treated wastewater - United Arab Emirates	Semerjian et al. (2017)
		3200	Treated wastewater - China	Yang et al. (2017)
	Roxithromycin	0.27	Surface water - China	Xu et al. (2019)
		28	Surface water - Japan	Managaki et al. (2007)
		294	Surface water - China	Yang et al. (2017)
		0.12	Drinking water - Canada	Kleywegt et al. (2011)
		0.9	Drinking water - China	Sun et al. (2015)
		1.02	Drinking water - China	Jiang et al. (2019)
		2.7	Drinking water - China	Lin et al. (2016)
		4.86	Raw wastewater - Greece	Papageorgiou et al. (2019)

Continuation

Therapeutic class	Compound	Concentration (ng/L)	Environment - Contry	Reference
		22	Raw wastewater - New Zealand	Kumar et al. (2019) b
		25.3	Raw wastewater - China	Li et al. (2009)
		99.4	Raw wastewater - China	Yang et al. (2017)
		110	Raw wastewater - Germany	Savin et al. (2020)
		122	Raw wastewater - China	Zhang et al. (2019)
		329.55	Raw wastewater - China	Hu et al. (2018)
		404	Raw wastewater - China	Yan et al. (2013)
		1275.6	Raw wastewater - South Africa	Faleye et al. (2019)
		3	Treated wastewater - New Zealand	Kumar et al. (2019) b
		4.25	Treated wastewater - Greece	Papageorgiou et al. (2019)
		14.2	Treated wastewater - China	Li et al. (2009)
		41.5	Treated wastewater - China	Yang et al. (2017)
		75	Treated wastewater - China	Zhang et al. (2019)
		130	Treated wastewater - Germany	Savin et al. (2020)
		347.5	Treated wastewater - China	Yan et al. (2013)
		443.32	Treated wastewater - China	Hu et al. (2018)
	Sulfamethoxazale	1.39	Surface water - Spain	López-Serna et al. (2012)
		2.92	Surface water - China	Xu et al. (2019)
		13.8	Surface water - Spain	Moreno-González et al. (2014)
		27.5	Surface water - India	Sharma et al. (2016)
		105.65	Surface water - Portugal	Palma et al. (2020)
		210	Surface water - China	Yang et al. (2017)
		642	Surface water - Mexico	Rivera-Jaimes et al. (2018)
		0.2345	Drinking water - Malaysia	Mohd Nasir et al. (2019)
		1.8	Drinking water - China	Lin et al. (2016)
		1.9	Drinking water - Korea	Kim et al. (2020)
		2.8	Drinking water - Spain	Boleda et al. (2011)
		2.9	Drinking water - Holland	Houtman et al. (2014)
		3	Drinking water - Taiwan	Yang et al. (2014)

Continuation

		3.49	Drinking water - India	Sharma et al. (2016)
		8.2	Drinking water - USA	Wang et al. (2011)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
		8.25	Drinking water - China	Jiang et al. (2019)
		104	Raw wastewater - Greece	Papageorgiou et al. (2016)
		217	Raw wastewater - China	Yang et al. (2017)
		450	Raw wastewater - Spain	Petrovic et al. (2006)
		713	Raw wastewater - New Zealand	Kumar et al. (2019) b
		1480	Raw wastewater - Mexico	Rivera-Jaimes et al. (2018)
		19	Treated wastewater - Egypt	Abdallah et al. (2018)
		44.1	Treated wastewater - Greece	Papageorgiou et al. (2016)
		49.4	Treated wastewater - China	Yang et al. (2017)
		264	Treated wastewater - New Zealand	Kumar et al. (2019) b
		313	Treated wastewater - Spain	Campos-Mañas et al. (2017)
		400	Treated wastewater - Spain	Petrovic et al. (2006)
		432	Treated wastewater - Canada	Petrović et al. (2014)
		695	Treated wastewater - Mexico	Rivera-Jaimes et al. (2018)
		907	Treated wastewater - USA	Oppenheimer et al. (2011)
		2080	Treated wastewater - USA	Scott et al. (2018)
	Sulfadiazine	0.91	Surface water - China	Xu et al. (2019)
		13.7	Surface water - China	Yang et al. (2017)
		75.24	Surface water - Portugal	Palma et al. (2020)
		1000	Surface water - Croatia	Ivešić et al. (2017)
		3.6	Drinking water - China	Jiang et al. (2019)
		4.54	Raw wastewater - Greece	Papageorgiou et al. (2019)
		73	Raw wastewater - China	Li et al. (2009)
		88.9	Raw wastewater - China	Yang et al. (2017)
		185	Raw wastewater - Greece	Papageorgiou et al. (2016)
		229.9	Raw wastewater - China	Yan et al. (2013)
		1109	Raw wastewater - Spain	Veiga-Gómez et al. (2017)

Continuation

		5.62	Treated wastewater - China	Yang et al. (2017)
		9.87	Treated wastewater - Greece	Papageorgiou et al. (2019)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
	Ofloxacin	16.2	Treated wastewater - China	Li et al. (2009)
		155	Treated wastewater - China	Yan et al. (2013)
		10.2	Surface water - Spain	López-Serna et al. (2012)
		22.16	Surface water - China	Xu et al. (2019)
		31.7	Surface water - Portugal	Palma et al. (2020)
		379	Surface water - China	Yang et al. (2017)
		2.42	Drinking water - China	Jiang et al. (2019)
		120	Raw wastewater - Canada	Guerra et al. (2014)
		205	Raw wastewater - China	Yang et al. (2017)
		335.9	Raw wastewater - China	Li et al. (2009)
		536	Raw wastewater - China	Zhang et al. (2019)
		845.9	Raw wastewater - United Arab Emirates	Semerjian et al. (2017)
		45	Treated wastewater - Canada	Guerra et al. (2014)
		51.9	Treated wastewater - China	Yang et al. (2017)
		220	Treated wastewater - Canada	Petrovic et al. (2014)
		331	Treated wastewater - China	Zhang et al. (2019)
		510.8	Treated wastewater - United Arab Emirates	Semerjian et al. (2017)
		556.4	Treated wastewater - China	Li et al. (2009)
		1135	Treated wastewater - Spain	Campos-Mañas et al. (2017)
	Norfloxacin	4.07	Surface water - China	Xu et al. (2019)
		18.9	Surface water - China	Yang et al. (2017)
		120	Surface water - USA	Kolpin et al. (2002)
		210	Drinking water - Brazil	Reis et al. (2019)
		< 55	Raw wastewater - Canada	Guerra et al. (2014)
		59.5	Raw wastewater - China	Li et al. (2009)
		90.5	Raw wastewater - China	Yang et al. (2017)
		203	Raw wastewater - China	Yan et al. (2013)

Continuation

		2034	Raw wastewater - China	Zhang et al. (2019)
		13.9	Treated wastewater - China	Li et al. (2009)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
		18.7	Treated wastewater - China	Yang et al. (2017)
		< 30	Treated wastewater - Canada	Guerra et al. (2014)
		30.4	Treated wastewater - China	Yan et al. (2013)
		222	Treated wastewater - Spain	Campos-Mañas et al. (2017)
		2730	Treated wastewater - China	Zhang et al. (2019)
Antifungal	Fluconazole	6.91	Surface water - China	Zhang et al. (2019)
		32	Surface water - Spain	Casado et al. (2014)
		58.9	Surface water - China	Yang et al. (2017)
		75.7	Surface water - Thailand	Juksu et al. (2019)
		230.2	Surface water - South Africa	Assress et al. (2020)
		573.8	Surface water - Brazil	Couto et al. (2020)
		583	Surface water - Brazil	Reis et al. (2019)
		170.8	Drinking water - South Africa	Assress et al. (2020)
		278	Drinking water - Brazil	Reis et al. (2019)
		58.6	Raw wastewater - China	Yang et al. (2017)
		86	Raw wastewater - Spain	Casado et al. (2014)
		102	Raw wastewater - Thailand	Juksu et al. (2019)
		250.4	Raw wastewater - Greece	Papageorgiou et al. (2019)
		9959	Raw wastewater - South Africa	Assress et al. (2020)
		72	Treated wastewater - Spain	Casado et al. (2014)
		82.7	Treated wastewater - China	Yang et al. (2017)
		101	Treated wastewater - Thailand	Juksu et al. (2019)
		166.1	Treated wastewater - Greece	Papageorgiou et al. (2019)
		309.9	Treated wastewater - South Africa	Assress et al. (2020)
		555000	Treated wastewater - USA	Scott et al. (2018)
	Miconazole	3.32	Surface water - Thailand	Juksu et al. (2019)
		13.6	Surface water - South Africa	Assress et al. (2020)

Continuation

		16.3	Surface water - China	Yang et al. (2017)
		8	Drinking water - South Africa	Assress et al. (2020)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
		1.97	Raw wastewater - China	Wang et al. (2018)
		6.3	Raw wastewater - South Africa	Huang et al. (2012)
		10	Raw wastewater - Canada	Guerra et al. (2014)
		16.7	Raw wastewater - South Africa	Assress et al. (2020)
		20	Raw wastewater - Thailand	Juksu et al. (2019)
		26	Raw wastewater - China	Yang et al. (2017)
		337.9	Raw wastewater - Belgium	Van De Steene et al. (2010)
		0.54	Treated wastewater - South Africa	Huang et al. (2012)
		1.31	Treated wastewater - China	Wang et al. (2018)
		3.24	Treated wastewater - Thailand	Juksu et al. (2019)
		3.75	Treated wastewater - China	Yang et al. (2017)
		6.1	Treated wastewater - Canada	Guerra et al. (2014)
		7.9	Treated wastewater - South Africa	Assress et al. (2020)
		35.7	Treated wastewater - Belgium	Van De Steene et al. (2010)
	Thiabendazole	2.16	Surface water - Thailand	Juksu et al. (2019)
		3.7	Surface water - Spain	Moreno-González et al. (2014)
		0.263	Raw wastewater - China	Wang et al. (2018)
		0.91	Raw wastewater - China	Yang et al. (2017)
		0.91	Raw wastewater - China	Yang et al. (2017)
		2.77	Raw wastewater - Portugal	Santos et al. (2013)
		7.1	Raw wastewater - Thailand	Juksu et al. (2019)
		26	Raw wastewater - Canada	Guerra et al. (2014)
		0.321	Treated wastewater - China	Wang et al. (2018)
		0.96	Treated wastewater - China	Yang et al. (2017)
		0.96	Treated wastewater - China	Yang et al. (2017)
		4.95	Treated wastewater - Portugal	Santos et al. (2013)
		6.2	Treated wastewater - Thailand	Juksu et al. (2019)

Continuation

		28	Treated wastewater - Canada	Guerra et al. (2014)
		113	Treated wastewater - USA	Scott et al. (2018)
		168	Treated wastewater - Spain	Campos-Mañas et al. (2017)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
Antihistamine	Loratadine	1.14	Surface water - Spain	López-Serna et al. (2012)
		6.46	Surface water - England	Burns et al. (2018)
		486	Surface water - Brazil	Reis et al. (2019)
		67	Drinking water - Brazil	Reis et al. (2019)
		330	Raw wastewater - Spain	Huerta-Fontela et al. (2010)
		8100	Raw wastewater - Colombia	Serna-Galvis et al. (2019)
		63.9	Treated wastewater - USA	Scott et al. (2018)
	Fexofenadine	180	Raw wastewater - Czech Republic	Golovko et al. (2014)
		170	Treated wastewater - Czech Republic	Golovko et al. (2014)
		17400	Treated wastewater - USA	Scott et al. (2018)
Beta-blockers	Atenolol	0.35	Surface water - China	Xu et al. (2019)
		1.3	Surface water - India	Sharma et al. (2016)
		6.2	Surface water - Spain	Robles-Molina et al (2014)
		27	Surface water - Mexico	Rivera-Jaimes et al. (2018)
		39.3	Surface water - Spain	López-Serna et al. (2012)
		50.6	Surface water - Canada	Petrović et al. (2014)
		90.5	Surface water - Portugal	Palma et al. (2020)
		470	Surface water - Spain	Huerta-Fontela et al. (2011)
		39100	Surface water - South Africa	Agunbiade e Moodley, 2014
		0.5	Drinking water - Holland	Houtman et al. (2014)
		12	Drinking water - Spain	Huerta-Fontela et al. (2011)
		30	Raw wastewater - Sweden	Bendz et al. (2005)
		80	Raw wastewater - Mexico	Rivera-Jaimes et al. (2018)
		230	Raw wastewater - Spain	Petrovic et al. (2006)
		753	Raw wastewater - New Zealand	Kumar et al. (2019) b
		1882	Raw wastewater - Greece	Papageorgiou et al. (2016)

Continuation

		2390	Raw wastewater - Spain	Huerta-Fontela et al. (2010)
		45	Treated wastewater - Mexico	Rivera-Jaimes et al. (2018)
		160	Treated wastewater - Sweden	Bendz et al. (2005)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
		237	Treated wastewater - New Zealand	Kumar et al. (2019) b
		280	Treated wastewater - Spain	Petrovic et al. (2006)
		670	Treated wastewater - Canada	Petrović et al. (2014)
		1300	Treated wastewater - Australia	Leusch et al. (2018)
		1310	Treated wastewater - USA	Oppenheimer et al. (2011)
		1564	Treated wastewater - Greece	Papageorgiou et al. (2016)
		2106	Treated wastewater - Spain	Campos-Mañas et al. (2017)
		3230	Treated wastewater - USA	Scott et al. (2018)
		9929	Treated wastewater - Spain	Huerta-Fontela et al. (2010)
	Metoprolol	0.8	Surface water - Spain	Moreno-González et al. (2014)
		3.08	Surface water - China	Xu et al. (2019)
		6.33	Surface water - Spain	López-Serna et al. (2012)
		17	Surface water - Egypt	Abdallah et al. (2018)
		26.3	Surface water - Canada	Petrović et al. (2014)
		41	Surface water - Netherlands	De Jongh et al. (2012)
		70	Surface water - Sweden	Bendz et al. (2005)
		90	Surface water - Spain	Huerta-Fontela et al. (2011)
		115.08	Surface water - Portugal	Palma et al. (2020)
		0.1	Drinking water - China	Sun et al. (2015)
		<1	Drinking water - Nigeria	Ebele et al., 2020
		1.3	Drinking water - Holland	Houtman et al. (2014)
		3.5	Drinking water - Canada	Petrović et al. (2014)
		3.98	Drinking water - China	Jiang et al. (2019)
		96	Raw wastewater - Spain	Huerta-Fontela et al. (2010)
		122	Raw wastewater - China	Wang et al. (2013)
		186	Raw wastewater - Greece	Papageorgiou et al. (2016)

Continuation

		5242	Raw wastewater - New Zealand	Kumar et al. (2019) b
		126	Treated wastewater - China	Wang et al. (2013)
		351	Treated wastewater - Spain	Huerta-Fontela et al. (2010)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
		574	Treated wastewater - Canada	Petrović et al. (2014)
		601	Treated wastewater - Greece	Papageorgiou et al. (2016)
		1089	Treated wastewater - Egypt	Abdallah et al. (2018)
		3097	Treated wastewater - New Zealand	Kumar et al. (2019) b
		6990	Treated wastewater - USA	Scott et al. (2018)
	Propanolol	2	Surface water - Spain	Moreno-González et al. (2014)
		7	Surface water - Egypt	Abdallah et al. (2018)
		10.4	Surface water - Canada	Petrović et al. (2014)
		54	Surface water - Spain	Huerta-Fontela et al. (2011)
		4	Drinking water - Holland	Houtman et al. (2014)
		4.3	Drinking water - Canada	Petrović et al. (2014)
		11	Raw wastewater - Spain	Huerta-Fontela et al. (2010)
		32.4	Raw wastewater - Greece	Papageorgiou et al. (2016)
		52.55	Raw wastewater - Greece	Papageorgiou et al. (2019)
		7.89	Treated wastewater - Greece	Papageorgiou et al. (2019)
		17	Treated wastewater - Spain	Huerta-Fontela et al. (2010)
		33.1	Treated wastewater - Greece	Papageorgiou et al. (2016)
		78.5	Treated wastewater - Canada	Petrović et al. (2014)
		187	Treated wastewater - Egypt	Abdallah et al. (2018)
		215	Treated wastewater - USA	Scott et al. (2018)
		1350	Treated wastewater - Spain	Gómez et al. (2006)
Hormone	Ethinylestradiol	1	Surface water - Luxembourg	Pailler et al. (2009)
		1.4	Surface water - France	Vulliet et al. (2011)
		2.5	Surface water - Spain	Huerta-Fontela et al. (2011)
		6	Surface water - Italy	Merlo et al. (2019)
		310	Surface water - Brazil	Sodré et al. (2007)

Continuation

		32	Drinking water - Brazil	Montagner et al. (2019)
		1.4	Raw wastewater - Malaysia	Fang et al. (2018)
		1.85	Raw wastewater - Iran	Amin et al. (2018)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
		13.34	Raw wastewater - China	Jiang et al. (2020)
		21	Raw wastewater - Italy	Marcantonio et al. (2020)
		24	Raw wastewater - Luxembourg	Pailler et al. (2009)
		34	Raw wastewater - Spain	Huerta-Fontela et al. (2010)
		40	Raw wastewater - Spain	Bizkarguenaga et al. (2012)
		0.04	Treated wastewater - Iran	Amin et al. (2018)
		< 1	Treated wastewater - Hungary	Fenyvesi et al. (2019)
		1	Treated wastewater - Malaysia	Fang et al. (2018)
		7	Treated wastewater - Spain	Huerta-Fontela et al. (2010)
		11.5	Treated wastewater - China	Jiang et al. (2020)
		15	Treated wastewater - Italy	Merlo et al. (2019)
		< 20	Treated wastewater - Italy	Marcantonio et al. (2020)
		29	Treated wastewater - Spain	Bizkarguenaga et al. (2012)
		219	Treated wastewater - Egypt	Abdallah et al. (2018)
	β Estradiol	0.2	Surface water - France	Vulliet et al. (2011)
		1.7	Surface water - Canada	Goeury et al. (2019)
		6	Surface water - Luxembourg	Pailler et al. (2009)
		7.6	Surface water - China	Tang et al. (2020)
		34	Surface water - Italy	Merlo et al. (2019)
		2510	Surface water - Brazil	Sodré et al. (2007)
		25	Drinking water - Brazil	Montagner et al. (2019)
		5	Raw wastewater - Italy	Palli et al. (2019)
		6.7	Raw wastewater - China	Ben et al. (2018)
		< 10	Raw wastewater - Italy	Marcantonio et al. (2020)
		15	Raw wastewater - Canada	Goeury et al. (2019)
		16.2	Raw wastewater - China	Tang et al. (2020)

Continuation

		22	Raw wastewater - Mexico	Gibson et al. (2007)
		23.71	Raw wastewater - China	Jiang et al. (2020)
		32	Raw wastewater - Iran	Amin et al. (2018)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
		93.9	Raw wastewater - Malaysia	Fang et al. (2018)
		102	Raw wastewater - Luxembourg	Pailler et al. (2009)
		274	Raw wastewater - Spain	Bizkarguenaga et al. (2012)
		0.8	Treated wastewater - China	Ben et al. (2018)
		< 1	Treated wastewater - Hungary	Fenyvesi et al. (2019)
		2.8	Treated wastewater - Iran	Amin et al. (2018)
		5	Treated wastewater - Italy	Palli et al. (2019)
		< 10	Treated wastewater - Italy	Di Marcantonio et al. (2020)
		22	Treated wastewater - Spain	Bizkarguenaga et al. (2012)
		23.1	Treated wastewater - China	Jiang et al. (2020)
		31	Treated wastewater - Canada	Goeury et al. (2019)
		85	Treated wastewater - Luxembourg	Pailler et al. (2009)
		85.2	Treated wastewater - Malaysia	Fang et al. (2018)
		165	Treated wastewater - Egypt	Abdallah et al. (2018)
	Estrone	0.5	Surface water - France	Vulliet et al. (2011)
		0.5	Surface water - Canada	Goeury et al. (2019)
		2.3	Surface water - USA	He et al. (2019)
		11.4	Surface water - China	Tang et al. (2020)
		12	Surface water - Luxembourg	Pailler et al. (2009)
		17	Surface water - England	Xiao et al. (2001)
		22	Surface water - Spain	Rodriguez-Mozaz et al. (2004)
		76	Surface water - Italy	Merlo et al. (2019)
		1.7	Drinking water - Canada	Yu et al. (2007)
		9	Raw wastewater - Luxembourg	Pailler et al. (2009)
		13	Raw wastewater - Italy	Di Marcantonio et al. (2020)
		21	Raw wastewater - Canada	Goeury et al. (2019)

Continuation

Therapeutic class	Compound	Concentration (ng/L)	Environment - Contry	Reference
		24.78	Raw wastewater - China	Jiang et al. (2020)
		47	Raw wastewater - Korea	Behera et al. (2011)
		62.9	Raw wastewater - China	Tang et al. (2020)
		72.7	Raw wastewater - China	Ben et al. (2018)
		78	Raw wastewater - Spain	Bizkarguenaga et al. (2012)
		80	Raw wastewater - Iran	Amin et al. (2018)
		80	Raw wastewater - Mexico	Gibson et al. (2007)
		4.7	Treated wastewater - China	Ben et al. (2018)
		6	Treated wastewater - Korea	Behera et al. (2011)
		9	Treated wastewater - Iran	Amin et al. (2018)
		< 10	Treated wastewater - Italy	Di Marcantonio et al. (2020)
		14	Treated wastewater - Luxembourg	Pailler et al. (2009)
		14.7	Treated wastewater - China	Tang et al. (2020)
		16.15	Treated wastewater - China	Jiang et al. (2020)
		39	Treated wastewater - Italy	Merlo et al. (2019)
		42	Treated wastewater - Spain	Bizkarguenaga et al. (2012)
		44	Treated wastewater - Canada	Goeury et al. (2019)
		48	Treated wastewater - Italy	Castiglioni et al. (2005)
Lipid regulator	Bezafibrate	1.5	Surface water - Canada	Petrović et al. (2014)
		3.6	Surface water - Spain	Moreno-González et al. (2014)
		4.05	Surface water - Spain	López-Serna et al. (2012)
		5	Surface water - Netherlands	De Jongh et al. (2012)
		328.02	Surface water - Portugal	Palma et al. (2020)
		1513	Surface water - Mexico	Rivera-Jaimes et al. (2018)
		3.41	Raw wastewater - Greece	Papageorgiou et al. (2019)
		51.8	Raw wastewater - Greece	Papageorgiou et al. (2016)
		1369.4	Raw wastewater - Portugal	Pereira et al. (2015)
		3105	Raw wastewater - Mexico	Rivera-Jaimes et al. (2018)
		2.75	Treated wastewater - Greece	Papageorgiou et al. (2019)

		< 15	Treated wastewater - Australia	Busetti et al. (2009)
		40.5	Treated wastewater - Canada	Petrović et al. (2014)
Continuation		42	Treated wastewater - Spain	Campos-Mañas et al. (2017)
		302.2	Treated wastewater - Portugal	Pereira et al. (2015)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
		748	Treated wastewater - Mexico	Rivera-Jaimes et al. (2018)
	Simvastatin	6	Surface water - Malaysia	Al-Qaim et al. (2014)
		< 50	Surface water - UK	Kasprzyk-Hordern et al. (2009)
		4	Raw wastewater - Canada	Miao et al. (2013)
		27	Raw wastewater - Malaysia	Al-Qaim et al. (2014)
		39.6	Raw wastewater - Greece	Kosma et al. (2014)
		60.5	Raw wastewater - Greece	Papageorgiou et al. (2016)
		115	Raw wastewater - United Kingdom	Kasprzyk-Hordern et al. (2009)
		117.5	Raw wastewater - China	Yan et al. (2013)
		2652.1	Raw wastewater - Portugal	Pereira et al. (2015)
		1	Treated wastewater - Canada	Miao et al. (2013)
		5	Treated wastewater - United Kingdom	Kasprzyk-Hordern et al. (2009)
		12	Treated wastewater - Malaysia	Al-Qaim et al. (2014)
		19.8	Treated wastewater - China	Yan et al. (2013)
		39.3	Treated wastewater - Portugal	Pereira et al. (2015)
		621	Treated wastewater - Greece	Papageorgiou et al. (2016)
	Fenofibrate	16.21	Surface water - Portugal	Palma et al. (2020)
		3.3	Drinking water - Holland	Houtman et al. (2014)
		21	Drinking water - Japan	Simazaki et al. (2015)
		93	Raw wastewater - Greece	Kosma et al. (2014)
		780	Raw wastewater - South Africa	Tete et al. (2019)
		51.3	Treated wastewater - USA	Scott et al. (2018)
		140	Treated wastewater - Greece	Andreozzi et al. (2003)
		710	Treated wastewater - South Africa	Tete et al. (2019)
Psychiatric	Fluoxetine	1.56	Surface water - China	Xu et al. (2019)

Continuation

		4.72	Surface water - Spain	López-Serna et al. (2012)
		5.3	Surface water - China	Ma et al. (2016)
		41	Treated wastewater - Spain	Campos-Mañas et al. (2017)
		43.3	Treated wastewater - USA	Scott et al. (2018)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
	Diazepam	240	Treated wastewater - Australia	Althakafy et al. (2017)
		3	Surface water - Spain	Huerta-Fontela et al. (2011)
		4.7	Surface water - Portugal	Palma et al. (2020)
		5	Surface water - Spain	Moreno-González et al. (2014)
		9	Surface water - Egypt	Abdallah et al. (2018)
		24.3	Surface water - China	Wu et al. (2015)
		33	Surface water - Germany	Ternes et al. (2001)
		335	Surface water - Brazil	Ferreira (2014)
		0.2	Drinking water - Holland	Houtman et al. (2014)
		1.9	Drinking water - China	Wu et al. (2015)
		9.5	Raw wastewater - China	Wu et al. (2015)
		49	Raw wastewater - Spain	Huerta-Fontela et al. (2010)
		< 5	Treated wastewater - Australia	Busetti et al. (2009)
		9.7	Treated wastewater - China	Wu et al. (2015)
		58	Treated wastewater - Egypt	Abdallah et al. (2018)
		140	Treated wastewater - Spain	Campos-Mañas et al. (2017)
		4770	Treated wastewater - USA	Scott et al. (2018)
	Oxazepam	0.69	Surface water - Hungary	Kondor et al. (2020)
		20	Surface water - Spain	Huerta-Fontela et al. (2011)
		22.5	Surface water - USA	Skees et al. (2018)
		40	Surface water - Germany	Hass et al. (2012)
		0.02	Drinking water - China	Wang et al. (2020)
		0.4	Drinking water - Holland	Houtman et al. (2014)
		<2	Drinking water - Nigeria	Ebele et al. (2020)
		6.52	Raw wastewater - USA	Subedi and Kannan (2015)

Continuation

		54.1	Raw wastewater - USA	Skees et al. (2018)
		82	Raw wastewater - Spain	Racamonde et al. (2014)
		100	Raw wastewater - Spain	González-Mariño et al. (2018)
		106	Raw wastewater - Czech Republic	Baker et al. (2012)
Therapeutic class	**Compound**	**Concentration (ng/L)**	**Environment - Contry**	**Reference**
		143	Raw wastewater - China	Wang et al. (2013)
		281	Raw wastewater - UK	Castrignanò et al. (2016)
		330	Raw wastewater - Spain	Huerta-Fontela et al. (2010)
		400	Raw wastewater - Sweden	Lavén et al. (2009)
		7.72	Treated wastewater - USA	Subedi and Kannan (2015)
		30	Treated wastewater - Spain	González Alonso et al. (2010)
		39	Treated wastewater - Egypt	Abdallah et al. (2018)
		59.7	Treated wastewater - USA	Skees et al. (2018)
		70	Treated wastewater - Spain	Racamonde et al. (2014)
		149	Treated wastewater - Spain	Huerta-Fontela et al. (2010)
		161	Treated wastewater - USA	Scott et al. (2018)
		168	Treated wastewater - China	Wang et al. (2013)
		540	Treated wastewater - Sweden	Lavén et al. (2009)
	Carbamazepine	1.15	Surface water - China	Xu et al. (2019)
		6.07	Surface water - China	Yang et al. (2017)
		8	Surface water - Egypt	Abdallah et al. (2018)
		13	Surface water - Spain	Huerta-Fontela et al. (2011)
		16.1	Surface water - India	Sharma et al. (2016)
		25.2	Surface water - China	Wu et al. (2015)
		82.6	Surface water - Spain	Moreno-González et al. (2014)
		90	Surface water - Mexico	Rivera-Jaimes et al. (2018)
		689.65	Surface water - Portugal	Palma et al. (2020)
		0.2	Drinking water - China	Sun et al. (2015)
		0.21	Drinking water - Canada	Kleywegt et al. (2011)
		0.65	Drinking water - China	Lin et al. (2016)

Continuation

Therapeutic class	Compound	Concentration (ng/L)	Environment - Contry	Reference
		0.67	Drinking water - Korea	Kim et al. (2020)
		<1	Drinking water - Nigeria	Ebele et al. (2020)
		1.16	Drinking water - China	Jiang et al. (2019)
		1.5	Drinking water - Sweden	Tröger et al. (2018)
		3.1	Drinking water - Holland	Houtman et al. (2014)
		5.6	Drinking water - Canada	Garcia-Ac et al. (2009)
		6.8	Drinking water - USA	Wang et al. (2011)
		7.61	Drinking water - Italy	Riva et al. (2018)
		8.7	Drinking water - Canada	Petrović et al. (2014)
		10.5	Drinking water - India	Sharma et al. (2016)
		19	Drinking water - Japan	Simazaki et al. (2015)
		11.7	Raw wastewater - China	Yang et al. (2017)
		25.9	Raw wastewater - Greece	Papageorgiou et al. (2016)
		45.2	Raw wastewater - China	Wu et al. (2014)
		85	Raw wastewater - Spain	Huerta-Fontela et al. (2010)
		290	Raw wastewater - Mexico	Rivera-Jaimes et al. (2018)
		400	Raw wastewater - Spain	Petrovic et al. (2006)
		589	Raw wastewater - New Zealand	Kumar et al. (2019) b
		14.2	Treated wastewater - China	Yang et al. (2017)
		34.5	Treated wastewater - China	Wu et al. (2014)
		101.7	Treated wastewater - Greece	Papageorgiou et al. (2016)
		110	Treated wastewater - Spain	Huerta-Fontela et al. (2010)
		188	Treated wastewater - Mexico	Rivera-Jaimes et al. (2018)
		261	Treated wastewater - Spain	Campos-Mañas et al. (2017)
		303	Treated wastewater - Canada	Petrović et al. (2014)
		342	Treated wastewater - Egypt	Abdallah et al. (2018)
		360	Treated wastewater - Spain	Petrovic et al. (2006)
		691	Treated wastewater - New Zealand	Kumar et al. (2019) b

Conclusion

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