UNIVERSIDADE FEDERAL DE MINAS GERAIS
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Carolina Rodrigues dos Santos

ENVIRONMENTAL IMPLICATIONS OF TRACE ORGANIC COMPOUNDS AND THEIR REMOVAL BY CONFIGURATIONS OF GRANULAR ANAEROBIC MEMBRANE BIOREACTORS

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"Environmental Implications Of Trace Organic Compounds And Their Removal By Configurations Of Granular Anaerobic Membrane Bioreactors"

CAROLINA RODRIGUES DOS SANTOS

Tese defendida e aprovada pela banca examinadora constituída pelos Senhores:

Profa Miriam Cristina Santos Amaral Moravia

Profa Lucilaine Valeria de Souza Santos - Coorientadora

Prof. Eduardo Lucas Subtil

Prof. Tiago José Belli

Profa Luzia Sergina de França Neta

Profa Ann Honor Mounteer

Aprovada pelo Colegiado do PG SMARH por

Prof. Eduardo Coutinho de Paula Santos Amaral Moravia
Coordenador

Versão Final aprovada

Profª. Miriam Cristina
Orientadora

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LIST OF PUBLICATIONS

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DOS SANTOS, CAROLINA RODRIGUES; ROSA E SILVA, GUILHERME OTÁVIO; VALIAS, CAMILA DE FIGUEIREDO; SANTOS, LUCILAINE VALÉRIA DE SOUZA; AMARAL, MÍRIAM CRISTINA SANTOS. Ecotoxicological study of seven pharmaceutically active compounds: Mixture effects and environmental risk assessment. AQUATIC TOXICOLOGY, v. 275, p. 107068, 2024.

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RESUMO

A ocorrência de compostos orgânicos traço (TrOCs), como compostos farmacêuticos ativos (PhACs) e compostos desreguladores endócrinos (EDCs), em compartimentos aquáticos, é evidenciada em vários estudos. Muitos processos atualmente utilizados em estações de tratamento de efluentes (ETEs) são uma fonte de liberação de TrOCs no meio ambiente, devido à baixa eficiência de remoção. Isso é agravado devido aos perigos potenciais dos TrOCs aos organismos aquáticos e à saúde humana, mensurados por testes ecotoxicológicos e avaliações de risco. Dessa forma, é necessário aumentar a eficiência de remoção de TrOCs pela otimização de tratamentos biológicos, e aplicação de tecnologias mais avançadas, como os biorreatores de membranas (MBRs), que vêm mostrando eficácia para essa finalidade. É importante ressaltar que a escolha das tecnologias deve ser baseada em uma análise multicritério, uma vez que elas podem atingir um efluente de alta qualidade, mas causar impactos ao meio ambiente, como emissões de dióxido de carbono, toxicidade e riscos ecológicos, além de demandarem altos custos. Dessa forma, esse estudo investigou os PhACs em duas linhas: (1) uma revisão avaliando processos aplicados à remoção de diversos PhACs - focando na biodegradação -, incluindo a remoção dos riscos ambientais, e pegada de carbono dos processos; e (2) testes de toxicidade e riscos ambientais de PhACs pouco explorados na literatura, sozinhos e em misturas binárias e terciárias. Além disso, o estudo investigou os impactos ambientais e remoção de EDCs - focando em bisfenóis (BPs) - em três linhas: (1) uma revisão avaliando a ocorrência, toxicidade, riscos ambientais, e remoção de BPs por MBRs; (2) avaliação da remoção de bisfenol A (BPA) por um biorreator de membranas anaeróbio com lodo granular (G-AnMBR) associado à um módulo híbrido de destilação por membranas (MD) e osmose direta (FO); e (3) avaliação da remoção de BPA por um EGSB-MBR usando um módulo de ultrafiltração reciclada (UF_r). Em relação aos PhACs, a linha (1) mostrou que a biodegradação é fundamental na remoção de PhACs. Entre os compostos avaliados, os mais biodegradáveis foram paracetamol, 17β-estradiol e ibuprofeno; e das tecnologias avaliadas, lodos ativados associado à UASB teve baixa pegada de carbono e foi eficaz na remoção de PhACs mais biodegradáveis; enquanto isso, AnMBR/FO-MD foi eficiente na remoção da maioria dos PhACs e apresentou baixa pegada de carbono quando a MD utiliza calor residual. Na linha (2) foi possível verificar que os PhACs fenofibrato (FEN), loratadina (LOR) e cetoprofeno (KET) foram os mais tóxicos para *Aliivibrio fischeri*, e efeitos sinérgicos das misturas foram observados para FEN + LOR, KET + LOR e KET + FEN + LOR. Além disso, os riscos ambientais foram elevados para KET e LOR. Em relação aos EDCs, a linha (1) evidenciou altas concentrações de BPs em águas superficiais de diversos locais do mundo, inclusive compostos análogos ao BPA ainda pouco discutidos. Além disso, diversos BPs foram classificados com alto risco ambiental, principalmente em países como China, India, Portugal e Taiwan. A revisão mostrou ainda que, apesar da necessidade de mais investigações, MBR e AnMBR híbridos, e modificações em MBRs biológicos podem ser alternativas efetivas para a remoção de BPs. A linha (2) mostrou remoções do G-AnMBR/FO-MD quanto à DQO, $P\text{-}PO_4^{3-}$, $N\text{-}NH_4^+$, e BPA de 95,6, 99,6, 91 e 94,7%, respectivamente. O sistema eliminou os altos riscos ambientais e à saúde humana, e o efluente final não apresentou toxicidade. O custo estimado foi de US$ 3,91 m^{-3}. Por fim, a linha (3) mostrou remoções do EGSB-MBR usando UF_r quanto à DQO, $P\text{-}PO_4^{3-}$ e BPA de 95.1, 27, e 91,1%, respectivamente. Esse sistema também eliminou os riscos ambientais e à saúde humana, enquanto para a toxicidade do efluente final foi detectada hormesis. O custo estimado para essa tecnologia foi de US$ 0,21 m^{-3}. Dessa forma, o presente estudo contribuiu e avançou no entendimento e minimização dos impactos ambientais por meio da remoção de TrOCs.

Palavras-chave: compostos orgânicos traços; toxicidade; avaliação de risco; biorreator de membranas; lodo granular.

ABSTRACT

The occurrence of trace organic compounds (TrOCs), such as pharmaceutically active compounds (PhACs) and endocrine disrupting compounds (EDCs), in aquatic compartments has been demonstrated in several studies. Due to low removal efficiency, many processes currently used in wastewater treatment plants (WWTPs) are a source of TrOCs released into the environment. This is aggravated by the potential hazards of TrOCs to aquatic organisms and human health, measured by ecotoxicological tests and risk assessments. Therefore, it is necessary to increase the efficiency of TrOCs removal by improving biological treatments and applying more advanced technologies, such as membrane bioreactors (MBRs), which have shown efficacy for this purpose. It is important to emphasize that the choice of technologies should be based on a multicriteria analysis since they can achieve high-quality effluent but cause impacts to the environment, such as carbon dioxide emissions, toxicity, and ecological risks, in addition to demanding high costs. Thus, this study investigated PhACs in two aspects: (1) a review evaluating processes applied to the removal of several PhACs - focusing on biodegradation -, including the removal of environmental risks and carbon footprint of the processes; and (2) toxicity tests and environmental risks of PhACs little explored in the literature, alone and in binary and tertiary mixtures. In addition, the study investigated the environmental impacts and removal of EDCs - focusing on bisphenols (BPs) - in three aspects: (1) a review evaluating the occurrence, toxicity, environmental risks, and removal of BPs by MBRs; (2) evaluation of the removal of bisphenol A (BPA) by an anaerobic membrane bioreactor with granular sludge (G-AnMBR) associated with a hybrid membrane distillation (MD) and forward osmosis (FO) module; and (3) evaluation of BPA removal by an EGSB-MBR using recycled ultrafiltration (UF_r) module. Regarding PhACs, aspect (1) showed that biodegradation is essential for PhAC removal. Among the compounds evaluated, the most biodegradable were paracetamol, 17β-estradiol, and ibuprofen; and of the technologies evaluated, activated sludge associated with UASB had a low carbon footprint and was effective in removing the most biodegradable PhACs; meanwhile, AnMBR/FO-MD was efficient in removing most PhACs and presented a low carbon footprint when MD uses waste heat. In aspect (2) it was possible to verify that the PhACs fenofibrate (FEN), loratadine (LOR) and ketoprofen (KET) were the most toxic to *Aliivibrio fischeri*, and synergistic effects of the mixtures were observed for FEN + LOR, KET + LOR and KET + FEN + LOR. Furthermore, environmental risks were high for KET and LOR. Regarding EDCs, aspect (1) showed high concentrations of BPs in surface waters from several locations worldwide, including compounds analogous to BPA that are still little discussed. In addition, several BPs were classified as high environmental risk, mainly in countries such as China, India, Portugal, and Taiwan. The review also showed that, despite the need for further investigation, hybrid MBR and AnMBR, as well as modifications in biological MBRs, can be effective alternatives for BPs removal. Aspect (2) showed removals of G-AnMBR/FO-MD for COD, $P\text{-}PO_4^{3-}$, $N\text{-}NH_4^+$, and BPA of 95.6, 99.6, 91, and 94.7%, respectively. The system eliminated the high environmental and human health risks, and the final effluent presented no toxicity. The estimated cost was US$ 3.91 m^{-3}. Finally, aspect (3) showed removals of EGSB-MBR using UF_r regarding COD, $P\text{-}PO_4^{3-}$ and BPA of 95.1, 27, e 91,1%, respectively. This system also eliminated environmental and human health risks, while hormesis was detected for the final effluent toxicity. The estimated cost for this technology was US$ 0.21 m^{-3}. Thus, the present study contributed to advanced understanding and minimization of the environmental impacts by removing TrOCs.

Keywords: trace organic compounds; toxicity; risk assessment; membrane bioreactor; granular sludge.

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LIST OF ABBREVIATIONS, ACRONYMS AND SYMBOLS

3D-EEM - Three-dimensional excitation–emission matrix

A^2O - Anaerobic-anoxic-oxic

BET - Betamethasone

BPA - Bisphenol A (BPA)

BPA - Bisphenol Z

BPAF - Bisphenol AF

BPAP - Bisphenol AP

BPB - Bisphenol B

BPC - Bisphenol C

BPE - Bisphenol E

BPF - Bisphenol F

BPFL - Bisphenol FL

BPS - Bisphenol S

BPs - Bisphenols

CA - Concentration Addition

CAPEX - Capital expenditures

CAS - Conventional activated sludge

COD - Chemical oxygen demand

DEHP - Bis(2-ethylhexyl) phthalate

DIBP - Diisobutyl phthalate

DL - Design lifespan

DOC - Dissolved organic carbon

DS - Draw solution

DT - Distillate

DWEL - Drinking water equivalent level

EC_{50} - Effect concentration

EDCs - Endocrine disrupting compounds

EE2 - 17α-ethynylestradiol

LIST OF ABBREVIATIONS, ACRONYMS AND SYMBOLS

EEQ - 17β-estradiol equivalents

EGSB - Expanded granular sludge bed reactors

EMBR - Enzymatic membrane bioreactor

EoL - End-of-life

EPS - Extracellular polymeric substance

EPS - Extracellular polymeric substance

FEN - Fenofibrate

FLU - Fluconazole

FMN - Flavin Mononucleotide

FO - Forward osmosis

FS - Feed solution

GAC - Granular activated carbon

G-AnMBR - Granular anaerobic membrane reactor

G-AnOMBR-MD - Granular anaerobic membrane reactor associated with FO-MD

GHG - Greenhouse gases

GS - Granular sludge

H - Henry coefficient

HI - Hazard index

HRT - Hydraulic retention time

IA - Independent Action

ICP - Internal concentration polarization

J_{FO} - Forward osmosis flux

J_{MD} - Membrane distillation flux

K_{Bio} - Biodegradation constant

K_d - Equilibrium partitioning coefficient

KET - Ketoprofen

LC_{50} - Lethal concentration

LCA - Life cycle analysis

LIST OF ABBREVIATIONS, ACRONYMS AND SYMBOLS

LOD - Limit of detection

log K_{ow} - n-octanol/water partition coefficient

LOQ - limit of quantification

LOR - Loratadine

mAChRs - Muscarinic acetylcholine receptor

MBBR - Moving bed biofilm bioreactors

MBBR–MBR - Moving bed biofilm reactor–membrane bioreactor

MBRs - Membrane bioreactors

MD - Membrane distillation

MEC - Measured concentration

MF - Microfiltration

ML - Mixed liquor

MSP - Membrane separation processes

MT - Membrane tank

MWCO - Molecular weight cut-off

$N - NH_4^+$ - Ammoniacal nitrogen

NADH - Nicotinamide Adenine Dinucleotide

NF - Nanofiltration

NOEC - No observed effect concentration

OEC - Observed effect concentration

OMBR-MD - Osmotic membrane bioreactor with membrane distillation

OPEX - Operating expenditures

$P - PO_4^{3-}$ - Total phosphorus

PAOs - Polyphosphate accumulating organisms

PhACs - Pharmaceutically active compounds

PNEC - Predicted no-effect concentration

PRE - Prednisone

PT - Permeate

LIST OF ABBREVIATIONS, ACRONYMS AND SYMBOLS

PTFE - Polytetrafluoroethylene

RO - Reverse osmosis

ROS - Reactive oxygen species

RP - Relative potency

RQ - Risk quotient

RT - Retention time

RWW - Raw wastewater

SBR-MBR - Sequencing batch membrane bioreactor

SEC - Specific energy consumption

SIM - Selected ion monitoring

SMP - Soluble microbial products

SPC - Specific produced permeate cost

SRT - Solid retention time

TBBP - Tetrabromobisphenol A

TPs - Transformation products

TrOCs - Trace organic compounds

TSEC - Thermal specific energy consumption

TSS - Total suspended solids

TWW - Treated wastewater

UASB – Upflow anaerobic sludge blanket

UF - Ultrafiltration

UF_r - Recycled ultrafiltration

UT - Toxic unit

VFA - Volatile fatty acids

VSS - Volatile suspended solids

WWTPs - Wastewater treatment plants

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CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

Trace organic compounds (TrOCs), such as pharmaceutically active compounds (PhACs), and endocrine disrupting compounds (EDCs), are present in raw and treated wastewater, surface water and drinking water worldwide (Dos Santos et al., 2021; Czarny-Krzyminska et al., 2023). These TrOCs can pose a severe risk to the aquatic ecosystem, even at low concentrations, due to their toxic potential (Liu et al., 2011; Sieratowicz et al., 2011; Vestel et al., 2016). One of the main sources of TrOCs discharge into aquatic compartments is wastewater treatment plants (WWTPs) since conventional methods employed for wastewater treatment, such as the activated sludge process and upflow anaerobic sludge blanket reactors, may not guarantee an efficient removal of TrOCs when used individually (Czarny-Krzyminska et al., 2023).

In exchange, biological degradation has a lower cost than other treatment technologies, its application is less complex and more environmentally safe (Ungureanu et al., 2015), and it can be an efficient technology for TrOCs removal when the operating conditions are optimized for this purpose, such as hydraulic retention time, solids retention time, sludge granulation, organic loading rates, temperature, and pH (Zhu et al., 2021). The transformation and removal of TrOCs compounds in biological processes occurs through various mechanisms, such as volatilization/stripping, oxidation processes, sorption onto biosolids, and biodegradation. The efficiency of these mechanisms depends on operating conditions and TrOCs characteristics, such as biodegradability and hydrophobicity.

Granular sludge (GS) has stood out among the alternatives to improve biodegradation efficiency. Yu et al. (2001) defined sludge as granular when at least 10% of the granules are larger than 2 mm. This requires several steps: (1) transport of a cell to the surface of an uncolonized inert material or another cell; (2) initial reversible adsorption on the substrate by physicochemical forces; (3) irreversible adhesion of cells to the substrate by extracellular polymeric substance (EPS) that fix the cells to the substrate; and (4) cell multiplication and the development of stable granules (Lim and Kim, 2014; Show et al., 2020). Compared to floccular sludge, the larger size of GS promotes a denser structure, greater sedimentation characteristics, and greater filtration capacity (Jing-Feng et al., 2012). Thus, studies have shown greater retention of specific microorganisms by GS, which can more easily degrade recalcitrant compounds, such as TrOCs (Fan et al., 2022; Arias et al., 2018a; Queiroz et al., 2012).

Furthermore, the biological removal of TrOCs can be improved when associated with advanced technologies, such as membrane bioreactors (MBRs), which have been applied to the treatment of wastewater containing TrOCs with high performances (Faria et al., 2020; Lastre-Acosta et al., 2020; Asif et al., 2020). MBRs integrate aerobic or anaerobic biological treatment with membrane separation processes, and the high efficiency of solids retention by membranes contributes to a higher biomass concentration, greater biodiversity, and solid retention time (SRT) in MBRs compared with activated sludge, for example. Thus, the feed/microorganism ratio is lower, and the efficiency in TrOCs removal can be high (Sipma et al., 2010). Besides biological degradation, the high SRT contributes to TrOCs adsorption onto the sludge (Verlicchi et al., 2012). Furthermore, membranes can act as a physical barrier to TrOCs, mainly more selective membranes, such as reverse osmosis (RO), nanofiltration (NF), forward osmosis (FO), and membrane distillation (MD). However, some conditions may limit MBRs application, such as not removing recalcitrant TrOCs with smaller molar masses, energy demand for aerobic MBRs, membrane fouling, and costs (Grandclément et al., 2017). Thus, several configurations of MBRs have been studied for TrOCs removal, seeking to overcome these challenges (Ricci et al., 2021; Arcanjo et al., 2022).

The choice of treatment technologies aimed at removing TrOCs should be based on a multicriteria analysis since the processes can achieve a high-quality effluent but cause impacts to the environment, such as consumption of resources and energy, carbon dioxide (CO_2) emissions and generation of waste (Takeshita et al., 2020). Thus, carbon footprint assessment is fundamental in choosing more environmentally safe treatment technologies, reducing the environmental imbalance and process costs. Furthermore, wastewater treatment technologies may have high TrOCs removals but not remove the toxicity and environmental and human health risks related to them (García-Galán et al., 2016; Beretsou et al., 2020; Pretali et al., 2020). Thus, the evaluation of TrOCs removal must be accompanied by ecotoxicological tests and risk assessment to guarantee the removal of adverse effects on the environment and health. The risk assessment considers the concentration values of pollutants in aquatic compartments and their toxicity values. Thus, the environmental and human health risk classifications can determine whether the treated wastewater is safe.

To assess the environmental risks related to TrOCs and other pollutants in aquatic compartments, toxicity tests are essential. Toxicity tests are laboratory analyses that use living organisms to quantify or qualify a sample's toxic effect after a specific exposure time. Physical and chemical analyses for monitoring the water and wastewater cannot measure the impact caused by TrOCs on the ecosystem since only biological systems can detect toxic effects

(Connon et al., 2012). Also, the mixture of TrOCs present in natural ecosystems is inevitable, which can cause an increase in toxicity (synergistic effect) or a reduction in toxicity (antagonistic effect). Therefore, toxicity tests measuring the dangers of mixing between TrOCs better represent what happens in the ecosystem.

In addition to toxicity and risks, the cost of technologies is a critical factor for application, especially on a large scale. Thus, studies have sought to develop more economically viable MBR configurations, mainly through increasing permeate flux and using lower-cost materials (Siagian et al., 2023; Ugarte et al., 2022). In this context, recycled membranes have emerged. It consists of reusing end-of-life (EoL) membranes, which would otherwise be discarded due to loss of performance in the filtration processes. This can be made possible by converting membranes, usually from RO or NF, using the chemical conversion technique through oxidative attack, which removes the selective dense layer made of aromatic polyamide and produces a porous membrane, such as recycled ultrafiltration (UF_r) (Coutinho de Paula and Amaral, 2017; Lawler et al., 2012a).

In this context, measuring the environmental impacts of TrOCs and selecting the best routes to remove these compounds in wastewater treatment can be complex. Thus, this study aims to fill in some gaps about the occurrence, toxicity, and risks of PhACs and EDCs. Besides, it aims to evaluate technologies for the removal of TrOCs through a granular anaerobic membrane reactor associated with FO-MD (G-AnOMBR-MD) and granular anaerobic membrane reactor associated with UF_r (EGSB-MBR) in sewage treatment.

1.2 JUSTIFICATION

The selection of the more efficient treatment routes for the TrOCs removal should be based on studies that fully understand the ecological aspects, considering the removal efficiency of these compounds, the toxicity and risks related to them, and the environmental impacts of treatment technologies, especially regarding the waste generation and atmospheric emissions. In this sense, a preliminary analysis of the environmental risks and the carbon footprint of the technologies and their impacts is essential, seeking to adopt "environmentally friendly" practices in wastewater treatment and contributing to reducing environmental imbalance (Zouboulis and Peleka, 2019).

In this context, this study proposes themes that can contribute to scientific knowledge about aquatic ecotoxicology, including the toxicity of TrOCs and their mixtures and the reduction of environmental impacts by wastewater treatment technologies. For the ecotoxicological studies,

seven pharmaceutically active compounds (PhACs) were selected, found in raw and treated effluents, surface water, and drinking water worldwide (Herrero et al., 2012; Papageorgiou et al., 2016; Skees et al., 2018; Reis et al., 2019; Montagner et al., 2019; Mohd Nasir et al., 2019; Jiang et al., 2019; Assress et al., 2020). However, ecotoxicological studies are scarce for these PhACs, especially concerning their interaction and comparing the experimental effects with the toxicity prediction models.

Besides PhACs, EDCs are a recent environmental concern due to their presence in wastewater, surface water, and drinking water worldwide, which has been the subject of several studies (Czarny-Krzymińska et al.., 2022; Santos et al., 2024). Among them, the BPA is one of the most produced and consumed industrial compounds globally, which results in its presence in several aquatic compartments (Santos et al., 2024), posing serious health risks, including cancer, diabetes, brain function disorders, hormonal changes, immunodeficiency, among others (Huang et al., 2018; Prins et al., 2014). Furthermore, BPA can be highly toxic for aquatic organisms, affecting fish (Moreman et al., 2017; Staples et al., 2011), crustaceans (Jung et al., 2020; Mihaich et al., 2009), and algae (Czarny -Krzymińska et al., 2022). Despite this, no study has evaluated in detail the occurrence, toxicity and environmental risks of BPA and others BPs.

Some configurations of AnMBRs have been used for this purpose when seeking to remove TrOCs. AnMBRs are lower-cost technologies than MBRs; they also promote less sludge generation and the possibility of generating biogas as a renewable energy source, which is an important factor in the search for more sustainable technologies with a lower carbon footprint. However, some challenges still need to be overcome, such as low membrane fluxes, lower-than-expected nutrients, and specific TrOCs removal (Ricci et al., 2020; Arcanjo et al., 2021; Arcanjo et al., 2022). Thus, applying this process using anaerobic GS can be an alternative to reduce membrane fouling and improve performance in nutrients and TrOCs removal, as observed in other studies (Shen et al., 2015; Lin et al., 2023).

Furthermore, in the effort to seek more economical and sustainable alternatives, the use of recycled membranes has gained ground in recent studies (Aguilar et al., 2023; Coutinho de Paula et al., 2017; de Oliveira et al., 2020; Mota et al., 2024). Generally, discarded membrane modules are classified as inert solid waste, disposed of in landfills or incinerated, with few reuse alternatives (Lawler et al., 2012b). In this sense, thousands of tons of EoL RO membranes have been discarded annually (Grossi et al., 2021; Senán-Salinas et al., 2021). Therefore, recycling can be an alternative to environmental liability related to the increasing disposal of EoL membranes.

Given the above, this study evaluated two innovative technologies for removing TrOCs: G-AnOMBR-MD and EGSB-MBR using UF_r. The pollutants removal efficiencies, toxicity, environmental and human health risks, and costs were studied for both technologies. Therefore, the study will address topics that are at the frontier of knowledge at the national and international level, enabling (1) evaluation of the wastewater treatment technologies regarding TrOCs removal, occurrence of TrOCs in environment, environmental risks, and carbon footprint; (2) understanding the toxicity and the synergistic and antagonistic effects of the mixture between TrOCs with data hitherto scarce in the literature; (3) and apply new sewage treatment processes focused on removal of TrOCs and ecotoxicological risks.

1.3 OBJECTIVES, PREMISES AND HYPOTHESES

1.3.1 General objectives

This study aims to investigate the environmental impacts of TrOCs, namely PhACs and BPs, in aquatic compartments, and study the wastewater treatment routes for these compounds' removal, focusing on configurations of granular anerobic membrane bioreactors.

1.3.2 Specific objectives, premises, and hypotheses

The specific objectives, premises, and hypotheses of the study are presented in Table 1.

Table 1 - Specific objectives, premises, and hypotheses of the study.

ID	Premises	Hypotheses	Specific objectives	Chapter
1	PhACs present in water bodies can pose a risk to the aquatic ecosystem, and many conventional wastewater treatments are not projected to the PhACs removal.	Treatment technologies based on biodegradation pose a crucial role in PhACs removal but do not entirely remove their environmental risks, in addition to promoting other sources of environmental impacts, such as using natural resources and atmospheric emissions.	Appraise, through a critical literature review, the removal of PhACs - focusing on biodegradation -, environmental risk, and the carbon footprint of wastewater treatment technologies.	2

2	In aquatic ecosystems, PhACs are subject to interactions and modifications, capable of potentiating or reducing their toxic effect, and the toxicity prediction models do not consider interactions between the compounds.	Toxicity tests will allow the classification of PhACs according to environmental risks, and their mixtures will cause synergistic or antagonistic effects regarding toxicity prediction models.	To investigate the toxicity of seven single PhACs to the bacteria *A. fischeri* and measure the effect of binary and tertiary mixture of them, comparing the results with the models of Concentration Addition and Independent Action.	3
3	BPA and other BPs are widely used throughout the world and can reach the aquatic ecosystem, causing environmental impacts.	BPA and its BPs analogues are present in the aquatic environment at concentrations of high environmental risk, and MBRs can be effective technologies for reducing them in wastewater.	To evaluate, through a critical literature review, the occurrence of BPs in surface water worldwide, as well as their toxicity, environmental risk, and removal by MBRs.	4
4	AnMBR associated with FO-MD is efficient for removing some TrOCs, but gaps must be overcome, such as low membrane fluxes, costs, and lower-than-expected ammonia removal.	The configuration of AnMBR associated with FO-MD using granular sludge in EGSB reactor will show high efficiency in the removal of organic matter, nutrients, BPA, and will have higher fluxes, and lower costs.	Evaluate the performance of G-AnOMBR-MD regarding removal of organic matter, nutrients, and BPA from sewage, and assess the environmental and human health risk, besides the costs.	5
5	UF_r membranes are an economically and environmentally viable alternative, but their efficiency for TrOCs removal is still unknown, mainly in AnMBRs.	The configuration of AnMBR using UF_r and granular sludge will show high efficiency in BPA removal and will have lower costs and great environmental benefits.	Evaluate the performance of EGSB-MBR using UF_r regarding removal of organic matter, nutrients, and BPA from sewage, and assess the environmental and human health risk, besides the costs.	6

1.4 DOCUMENT STRUCTURE

The present study was divided into seven stages. The first of these is this Introductory Chapter. Chapter 2 comprised the study of several wastewater treatment technologies, focusing on PhACs removal by biodegradation, environmental risk assessment, and carbon footprint. The third phase, presented in Chapter 3, evaluated the experimental toxic effect of individual PhACs

and their mixtures, comparing them with toxic effects predicted by mathematical models. Chapter 4 investigated the occurrence, toxicity, environmental risks, and removal of BPs by MBRs. The fifth step, presented in Chapter 5, evaluated the G-AnMBR associated with FO-MD membranes, focusing on organic matter, nutrients, and BPA removal. The sixth section, in Chapter 6, evaluated the EGSB-MBR using UF_r membranes, focusing on organic matter, nutrients, and BPA removal. Finally, in Chapter 7, a general conclusion of the study was made.

CHAPTER 2

BIODEGRADABILITY, ENVIRONMENTAL RISK ASSESSMENT AND CARBON FOOTPRINT IN WASTEWATER TECHNOLOGIES FOR PHARMACEUTICALLY ACTIVE COMPOUNDS REMOVAL

2.1 INTRODUCTION

Pharmaceutically active compounds (PhACs) present in water bodies pose a severe risk to the aquatic ecosystem, even at low concentrations, due to the toxic potential of several PhACs. Thus, risk elimination or reduction is the focus of recent studies, mainly related to evaluating wastewater treatment technologies aiming to achieve efficient removal of micropollutants (Khasawneh and Palaniandy, 2021). Many treatment methods currently used in wastewater treatment plants (WWTPs), such as the activated sludge process and upflow anaerobic sludge blanket reactors are not adequate for removing PhACs and thus, are a potential source of release of these compounds into the environment (Subedi et al., 2017; Hu et al., 2018). Other techniques such as advanced oxidative processes, activated carbon, nanofiltration and reverse osmosis have been used to replace or complement conventional treatments, and in this way, increase micropollutants removal efficiencies (Khanzada et al., 2020). However, these techniques often demand greater investments for implementation and higher operating costs compared to conventional treatment technologies (Zhu et al., 2021). In addition, they are typically more complex and can promote other environmental impacts, such as the generation of even more dangerous and difficult-to-dispose by-products, often not carefully monitored.

Since biological degradation has a lower cost than other treatment technologies, its application is less complex and more environmentally safe (Ungureanu et al., 2015), it is seen as a key technologies for the removal of PhACs. Operational conditions, such as hydraulic retention time, solids retention time, sludge granulation, organic loading rates, temperature, and pH, have been optimized to increase the biodegradation efficiency of even recalcitrant PhACs (Zhu et al., 2021).

Biological processes, the core of most WWTPs, have been demonstrated to remove some PhACs to a significant extent (Zhu et al., 2021) and act as a barrier to the discharge of these PhACs into the ecosystem. The transformation and removal of these compounds in biological processes can occur in multiple ways, including, but not limited to, volatilization/stripping, oxidation processes, sorption onto biosolids, and biodegradation (including biotransformation – partial biodegradation, and biomineralization – complete biodegradation).

Volatilization and stripping take place mostly in the aerobic part of a WWTP. It is relevant mainly for the removal of volatile compounds and depends on the vapor pressure of the PhAC in the liquid represented by the Henry coefficient (H), and its hydrophobicity (Besha et al., 2017). Due to the low PhAC's Henry constants (usually lower than 10^{-5} atm m^3 mol^{-1}), abiotic transformations, such as volatilization and stripping, are normally negligible in WWTPs

(Nguyen et al., 2021). Volatilization is only significant, when the Henry coefficient is between 10^{-2} and 10^{-3} atm m³ mol^{-1} (Larsen et al., 2004). Volatilization and stripping are negligible also for polyhydroxyalkanoates (PHAs) (Larsen et al., 2004). The amount of compound stripped or volatilized can be calculated by Equation 1.

$$B_{i,stripped} = C_{i,air} \cdot q_{air} \cdot Q = H \cdot C_{soluble} \cdot q_{air} \cdot Q \quad (1)$$

where $B_{i,stripped}$ (µg d^{-1}) is the amount of PhAC removed, $C_{i,air}$ (µg L_{air}^{-1}) the concentration of the PhAC in the gas phase, q_{air} (L_{air} $L_{wastewater}^{-1}$) the aeration applied per unit of wastewater treated, Q (L d^{-1}) wastewater flow rate. If the equilibrium between the aqueous-gas phase is assumed to be described by Henry's law, the PhAC concentration in the gas phase can be related to its concentration in the liquid phase ($C_{soluble}$).

The photo-degradation of PhACs can occur because WWTPs are typically run in an open atmosphere, exposing the wastewater at least in the upper layers to direct sunlight. Water in clarifiers or in open reactors are subjected to high levels of sunlight irradiation (especially during the summer), even though sunlight is attenuated by particles measured as turbidity (Zhang et al., 2008). Certain PhACs, especially those with high photo-degradation rates, may be affected by photo-transformation under optimal circumstances. Depending on the structure of PhAC, the penetration of light through the water, and the presence of other molecules and ions in the water matrix absorbing sunlight, photo-degradation may occur by direct photolysis or indirect photo-oxidation (Norvill et al., 2016). Fluorescent PhACs (e.g.: fluoroquinolone antibiotics) are commonly degraded by direct photolysis as a fraction of the photons absorbed induces chemical damage or covalent modification, a mechanism known as photo-bleaching (Norvill et al., 2016; Nguyen et al., 2021). In the top centimeters of wastewater basin, direct photolysis is more favorable (Norvill et al., 2016). The kinetics of PhACs photo-degradation are commonly described by pseudo-first order rates and are lower for conventional processes employed in WWTPs with low hydraulic retention time (HRT) in comparison with algal and stabilization ponds, with a high HRT and long exposure to sun light. Thus, photo-degradation can often be neglected in WWTPs that do not employ ponds as operational units. Otherwise, such as in photobioreactors, where UV light is employed at high intensity, photo-degradation starts to play a major role on the overall PhACs removal (Gros et al., 2010).

Besides, many PhACs in wastewater can absorb onto the lipid structure of bacterial community and onto the fat fraction of the wastewater sludge through hydrophobic interactions (e.g., aromatic groups and aliphatic). Furthermore, they can adsorb onto negatively charged polysaccharide structures on the outside of bacterial cells through electrostatic interactions

(e.g., amino groups) (Radjenović et al., 2007). The extent to which these PhACs are sorbed depends on (i) the characteristics of the sludge (e.g., biomass structure and particle size); (ii) the physicochemical properties of the PhACs (e.g., hydrophobicity, electrostatic interactions, dissociation, etc.); and (iii) the operating conditions (e.g., temperature, pH, ionic strength). The equilibrium partitioning (K_d) of a PhAC – the ratio between its equilibrium concentration in the aqueous and solid phases, can be used to assess the extent by which each PhAC is sorbed onto the sludge. Equation 2 shows how the K_d (L kg^{-1}) can be expressed, where C_{sorbed} (µg L^{-1}) is the sorbed PhAC concentration, x_{ss} (kg L^{-1}) is the concentration of the suspended solid in the raw wastewater, the primary or secondary sludge, and $C_{soluble}$ (µg L^{-1}) the soluble PhAC concentration.

$$K_d = \frac{C_{sorbed}}{x_{ss}\, C_{soluble}} \quad (2)$$

Previous studies have reported K_d values for the sorption of several PhACs to various primary, activated, and digested sludges (Blair et al., 2015). Recently, awareness has been raised towards the methodology used to estimate K_d, examples include the use of PhACs concentrations in the range of µg L^{-1} to ng L^{-1}, to match the range of which they are found in wastewaters, and the use of isotherms instead of a single point experiment (Stevens-Garmon et al., 2011). Besha et al. (2017) summarized the K_d values for different PhACs in WWTPs and showed that values lower than 500 L/kg leads to minimal sorption. Furthermore, they linked low K_d values to log K_{ow} greater than 4. Generally, K_d is slightly higher in the primary sludge than in the activated sludge. This fact can be explained by their higher concentration of PhACs in the primary sludge and presence or absence of specific ionic interaction between the sludge and the PhACs (Besha et al., 2017). Although PhACs sorption can occur, its contribution in an activated sludge system was considered insignificant compared to biodegradation. For example, sorption of antibiotic (erythromycin) was considered negligible and sorption of diclofenac has been reported to vary between negligible to 20% (Terzic et al., 2018).

Concerning biodegradation, the microorganisms such as bacteria, protozoa, fungi, and archaea are present in almost every aquatic environment and play an essential role in reducing contaminants, making them less active or their complete degradation. Thus, microbial degradation is generally the most crucial process in the mass balance among environmental transformations (Fenner et al., 2021). The biodegradation (biotransformation and biomineralization) of PhACs during biological processes are known to be linked to both primary metabolic and co-metabolic mechanisms of the microorganisms found in the mixed liquor (Tran et al., 2013). In the in primary metabolism, heterotrophic microorganisms take up

PhACs as a source of carbon and energy for cell growth. In co-metabolism, heterotrophic or autotrophic microorganisms biologically turn PhACs into a non-growth substrate in the presence of a different primary substrate (or growth substrate) (Nguyen et al., 2021). Both metabolic and co-metabolic pathways can be represented by Equations 3 and 4.

$$PhACs \xrightarrow{Microrganisms\ able\ to\ biodegrade\ PhACs} Biomass + Metabolites + CO_2 \quad (3)$$

$$PhACs \xrightarrow[COD \quad \overset{\curvearrowright}{} \quad Biomass + CO_2]{Biomass\ concentration\ in\ mixed\ liquor} Metabolites + CO_2 \quad (4)$$

Thus, there are reports on biodegradation carried out by specific degraders that could use PhACs as sources of carbon and energy to maintain cell growth (primary metabolism) and by co-metabolism as the major degradation mechanisms (Khunjar et al., 2011; Zhang et al., 2019). Nonetheless, the existence of readily biodegradable substrates, such as organic carbon or ammonia, as primary substrates, plays an important role in the biological transformation of PhACs in WWTPs, regardless of which metabolic mechanism occur. These substrates can stimulate non-specific catabolic enzymes for assimilation or biodegradation, or provide energy for biomass growth and maintenance, among other things (Nguyen et al., 2017). In summary, the PhAC biodegradation rate increases when carboxylic acids, hydroxyl groups, and carbonyl are present in its structure but decreases in the presence of halogens, aliphatic ethers, methyl groups, and ring structures. Complementarily, simple aliphatic and monocyclic aromatic compounds are readily biodegradable, while polycyclic structures are likely to be more persistent, although the aromatic substituents may increase or decrease biodegradability (Tadkaew et al., 2011). For several PhACs, biodegradation is the most effective removal mechanism (Nguyen et al., 2021). Equation 5 can be used to measure the biodegradation kinetics, where K_{Bio} (L/gMLSS/d) is the pseudo first order reaction rate constant.

$$\frac{dC}{dt} = K_{Bio}\, x_{ss}\, C_{soluble} \quad (5)$$

The interaction time between microorganisms and PhAC, characterized by the HRT, and the selection of organisms capable of transforming these compounds, characterized by the solids retention time (SRT), seems to affect K_{Bio} and the biodegradation efficiency. Different redox conditions have also great effects on PhAC biodegradation, mainly because changes in redox conditions can lead to different microbial activity and diversity as well as the enzymatic profile in the mixed liquor (Besha et al., 2017). Aerobic biodegradation tends to be the most successful, mainly due to nitrifying microorganisms' activity, while under anoxic and anaerobic conditions, favoring denitrification and biological phosphorus removal, are unlikely to provide significant

benefit to PhAC biodegradation (Suárez et al., 2010; Nguyen et al., 2021). This was reported by several authors, for example, Suárez et al. (2010) showed that biodegradation of 17β-estradiol, diclofenac and erythromycin, were higher under aerobic nitrification conditions rather than anoxic and anaerobic conditions. Diclofenac is known to be persistent in anoxic conditions (<2% biodegradation) but under aerobic conditions up to 80% of biodegradation has been reported (Suárez et al., 2010; Yang et al., 2011). However, most of biodegradation experiments are conducted under aerobic conditions, and there is only a limited number of studies on detailed anaerobic PhACs biodegradation (Kanaujiya et al., 2019). Thus, the need to determining role and mode of action of PhACs under these conditions is highlighted. Nonetheless, the interaction of several operating parameters as well as the resultant variations in microbial population composition, are likely to play a significant role in the relationship between the efficacies of PhAC biotransformation with the electron acceptor condition.

Ideally, biodegradation should be biomineralization, resulting in complete mineralization of PhACs to CO_2, H_2O, and other byproducts such as ammonium. However, in most cases, PhACs are bio-transformed to transformation products (TPs), which are either more polar, less acidic, and more readily biodegradable than their parent compounds, and in some cases may be further assimilated by other microorganisms found in the combined activated sludge or - in some cases - are even more hazardous than their parent compounds (Khunjar et al., 2011). Furthermore, although serious efforts have been put into the detection and identification of TPs (Nguyen et al., 2021), the information about the impact and the risks associated with TPs are still limited. This is mainly due to the challenges that analytical methods must overcome, such as the lack of available pure reference analytical standards and fast analytical methods for their detection and quantification of TPs in wastewater, a complex matrix with analytes in extremely low concentrations (Yin et al., 2017).

Anyway, it is also essential to consider that among the several factors that influence biodegradation, the concentration of the relevant contaminants is crucial. PhACs are generally present at low concentrations in the aquatic environment. In this way, the challenge is even greater, as biodegradation by abundant and specialized microorganisms with targeted and efficient enzymes becomes less competitive, even for fully dissolved contaminants (Stadler and Love, 2019; Fenner et al., 2021).

Therefore, in this review, the recent advances in biodegradation technologies for the removal of 18 selected PhACs due to their potential to promote high environmental risk were evaluated. The present study assessed which treatment technologies are effective in eliminating or

reducing environmental risks related to these PhACs together with their carbon footprint. It is the first review assessing the biodegradation of selected PhACs with a holistic approach of environmental aspects, including removing acute and chronic risks, and the carbon footprint associated with the biological processes. Only by understanding these processes in their entirety is it possible to determine the best means of PhACs removal, and at the same time, guarantee environmental protection.

2.2 MATERIALS AND METHODS

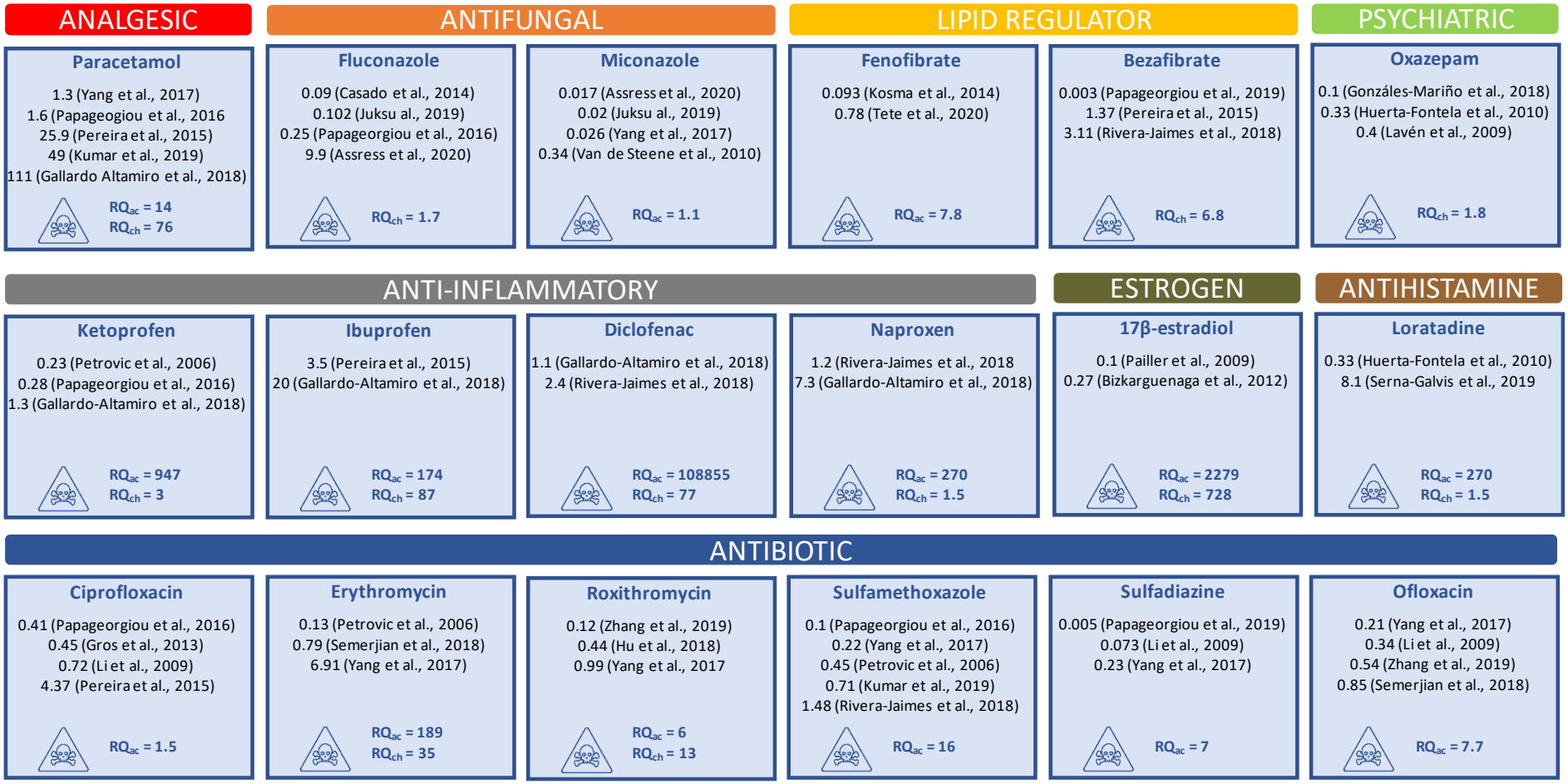
The review included the evaluation of several wastewater treatment technologies about PhACs removal efficiency, acute and chronic environmental risk, and carbon footprint. Scopus was selected as the main database for searching the literature. The 18 selected PhACs belong to eight therapeutic classes (analgesics, anti-inflammatories, antibiotics, antifungals, antihistamines, estrogen, lipid regulators, and psychiatric) and are highly consumed worldwide (Phoon et al., 2020). In addition, these PhACs have been detected in raw wastewater at concentrations that represent a high acute or chronic environmental risk (Figure 1).

The performance for selected PhACs removal by conventional activated sludge (CAS), anaerobic sludge blanket (UASB), moving bed biofilm bioreactors (MBBR), membrane bioreactors (MBRs), upflow and anaerobic-anoxic-oxic (A^2O) reactor alone or associated with other technologies was studied. The study considered the characteristics of PhACs and treatment technologies. PhACs classification in terms of biodegradability was carried out from the K_{Bio} values. Joss et al. (2006) reported that K_{Bio} < 0.1 L $gMLSS^{-1}$ d^{-1} leads to less than 20% of biodegradation, 0.1 < K_{Bio} < 10 L $gMLSS^{-1}$ d^{-1} leads to 20-90% of biodegradation and K_{Bio} > 10 L $gMLSS^{-1}$ d^{-1} leads to more than 90% of biodegradation.

Acute and chronic environmental risks were estimated for selected PhACs using the risk quotient (RQ) as shown in Equation 6, where MEC is the measured concentration, and PNEC is the ratio between acute or chronic toxicity for each PhAC and a correction factor (European Commission, 1996). For environmental risk, the classification of the European Commission (1996) was used: RQ> 1 (high risk); 0.1 ≤ QR ≤ 1 (medium risk); 0.01 ≤ QR < 0.1 (low risk); and RQ < 0.01 (negligible risk).

$$QR = \frac{MEC}{PNEC} \quad (6)$$

Figure 1 - Concentrations (μg L^{-1}) in raw wastewater and acute (RQ_{ac}) and chronic (RQ_{ch}) risks for selected PhACs.



The PhACs selected in this study were separated by therapeutic class. Concentration values (μg L^{-1}) of these PhACs in raw wastewater are shown in ascending order, and the respective acute (RQ_{ac}) and chronic (RQ_{ch}) environmental risks are also shown. Risks were calculated considering the concentration values and ecotoxicological data (see supplementary material) of the PhACs (European Commission, 1996). Risks greater than 1 are considered high (European Commission, 1996).

For each PhAC not achieving a reduction of acute and chronic risks during treatment, the maximum concentration that did not promote risk (low or negligible risks (RQ < 0.1)) in treated wastewater was calculated. The minimum removal efficiency that the technologies should achieve for risk elimination was also calculated based on the maximum concentration.

In addition to the environmental risk assessment, the carbon footprint is fundamental in choosing environmentally safer treatment technologies. Therefore, the environmental impact, focusing on CO_2 emission, was assessed for the wastewater treatment technologies that achieved low or negligible acute and chronic environmental risk related to PhACs in treated effluents. Carbon footprint (kg of CO_2 emitted per m^3 of effluent) was based on the methodology proposed by the International Energy Agency (IEA, 2015), which considers 725g of CO_2 per kWh for fossil fuel use. However, it is essential to note that this study considered the worst-case scenario (fossil fuel use). In addition, emissions were measured only for the operation phase of WWTPs, considering energy requirement values from the literature, which may differ depending on the applications of these technologies. The IEA (2018) also highlights that the estimate per kWh should be used with caution due to problems relating to electricity efficiencies for some locations.

2.3 RESULTS AND DISCUSSION

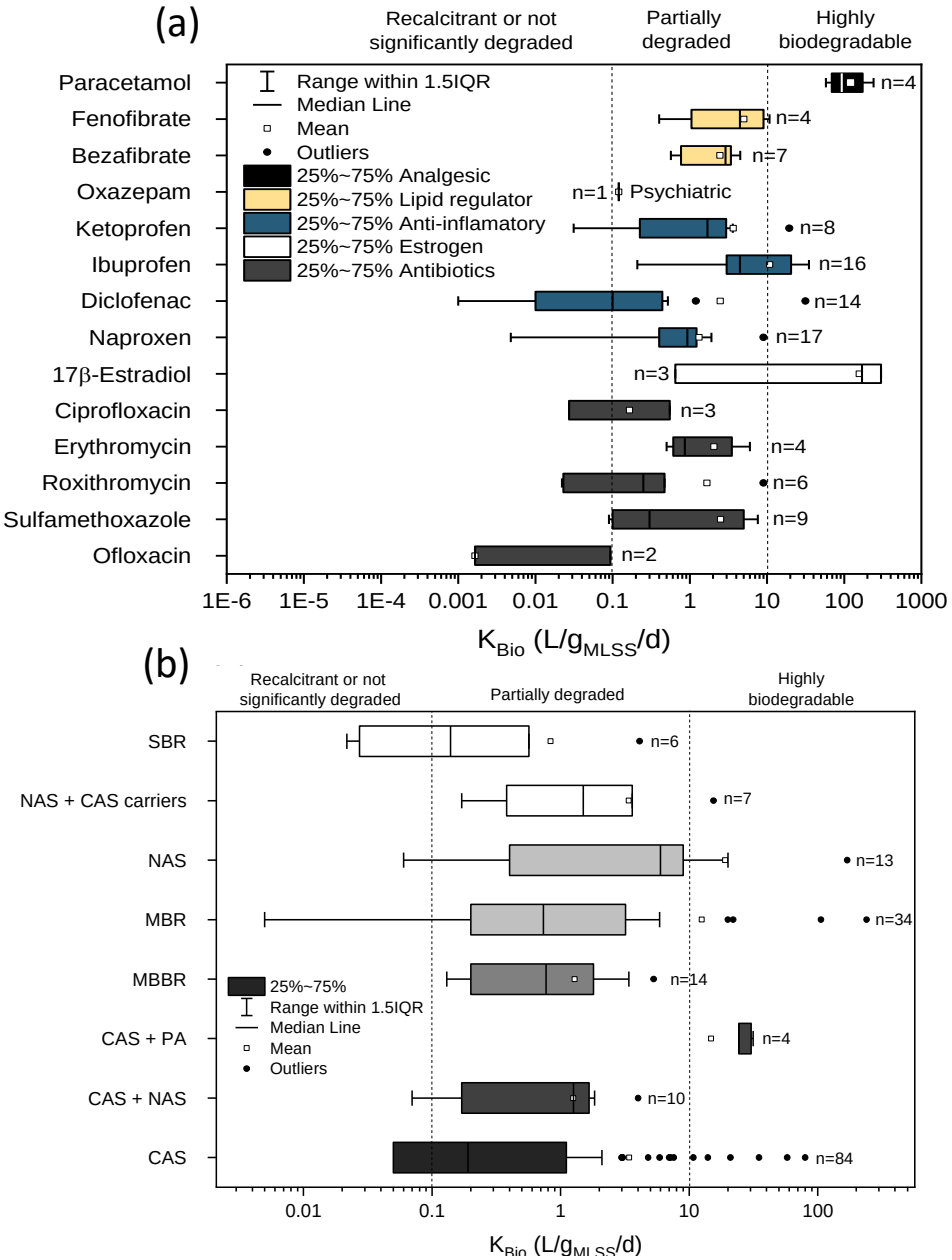
2.3.1 Biodegradation and environmental risks for selected PhACs

2.3.1.1 Activated sludge

In general, PhACs removal by CAS depends mainly on their biotransformation and sorption (Sipma et al., 2010). In most CAS, the photo-transformation contribution depends on the sunlight penetration (Zhang et al., 2008). For a better comparison, the K_{Bio} values for the selected PhACs are summarized in Figure 2a. Considering only the values obtained for CAS and discarding the negative values, K_{Bio} ranged from 0.001 L $gMLSS^{-1}$ d^{-1} (diclofenac, (Falås et al., 2012)) to 80 L $gMLSS^{-1}$ d^{-1} (paracetamol, (Joss et al., 2006)). If classified in terms of their biodegradability, the descending order PhACs would be: paracetamol > ibuprofen > fenofibrate (considered of high biodegradability, K_{Bio}> 10 L $gMLSS^{-1}$ d^{-1}) > sulfamethoxazole > bezafibrate > naproxen > erythromycin (partially degraded compounds, 0.1 < K_{Bio} < 10 L $gMLSS^{-1}$ d^{-1}) > 17-βEstradiol > ciprofloxacin > roxithromycin > ketoprofen > and diclofenac (recalcitrant or not significantly degraded 0.1 > K_{Bio}). Ofloxacin had a negative K_{Bio}, and data was not available for sulfadiazine, miconazole, loratadine and fluconazole. The results reinforce CAS limitation in PhACs removal as only 20% of the compounds were considered as highly

biodegradable (Figure 2a). In this context, for several PhACs, CAS did not achieve a satisfactory reduction of environmental risks, due to low-efficiency removal (Table 1). However, for paracetamol, considered an easily biodegradable PhAC, the technology achieved high removals and eliminated environmental risks (Figure 2a). The range of K_{Bio} values for several configurations of activated sludge are summarized in Figure 2b.

Figure 2 - Biological degradation constant (K_{Bio}) for (a) the PhACs selected and grouped by their therapeutic class, and (b) different biological units.



SBR: sequencing batch reactor (a variation of the CAS), CAS: conventional activated sludge, MBBR: moving bed biofilm reactor, MBR: membrane bioreactor, NAS: enriched nitrifying culture, and PA: prolonged aeration. PhACs or biological treatment technologies were classified as recalcitrant or not significantly degraded, partially degraded, and highly biodegradable, according to the KBio value. X-axes are in a log-scale and boxes represents P25% and P75%. Values adopted from Abegglen et al., 2009; Blair et al., 2015; Falås et al., 2012; Joss et al., 2006; Li and Zhang, 2010; Martínez-Alcalá et al., 2017; Plósz et al., 2010; Suarez et al., 2010; Suárez et al., 2008; Tran et al., 2009; Urase and Kikuta, 2005; Wei et al., 2019; Wick et al., 2009; Yang et al., 2011.

Associated with other technologies, such as activated carbon (AC) and MBR, activated sludge achieved removals of 99.9, 97 and 99.9% for paracetamol, fluconazole, and ibuprofen, respectively (Table 1), and the risks were low or negligible for these PhACs. Östman et al. (2019) demonstrated that fluconazole was easily removed using AC, mainly through adsorption and to a lesser extent by the biofilm formed on the grains. On the other hand, PhACs paracetamol and ibuprofen were removed mainly due to biodegradation in the MBR, which promotes long hydraulic and solids retention time (Kim et al., 2014).

It is important to consider that the hydraulic retention time (HRT) seems to have different impacts over PhACs removal and depends on the time required for half PhAC concentration removal, or PhACs half-live (t1/2) (Gros et al., 2010). Furthermore, there are cases that PhACs are actually readily biodegradable, but only hardly adsorb to the sludge flocs as a crucial step for their microbial uptake (Min et al., 2018). For these cases, increasing the HRT to promote an improved adsorption is not always possible in full-scale facilities, and alternative treatment trains should be considered to increase the overall removal efficiency. That phenomenon was reported by Min et al. (2018) for sulfamethoxazole. Other compounds, such as ciprofloxacin, was readily adsorbed and removed. Likewise, the solids retention time (SRT) has a straightforward implication on PhACs removal. Besides the adaptation of specific microorganisms responsible for PhACs degradation (enrichment of slowly growing bacteria and more diverse biocoenosis (Zhang et al., 2008)), a longer SRT would permit a higher interaction between PhACs that tend to accumulate into the sludge flocs, which also contributes to their removal (Kim et al., 2007).

The biomass concentration and food availability (food to microorganism ratio, F/M) is also an important parameter. Conditions of shortage in biodegradable organic matter (low F/M ratio) may force the microorganisms to metabolize poorly degradable compounds (Sipma et al., 2010), ultimately leading to a higher removal efficiency. The pH, on its turn, affects mainly ionizable compounds (e.g., antibiotics) and their interaction with the sludge flocs. In that case, the great contribution of medium pH would be on PhACs removal by adsorption. The influence of other parameters, like temperature and plant design, must still be better understood. For instance, higher temperatures and a plant design for enhanced carbon and nitrogen removal also seems to favor PhACs degradation, too (Verlicchi et al., 2012).

Table 1 - PhACs removal, operating conditions, and risk assessment for biological processes alone or associated with other technologies.

PhAC	RWW (ng/L)	TWW (ng/L)	Global $R_{efficiency}$ (%)	Biological processes $R_{efficiency}$ (%)	Treatment description	Reference	Operating conditions			Calculated RQ in TWW		Expected concentration in TWW (no risk)	Expected $R_{efficiency}$ (no risk) (%)
							MLSS (g/L)	SRT (d)	HRT (h)	Acute	Chronic		
Paracetamol	1611	55	96.6	96.6	CAS	Papageorgiou et al., 2016	-	-	3 - 5	$1.1 \cdot 10^{-3}$	$5.98 \cdot 10^{-3}$	-	-
	13640	417	96.9	96.9	UASB - CAS - A²O - disinfection	Bisognin et al., 2019	-	-	12	$8.34 \cdot 10^{-3}$	$4.53 \cdot 10^{-2}$	-	-
	11500	10	99.9	99.9	MBR (CAS - MF)	Kim et al., 2014	5.7	6 - 8	11	$4.98 \cdot 10^{-4}$	$3.13 \cdot 10^{-3}$	-	-
	37506	33	99.9	99.9	A²O - MBR	Son et al., 2021	7.66	8.4 - 47.8	8.7 - 17.5	$1.64 \cdot 10^{-3}$	$1.03 \cdot 10^{-2}$	-	-
	110942	1234	98.9	98.9	A²O	Gallardo-Altamirano et al., 2018	5.08	13.1	6.8	$6.14 \cdot 10^{-2}$	0.39	319.7	99.7
Fluconazole	323	9.69	97.0	31	CAS - AC	Östman et al., 2019	-	-	38	$9.69 \cdot 10^{-5}$	$1.62 \cdot 10^{-3}$	-	-
	2000	82.75	95.9	-	OMBR - MD	Ricci et al., 2021	-	-	-	$8.28 \cdot 10^{-4}$	$1.38 \cdot 10^{-2}$	-	-
Miconazole	42	25	40.5	40.5	UASB - CAS - disinfection	Subedi et al., 2017	-	-	-	$8.33 \cdot 10^{-2}$		-	-
	338	36	89.3	89.3	CAS	Van De Steene et al., 2010	-	-	-	0.12		30	-
Fenofibrate	780	710	9.0	-	CAS - AC	Tete et al., 2020	-	-	-	7.1	0.28	10	98.7
	2000	102.8	94.9	-	OMBR - MD	Ricci et al., 2021	-	-	-	1.03	$4.11 \cdot 10^{-2}$	10	99.5
Bezafibrate	104	31	70.2	70.2	IFAS - A²O	Gallardo-Altamirano et al., 2021	1.81	4	6.6	$5.85 \cdot 10^{-3}$	$6.74 \cdot 10^{-2}$	-	-

	3105	748	75.9	-	CAS - UV oxidation	Rivera-Jaimes et al., 2018	-	-	-	0.14	1.63	46	98.5
Oxazepam	573	31	94.6	94.6	CAS	Huerta-Fontela et al., 2010	-	-	3 - 9	$3.1 \cdot 10^{-3}$	0.31	10	98.3
	2000	0.81	100.0	-	OMBR-MD	Ricci et al., 2021	-	-	-	$2.7 \cdot 10^{-2}$	$8.71 \cdot 10^{-5}$	-	-
Ketoprofen	1288	737	42.8	42.8	A²O	Gallardo-Altamirano et al., 2018	5.08	13.1	6.8	24.57	$7.92 \cdot 10^{-2}$	3	99.8
	1006	144	85.7	85.7	Pre-denitrification - CAS - disinfection	Palli et al., 2019	-	-	-	4.8	$1.55 \cdot 10^{-2}$	3	99.7
	5320	52	99.0	99.0	MBR (CAS - MF)	Kim et al., 2014	5.7	6 - 8	11	$3.88 \cdot 10^{-3}$	$1.96 \cdot 10^{-3}$	-	-
Ibuprofen	1400	630	55.0	55.0	UASB - CAS - disinfection	Subedi et al., 2017	-	-	-	$4.70 \cdot 10^{-2}$	$2.37 \cdot 10^{-2}$	-	-
	20000	1638	91.8	91.8	A²O	Gallardo-Altamirano et al., 2018	5.08	13.1	6.8	0.12	$6.16 \cdot 10^{-2}$	1339	93.3
	4000	680	83.0	-	O_3/US - MBR	Prado et al., 2017	2.99	-	-	29.96	$2.12 \cdot 10^{-2}$	2.3	99.9
Diclofenac	2647	811	69.4	69.4	Pre-denitrification - CAS - disinfection	Palli et al., 2019	-	-	-	35.73	$2.53 \cdot 10^{-2}$	2.3	99.9
	5252	191	96.4	96.4	IFAS - A²O	Gallardo-Altamirano et al., 2021	1.81	4	6.6	0.42	$5.97 \cdot 10^{-2}$	45.1	99.1
Naproxen	258.8	3.95	98.5	-	A²O - MBR	Son et al., 2021	7.66	8.4 - 47.8	8.7 - 17.5	$8.76 \cdot 10^{-3}$	$1.23 \cdot 10^{-3}$	-	-
	2600	260	90.0	-	CAS - UV oxidation	Rivera-Jaimes et al., 2018	-	-	-	0.58	$8.13 \cdot 10^{-2}$	45.1	99.1
17β-estradiol	17	0.8	95.3	95.3	CAS	Amin et al., 2018	-	-	-	19.42	6.2	4.1·10-3	100.0

	19	0.1	99.5	99.5	MBBR	Amin et al., 2018	–	–	–	2.44	0.78	1.3·10-2	99.9
Loratadine	2000	0.71	100.0	-	OMBR - MD	Ricci et al., 2021	–	–	–	$2.37 \cdot 10^{-2}$	$1.34 \cdot 10^{-4}$	–	–
	247	115.7	53.2	53.2	A^2O - MBR	Son et al., 2021	7.66	8.4 - 47.8	8.7 - 17.5	$3.90 \cdot 10^{-2}$	$7.42 \cdot 10^{-3}$	–	–
Ciprofloxacin	12880	2130	83.5	70,3	Sponge-MBR - ozonation treatment	Vo et al., 2019	–	20	5 – 10	0.72	0.14	296.7	97.7
	445	147	67.0	67.0	CAS - disinfection	Gros et al., 2013	–	–	–	$4.95 \cdot 10^{-2}$	$9.42 \cdot 10^{-3}$	–	–
Erythromycin	2150	210	90.2	48.4	Sponge-MBR - ozonation	Vo et al., 2019	–	20	5 – 10	5.74	1.05	3.7	99.8
	785	541	31.1	31.1	CAS - disinfection	Semerjian et al., 2018	–	–	–	14.78	2.71	20	99.1
	443	329	25.7	25.7	CAS	Hu et al., 2018	–	–	–	1.56	3.29	10	97.7
Roxithromycin	122	75	38.5	38.5	Constructed wetland	Zhang et al., 2019	–	–	–	0.36	0.75	10	91.8
	22	3	86.4	-	Cyclic aeration stage - MBR	Kumar et al., 2019	4 – 5	12 – 20	13.5 – 19.6	$1.42 \cdot 10^{-2}$	$3 \cdot 10^{-2}$	–	–
	980	301	69.3	69.3	UASB - CAS - A^2O - disinfection	Bisognin et al., 2019	–	–	12	1.43	$9.41 \cdot 10^{-5}$	21	97.9
Sulfamethoxazale	540	6	98.9	98.9	MBR	Karaolia et al., 2017	–	30	9	$2.86 \cdot 10^{-2}$	$1.88 \cdot 10^{-6}$	–	–
	1480	695	53.0	-	CAS - UV oxidation	Rivera-Jaimes et al., 2018	–	–	–	3.31	$2.17 \cdot 10^{-4}$	21	98.6
Sulfadiazine	57	51	10.5	10.5	UASB - CAS - A^2O - disinfection	Bisognin et al., 2019	–	–	12	0.73	$1.02 \cdot 10^{-4}$	7	87.7
	73	16	78.1	-	CAS – UV disinfection	Li et al., 2009	–	–	–	0.23	$3.2 \cdot 10^{-5}$	7	90.4

Ofloxacin	281	34	87.9	87.9	UASB - CAS - A²O - disinfection	Bisognin et al., 2019	–	–	12	0.31	$1.36 \cdot 10^{-4}$	11	96.1
	360	145.9	59.5	59.5	A²O - MBR	Son et al., 2021	7.66	8.4 - 47.8	8.7 - 17.5	1.33	$5.84 \cdot 10^{-4}$	11	96.9
	536	331	38.2	38.2	Constructed wetland	Zhang et al., 2019	–	–	–	3.01	$1.32 \cdot 10^{-3}$	11	97.9

*Green area: low or negligible risk; yellow area: medium risk: red area: high risk. RWW (raw wastewater); TWW (treated wastewater); Refficiency (removal efficiency); MLSS (mixed liquor suspended solids); SRT (solids retention time); HRT (hydraulic retention time); RQ (risk quotient); CAS (conventional activated sludge) ; AC (activated carbon); UASB (upflow anaerobic sludge blanket); MBR (membrane bioreactor); MF (microfiltration); A²O (anaerobic-anoxic-oxic); OMBR (osmotic membrane bioreactor); MD (membrane distillation); IFAS (fixed film activated sludge).

Unlike CAS associated with AC and MBR, UASB-CAS achieved satisfactory removal only for paracetamol, eliminating both acute and chronic risks. Despite relatively low removals for ibuprofen and miconazole, the risks were also low. In contrast, the removals of sulfamethoxazole, sulfadiazine, and ofloxacin were 69.3, 10.5, and 87.9%, respectively, with medium or high risks. For the risk of these PhACs to be considered low or negligible, removals should be higher than 97.9, 87.7, and 96.1%, respectively (Table 1). It is essential to consider that the removal efficiency of PhACs may vary depending on the redox condition. For example, Arias et al. (2018) studied a UASB reactor followed by fixed film activated sludge (IFAS) and showed that PhACs 17β-estradiol and naproxen were considerably removed in the anaerobic reactor, while ibuprofen and erythromycin had greater removals under anoxic-aerobic conditions. In a similar way, 17β-estradiol proved to be biodegradable under nitrate-reducing conditions (Martins et al., 2018). Liu et al. (2020) also show that the redox condition influenced the biodegradation of sulfamethoxazole, which was more easily removed under aerobic conditions (75%), while ofloxacin had greater removals under anaerobic conditions (99.5%).

2.3.1.2 Anaerobic-anoxic-aerobic and cyclic aeration stage

The PhACs paracetamol, ketoprofen, ibuprofen, naproxen, sulfamethoxazole, sulfadiazine, and ofloxacin, presented medium or high risk after treatment by anaerobic-anoxic-aerobic (A^2O) or cyclic aeration stage. The removal efficiency of this technology ranged from 42.8-98.9% alone and 10.5-99.9% when combined with pre- or post-treatment. This broad variation was mainly due to the different biodegradability of evaluated PhACs. Paracetamol, for instance, had a removal of 98.9% (A^2O) and 99.9% (A^2O-MBR) (Table 1). In contrast, ketoprofen and ciprofloxacin had 42.8% (A^2O) and 53.2% (A^2O-MBR) removals, respectively. As already discussed, paracetamol is highly biodegradable, while ciprofloxacin and ketoprofen were recalcitrant or only partially biodegradable (Figure 2a). It is essential to highlight that the environmental risk was classified as medium even with the high removal of paracetamol by A^2O (Table 1). On the other hand, with post-treatment by MBR, the effluent risk was low or negligible. Hence, polishing with more advanced technologies can be needed for enable greater removal efficiencies, minimizing environmental impacts.

2.3.1.3 Membrane bioreactors

Membrane bioreactors and osmotic membrane bioreactors are biological reactors with different setup that can achieve a greater performance for PhACs removal. Their corresponding range of K_{Bio} values is summarized in Figure 2b. Risks were classified as low or negligible for most cases in which MBR was applied (Table 1). The high efficiency of solids retention by MF/UF

membranes contributes to a higher biomass concentration, greater biodiversity, and SRT in MBRs compared with CAS. Thus, the F/M ratio is lower, and the overall consequence is a higher efficiency in PhACs removal even at lower HRT, including compounds considered persistent (Sipma et al., 2010). The higher biomass concentration and SRT also favors the activity of slow growing microorganisms acting in nitrification and denitrification processes, providing a competitive advantage for organisms capable of degrading recalcitrant compounds (Zhang et al., 2008). Besides biological degradation, the high SRT also contributes to PhACs adsorption onto the sludge flocs (Verlicchi et al., 2012) ultimately resulting in an enhanced PhACs removal by MBRs. It is important to note that the influence of a MF/UF membrane is not majorly to abiotic removal pathways, such as physical retention through size exclusion. This is because MF/UF membranes has low efficiency for PhACs removal as these compounds have generally a molecular weight lower than the molecular weight cut-off (MWCO) of these membranes (Taheran et al., 2016).

As an alternative to the conventional MBRs, a setup called osmotic membrane bioreactor with membrane distillation (OMBR-MD) has been proposed for PhACs removal. In principle, OMBR-MD can be applied for PhACs removal as a combined result of the forward osmosis (FO) and membrane distillation (MD) rejection and aerobic or anaerobic biological degradation. In this context, OMBR-MD had high removal efficiencies and low risks for selected PhACs, except for fenofibrate, which had high acute risk (Table 1). The removal achieved for this PhAC was 94.9%, while the minimum for removing risks should be 99.5%. Despite the satisfactory removal achieved by system, fenofibrate has a high acute toxicity potential, which increases its environmental risk. According to Ricci et al. (2021), the OMBR-MD system presented limitations in removing fluconazole and ketoprofen due to the low anaerobic biodegradability of these PhACs. However, FO and MD membranes had a significant contribution in increasing removal. For fenofibrate, sorption contributed to removal due to increased HRT during the operation and the retention of this PhAC in the fouling layer. Finally, for loratadine removal, MD had a significant contribution due to the lower volatility of this compound (Ricci et al., 2021).

2.3.1.4 Moving bed biofilm reactors

The range of K_{Bio} values for moving bed biofilm reactors is summarized in Figure 2b. MBBRs simultaneously benefit from attached and suspended microorganisms by introducing carriers into the biological medium. For that reason, they generally have a higher PhACs degradation per unit of biomass compared with CAS and can operate with a higher loading rate (Tang et al.,

2017). Just like CAS, different operating conditions impacts the efficiency of MBBR in PhACs removal. Fatehifar et al. (2018) reported that the removal percentage increased at higher concentrations of ibuprofen and diclofenac. The HRT, which varied from 5 to 10 h, had a minor impact on diclofenac removal, whereas ibuprofen was greatly affected. The results suggested that half-life of ibuprofen was higher than that one of diclofenac requiring more time to be biodegraded. Finally, conditions of shortage in the availability of biodegradable organic matter (low F/M ratio) also forced the microorganisms to metabolize ibuprofen and diclofenac, which ultimately were removed to a greater extent. When median K_{Bio} values are compared for MBBRs (1.50 L g $MLSS^{-1}$ d^{-1}) and CAS (0.55 L g $MLSS^{-1}$ d^{-1}), it is possible to note improvements in terms of biodegradation, especially for the PhACs diclofenac (0.41 vs. 0.037 L g $MLSS^{-1}$ d^{-1} for MBBR and CAS) and ketoprofen (2.05 vs 0.16 L g $MLSS^{-1}$ d^{-1} for MBBR and CAS). Nevertheless, most compounds remain only partially removed (between 20 and 90%) by these systems.

It is essential to highlight that 17β-estradiol, even with removals of 99.5% by MBBR (Table 1), still presented high and medium risks. This is due to the high toxic potential of this estrogen (Kobayashi et al., 2021). In addition to high toxic potential, 17β-estradiol is hardly biodegradable (Figure 2a), reflecting a low removal efficiency. In this context, the removal of 17β-estradiol should be prioritized in wastewater treatment. This also reinforces the importance of evaluating the environmental risk during the treatment of wastewater with PhACs, as an indicator of the technologies performance and to define the minimum removal that must be achieved for the elimination or reduction of risks.

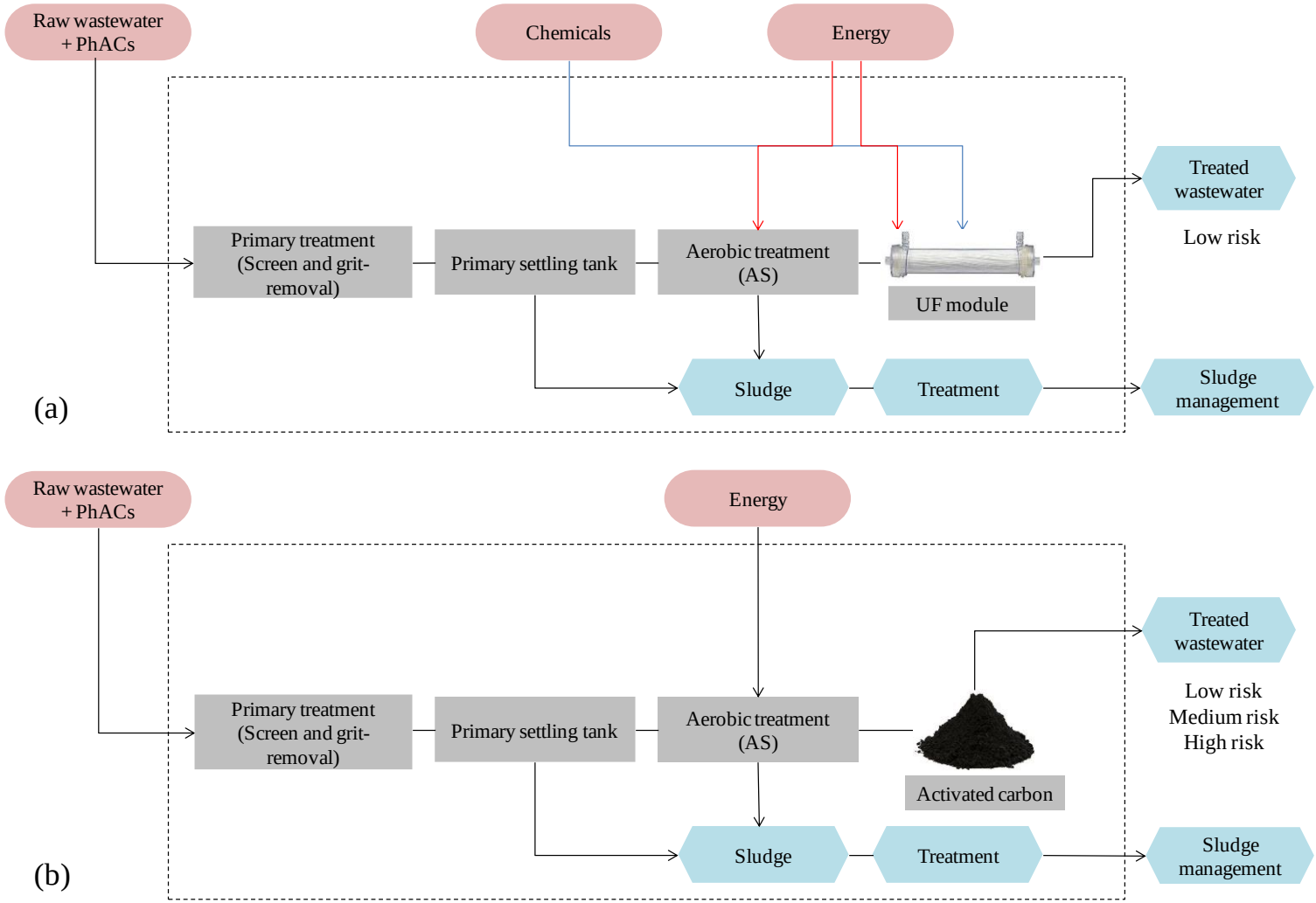
2.3.2 Environmental aspects of biological processes designed for PhACs removal

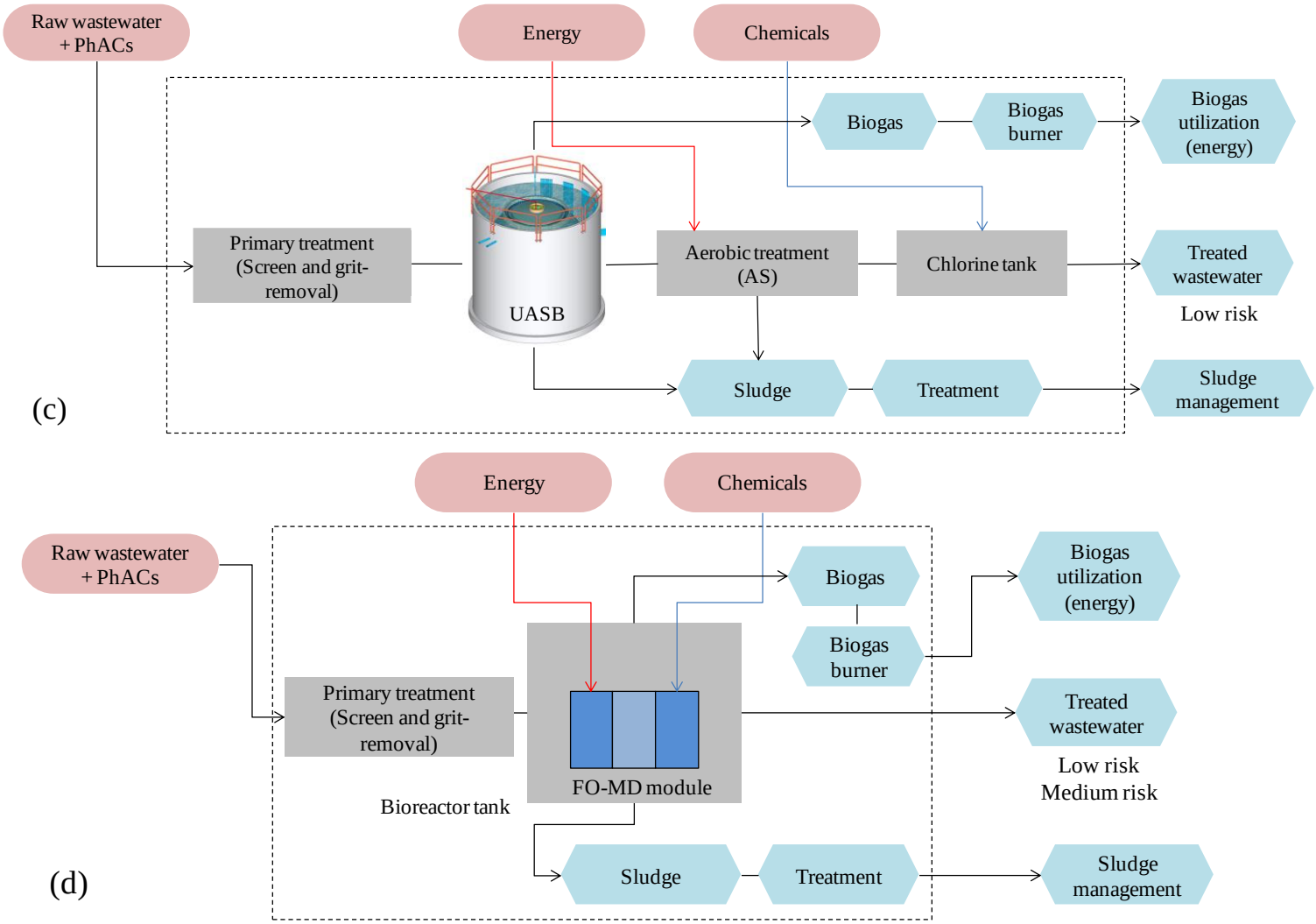
Carbon footprint assessment is fundamental in choosing more environmentally safe treatment technologies, aimed at removing PhACs. Carbon footprint measures the carbon dioxide (CO_2) emissions during this process. Footprint assessments show an imbalance between the demands of humankind compared to what the planet can renew (Zouboulis and Peleka, 2019). In this way, reducing the carbon footprint through adopting "environmentally friendly" practices in the treatment of wastewater can reduce this imbalance and reduce process costs. Through carbon footprint assessments, it is possible to understand the environmental limitations and potentials of bioprocesses, especially with the goal removing certain PhACs. Treatment technologies can cause impacts to the environment, such as consumption of resources and energy, atmospheric emissions, and generation of waste, which should also be evaluated (Takeshita et al., 2020).

Therefore, a holistic analysis of the treatment processes, and not just their removal efficiencies, is necessary.

The environmental impact, focusing on CO_2 emission, was assessed for the main wastewater treatment technologies (bioprocesses alone or associated with other technologies) that achieved low or negligible acute and chronic environmental risk related to PhACs in treated wastewater (Table 1), since they need to be environmentally viable in addition to removing risks (Takeshita et al., 2020). Thus, the possible impacts of wastewater treatments by: (a) CAS followed by UF membrane (MBR); (b) CAS with activated carbon (AC); (c) UASB reactor followed by CAS; (d) and anaerobic osmotic membrane bioreactor with membrane distillation (OMBR-MD) will be discussed. Figure 3 shows the life cycle analysis (LCA) flow diagrams with inputs and outputs for each system evaluated.

Figure 3 - LCA flow diagrams with inputs and outputs for: (a) activated sludge (AS) with ultrafiltration (UF), (b) AS with activated carbon, (c) upflow anaerobic sludge blanket (UASB) with AS, and (d) and anaerobic osmotic membrane bioreactor with membrane distillation (OMBR-MD).




Raw wastewater + PhACs
Energy
Chemicals
Biogas
Biogas burner
Biogas utilization (energy)
Primary treatment (Screen and grit-removal)
UASB
Aerobic treatment (AS)
Chlorine tank
Treated wastewater
Low risk
Sludge
Treatment
Sludge management
(c)
Energy
Chemicals
Raw wastewater + PhACs
Biogas
Biogas utilization (energy)
Biogas burner
Primary treatment (Screen and grit-removal)
FO-MD module
Treated wastewater
Low risk
Medium risk
Bioreactor tank
Sludge
Treatment
Sludge management
(d)

2.3.2.1 Conventional activated sludge

The main environmental impact related to CAS is the consumption of electricity due to the reactor aeration, with more than 40% of total plant energy demand (Chen et al., 2018). The energy consumption of CAS ranged from 0.27 – 0.67 kWh m^{-3} of effluent and CO_2 emission of 0.20 – 0.49 kg m^{-3} (Table 2). From all biological processes available, CAS is by far the most recurrent process in conventional WWTPs (224 out of 264 plants surveyed by Verlicchi et al. (2012) was equipped with a CAS unit). Therefore, WWTPs can considerably contribute to CO_2 emission, one of the leading greenhouse gases (GHG). It is essential to consider that the activated sludge alone is not efficient for removing several PhACs, as shown in Table 1. Thus, the association of CAS with other technologies for PhACs removal can further increase GHG emissions.

2.3.2.2 CAS followed by UF membrane (MBR)

According to Hao et al. (2018), for activated sludge – MBR, the energy consumption increases to 0.8 – 2.4 kWh m^{-3}, due to the driving force used in the membrane separation process, with energy representing 79.6% of the total operation costs of the MBR. Due to the high energy consumption, carbon footprint is highest for the AS-MBR system, ranged from 0.41 – 1.74 kg of CO_2 m^{-3} (Table 2). Despite the greater efficiency of PhACs removal, the MBR system increases GHG emissions.

2.3.2.3 CAS with activated carbon (AC)

AC is generally used in the activated sludge system due high adsorption potential, which increases the removal efficiencies. Tarpani and Azapagic (2018) showed that AC clearly influences the carbon footprint with an emission of 252 kg of CO_2 per 1000 m^3 of treated effluent. Awad et al. (2019) estimated a global warming potential of 954 kg of CO_2 equivalents per 1000 m^3 of treated wastewater for this type of adsorption. Despite requiring low energy for operation (necessary for mixing, dosing, and recirculating the PAC (Mousel et al., 2017)) (Table 2), the production, regeneration and disposal of AC are very energy intensive. According to Mousel et al. (2017), the energy requirement to produce 1 kg of AC can reach 57.9 kWh. In addition, incineration is the only safe way for AC disposal due to adsorbed toxic compounds. Besides, carbon footprint of activated carbon should be associated with the activated sludge system, which results in a range of 0.22 - 0.55 kg of CO_2 m^{-3}.

2.3.2.4 UASB reactor followed by CAS

The energy required for UASB operation is relatively low, it ranges from 0.01 – 0.07 kWh m^{-3} (Table 2). The anaerobic reactor is the technology with the lowest energy requirement, which is expected for this type of treatment. However, the release of dissolved CH_4 and H_2S in the effluent from UASB is a concern as it can increase GHG emissions (Chen et al., 2018). On the other hand, anaerobic digestion can generate biogas that is a renewable energy carrier. Biogas generated can be used on-site, partially, or totally supplying the energy demand of the WWTP (Sembera et al., 2019). Despite the energy benefits, to achieve satisfactory removals of PhACs (paracetamol and sulfadiazine), the UASB was combined with the activated sludge system (Table 1). The combination of the two technologies resulted in a CO_2 emission in the range of 0.21 - 0.54 kg CO_2 m^{-3}.

Table 2 - Energy requirement and calculated CO_2 emission per m^3 of the treated wastewater during operation.

	Energy requirement (kWh m^{-3})	**Reference**	**Calculated CO_2 emission (kg_{CO2} m^{-3})**
CAS	0.27	Gu et al., 2017	0.2
	0.29 - 0.67	Hao et al., 2018	0.21 - 0.49
	0.36	Mannina et al., 2020	0.26
AS-MBR	0.8 - 2.4	Hao et al., 2018	0.58 - 1.74
	0.65	Mannina et al., 2020	0.47
	0.57	Gao et al., 2022	0.41
Activated carbon	0.05 - 0.08	Kovalova et al., 2013	0.04 - 0.058
	0.05	Abegglen et al., 2009	0.04
	0.03 - 0.08	Mousel et al., 2016	0.02 – 0.058
UASB reactor	0.01 - 0.015	Mazhar et al., 2021	0.007 - 0.01
	0.03	Niwa et al., 2016	0.02
	0.07	Ji et al., 2020	0.05
OMBR-MD	0.5	Zhao et al., 2014	0.36
	0.72	Singh et al., 2021	0.52
	0.35	Ghaffour et al., 2019	0.25

2.3.2.5 Anaerobic osmotic membrane bioreactor with membrane distillation (OMBR-MD)

For this configuration of a membrane bioreactor, energy is required for the circulation pumps and the heat draw solution in the MD process (Ricci et al., 2021). For OMBR, the energy requirement is lower than in conventional MBRs since FO is not pressure driven. Therefore, FO energy consumption for circulation pumping is about 0.25 kWh m^{-3} (Zhao et al., 2014). The

same value (0.25 kWh m^{-3} for circulation pumping) can be adopted for MD (Zhao et al., 2014). MD can have an even higher energy consumption (29 kWh m^{-3} for 50ºC) due to thermal energy during operation (Zhao et al., 2014), with 21 kg of CO_2 emission per m^3. Studies show that the temperature gradient required for MD can be achieved using waste heat or solar energy (Li et al., 2018; Abusoglu et al., 2021). For example, Abusoglu et al. (2021) evaluated the district heating potentials of the WWTPs based on their biogas, electricity, and heat productions. The authors showed that based on an annual heating load of 0.9144 kW for each house in Gaziantep province (Turkey), 458 houses can be heated from the waste heat generated by GASKI WWTP. The WWTP has a daily capacity of 222,000 m^3, a capacity of hot water production of 135 tons h^{-1}, and a total annual electricity production of 8,760 GWh (Abusoglu et al., 2021). This result shows the potential for heat generation from anaerobic digestion, which can be applied to the MD thermal requirements. Without the application of waste heat or solar energy, OMBR-MD may not be environmentally advantageous due to the need for heating of the MD.

Besides, to create the osmotic pressure gradient as FO driving force, the concentration of the draw solution is an important variable. Holloway et al. (2016) observed that the greater the DS concentration in osmotic bioreactors is, the lower the energy consumption and hence, greenhouse gas emission, is.

The effluent produced by OMBR-MD can achieve high quality, including PhACs removal, with the potential of nonpotable and potable reuse (Morrow et al., 2018; Ricci et al., 2021). In addition, OMBRs have shown great potential in nutrient recovery (Li et al., 2018). Despite the relatively high energy consumption, variables such as generating water for reuse and nutrient recovery, can significantly reduce the carbon footprint of this system.

2.4 CONCLUSION

The study showed that biodegradation is fundamental in removing PhACs. The most biodegradable PhACs in descending order were paracetamol > 17β-estradiol > ibuprofen > bezafibrate > fenofibrate > ketoprofen > erythromycin > sulfamethoxazole > naproxen > roxithromycin > ciprofloxacin > diclofenac. Especially for recalcitrant PhACs, advanced processes are needed for the efficient removal of environmental risks. However, treatment technologies can have a significant carbon footprint. Of the technologies evaluated, CAS associated with anaerobic technologies, such as UASB, were satisfactory in the removal of some PhACs. In addition, they presented a low carbon footprint compared to other technologies, such as CAS-MBR. OMBR-MD proved efficient in removing the risks of PhACs and the

quality of the water produced besides having one of the smallest carbon footprints when it is possible to use waste heat or solar energy for the MD process. However, it is important that this technology is tested on a large scale for a better assessment of its applicability.

CHAPTER 3

TOXIC EFFECTS OF MIXTURED PHARMACEUTICALLY ACTIVE COMPOUNDS

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, therefore, are essential to promote health and quality of life to the population; however, the excessive use of PhACs has been a cause of concern in several countries (dos Santos et al., 2021). Due to incomplete removal at wastewater treatment plants (WWTPs), PhACs have been detected in several aquatic matrices, such as treated wastewater, surface water, and even drinking water (Reis et al., 2019; dos Santos et al., 2021).

Simultaneously, studies show that PhACs can cause adverse effects on the aquatic ecosystem, even at low concentrations (dos Santos et al., 2021). Despite the importance of physical and chemical analyses, they do not portray the impact caused by pollutants on the ecosystem. Thus, the application of ecotoxicological tests is fundamental to evaluating these effects. An acute toxicity test, in general, is a laboratory analysis that uses living organisms to quantify or qualify a sample's toxic effect after a short exposure time, promoting quicker responses (Connon et al., 2012). These tests can be evaluated under different endpoints, such as mortality, immobility, and changes in biological functions, such as luminescence (Connon et al., 2012). The results for acute toxicity are usually expressed as effect concentration (EC_{50}) or lethal concentration (LC_{50}). Besides, the most common species for toxicity tests are bacteria, algae, crustaceans, 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).

Among the test organisms, the bacteria *A. fischeri* has been appropriate for ecotoxicological studies with several PhACs. For example, Białk-Bielińska et al. (2022) evaluated the mixture of diclofenac (DIC), ibuprofen (IBU), naproxen (NAP), and sulfamethoxazole (SMZ). The authors show that for the mixture of DIC, IBU, and NAP, *A. fischeri* (30 min of exposure) was more sensitive than *Daphnia magna* (48 h). The same occurred with the DIC, IBU, NAP, and SMZ mixture. Drzymała and Kalka (2020a) also observed that the organism most sensitive to DIC was *A. fischeri*. In contrast, for SMZ, it was *Lemna minor*. Similarly, Tongur and Yıldız (2021) observed a greater sensitivity of *A. fischeri* (15 min) than *D. magna* (48 h) to Flurbiprofen. In contrast, in the same study, *D. magna* was more sensitive to Naproxen, Propranolol, and Carbamazepine. Thus, due to advantages such as short test duration and low volume requirement of samples and consumables, *A. fischeri* may be an excellent choice to evaluate the toxicity of several PhACs.

Despite the importance of these tests and considering the variety of PhACs already detected in the aquatic environment, ecotoxicological studies are still precarious or non-existent for many of these compounds. Furthermore, studies evaluating the effect of mixing PhACs are scarce. It is known that many water bodies continuously receive the discharge of raw or treated wastewater with several pollutants. Thus, PhACs are subject to interactions and modifications, capable of potentiating or reducing their toxic effects (Jacob et al., 2021). In this sense, it is essential to analyze the toxic potential of mixtures and not only individual contaminants, to represent more faithfully what occurs in natural ecosystems.

Thus, it is possible to measure the synergistic or antagonistic effects of the PhAC mixture by comparing the experimental results with toxicity prediction models. Synergism occurs when the experimental results of a mixture of chemical compounds are greater than the effects predicted by a model, while antagonism occurs when the combined, experimentally measured effects of compounds are smaller than those predicted by the models (Białk-Bielińska et al., 2011). The most used models are Concentration Addition (CA) and Independent Action (IA). These models provide an initial mathematical basis for predicting the effect of mixtures; however, it is crucial to highlight that interactions between the compounds can occur, leading to deviation from one or both models (Cedergreen, 2007).

The CA model assumes that each chemical compound in a mixture contributes, proportionally to its dose, to the toxicity of the mixture, expressed as the percentage of that dose of the compound alone that would be required to produce the given effect of the mixture. In addition, the concept of CA assumes that the components of a mixture share a common mechanism of action; that is, each component has the same specific interaction with the test organism. In this way, the substances could cause a typical toxicological response, for example, death or inhibition of reproduction (Cleuvers, 2003). In contrast, the IA model considers different actions between the components of a mixture, i.e., that toxic compounds interact with different molecular targets, resulting in a typical toxicological response, but through distinct reaction chains (Faust et al., 2003).

Therefore, experimental tests are fundamental to evaluate the real effects of mixtures and identify the accuracy of existing models. For example, Jacob et al. (2021) studied the mixture of the PhACs metformin, simvastatin omeprazole, and diazepam concerning EC_{10} for *A. fischeri*. Synergistic effects were found for the following mixtures for both CA and IA models: simvastatin-diazepam; simvastatin-omeprazole; diazepam-omeprazole; simvastatin-omeprazole-diazepam; metformin-omeprazole-diazepam; metformin-simvastatin-diazepam;

and simvastatin-omeprazole-diazepam-metformin. In addition, Godoy et al. (2019) observed that the effects of the binary mixtures' metformin-bisoprolol and metformin-ranitidine for *Daphnia similis* were greater than predicted by the IA model. The results by Jacob et al. (2021) and Godoy et al. (2019) showed that, for these cases, the models underestimated the effects of the mixtures.

Furthermore, from the toxicity results for the isolated PhACs, it is possible to calculate the environmental risks. Environmental risks are determined using risk quotients (RQ) to assess if a pollutant poses a hazard to aquatic organisms in environmental concentrations, classifying them as high, medium, low, or negligible risk (European Comission, 1996). Therefore, the risk assessment of PhACs allows identifying the most dangerous compounds whose removal from the aquatic environment should be prioritized. Due to the lack of monitoring of the release of PhACs in aquatic environments and the lack of environmental legislation related to these compounds, risk assessment is an important direction to select priority emerging compounds.

In this context, the present study evaluated the toxicity to the bacteria *A. fischeri* for seven PhACs still little explored in the literature, namely, ketoprofen (KET), fenofibrate (FEN), fluconazole (FLU), loratadine (LOR), prednisone (PRE), 17α-ethynylestradiol (EE2) and betamethasone (BET). All selected PhACs have been previously detected in seawater, an area where *A. fischeri* is commonly found (Huynh et al., 2023; Korkmaz et al., 2022; Afsa et al., 2020; Juksu et al., 2019; Peng et al., 2019; Gong et al., 2019; Nödler et al., 2014).

Notably, no studies in the literature investigate the mixture between these PhACs and, consequently, the synergistic and antagonistic effects. Thus, the results contributed to a better understanding of the interaction between these compounds. In addition, an environmental risk assessment was carried out for these PhACs by trophic level category, highlighting the RQ values for each location in which the studied PhACs were detected.

3.2 MATERIALS AND METHODS

3.2.1 Characteristics of the evaluated PhACs

The PhACs selected for the ecotoxicological studies were ketoprofen (KET), fenofibrate (FEN), fluconazole (FLU), loratadine (LOR), prednisone (PRE), 17α-ethynylestradiol (EE2) and betamethasone (BET). The choice of PhACs was based on the following criteria: the compound has already been detected in surface water, raw wastewater, treated wastewater, or drinking water (dos Santos, et al., 2021); scarcity of ecotoxicological data in the literature regarding the

compound; and high world consumption. The main properties of these PhACs are shown in Table 1.

Stock solutions of all PhACs were prepared immediately prior to toxicity analyses. Due to the different solubilities in water, the stock solutions were first prepared in methanol and then diluted in the test medium (NaCl 2%) so that the methanol content was not higher than 1% (Białk-Bielińska et al., 2011). According to the solubility of each PhAC, their 100% concentrations were: 20 mg L^{-1}, 10 mg L^{-1}, 50 mg L^{-1}, 10 mg L^{-1}, 100 mg L^{-1}, 20 mg L^{-1} e 100 mg L^{-1} for EE2, BET, KET, FEN, FLU, LOR and PRE. When necessary, the mixture was placed in an ultrasonic bath. The stock solutions were stored in a dark place at 4 °C to avoid photodegradation. In addition, controls with the maximum concentrations of solvent used were investigated in each toxicity test to verify if the addition of methanol caused toxic effects.

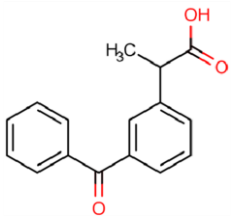
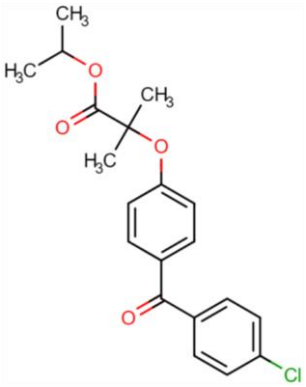
3.2.2 Effect of isolated PhACs

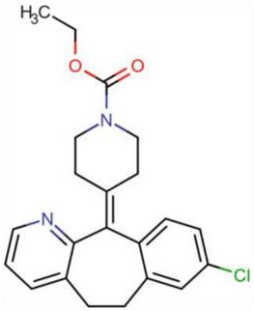
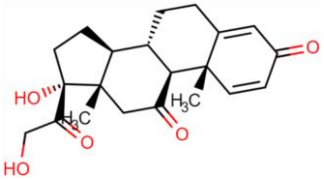
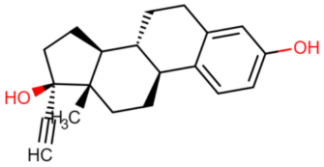
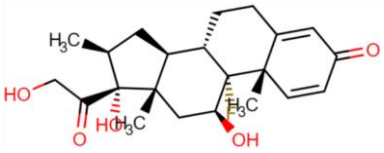
Ecotoxicological tests were carried out with the bacteria *Aliivibrio fischeri*, according to NBR 15411-3 (ABNT, 2006) and with the protocol established *by the MICROTOX* Omni Software, *version 4.1 of the MICROTOX*®® equipment. The advantages of using the *A. fischeri* as an indicator organism are the short test duration and low volume requirement of samples and consumables. Besides, the bacteria's sensitivity can be compared to fish and the microcrustacean (Pivato and Gaspari, 2006). In addition, the bacteria were chosen as a test organism due to the scarcity of studies related to this organism, which makes it challenging to measure environmental risks in a more representative and safe method. The toxic effect is determined with a software comparison between the sample dilutions and the diluent solution (control, composed of 2 NaCl 2%) concerning light emitted. 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.

The pH of the samples was verified and, when necessary, adjusted to the range of 6.0-8.5 with HCl or NaOH. The desired concentrations were achieved with sample dilution in the diluent solution. In addition, the salinity of the samples was verified with a High-Resolution Refractometer for Salinity Instrutherm RTS-101ATC. In the samples whose salinity was below the necessary for the osmotic balance of the bacteria (22%), an osmotic adjustment solution was added, composed of NaCl 22%. Also, to standardize and ensure the veracity and uniformity of the analyses, a sensitivity test was performed with the bacteria, according to NBR 15411-3 (ABNT, 2006), using as reference substance the zinc sulfate heptahydrate ($ZnSO_4.7H_2O$).

The isolated effect of the PhACs was analyzed for several concentrations (81.9%, 40.95%, 20.48%, 10.24%, 5.12%, 2.56%, 1.28%, 0.64%, and 0.32% v/v), which allowed a dose-response curve for the organism. The results of the tests were expressed in EC_{50}, that is, the average effective concentration of the toxic agent that caused adverse effects in 50% of the organisms observed, for an exposure time of 30 min. To facilitate the discussion, the EC_{50} values were converted to toxic unit (UT) values according to the equation: $UT = 100 / EC_{50}$. The results were classified as proposed by Persoone et al. (2003): class I ($TU < 1$) - slightly toxic; class II ($1 \leq TU < 10$) - toxic; class III ($10 \leq TU < 100$) - very toxic; class IV ($TU \geq 100$) - highly toxic.

Table 1 - Properties of selected PhACs

PhAC	Molecular formula	Molecular structure	Therapeutic class	Molecular weight (g mol^{-1})	Log Kow	pKa	Charge at pH 7	pKH (Pa m^3 mol^{-1})
KET	$C_{16}H_{14}O_3$		Anti-inflammatory	254.28	3.61	3.88	Negative	10.67
FEN	$C_{20}H_{21}ClO_4$		Lipid regulator	360.83	5.28	-	Neutral	8.34
FLU	$C_{13}H_{12}F_2N_6O$		Antifungal	306.28	0.56	2.3	Neutral	12.98

LOR	$C_{22}H_{23}ClN_2O_2$		Antihistamine	382.89	4.55	4.33	Neutral	12.49
PRE	$C_{21}H_{26}O_5$		Anti-inflammatory	358.43	1.66	12.58	Neutral	9.54
EE2	$C_{20}H_{24}O_2$		Synthetic hormone	296.41	3.9	10.33	Neutral	11.09
BET	$C_{22}H_{29}FO_5$		Anti-inflammatory	392.47	1.68	12.42	Neutral	7.14

3.2.3 Effects of PhACs on the mixture

The composition of each mixture was established based on the results obtained for the EC_{50} of isolated compounds. Only PhACs with determined EC_{50} values were investigated for mixture since EC_{50} greater than 100% is not harmful to aquatic organisms (European Commission 1996). Thus, the interaction between toxic PhACs was evaluated from binary and tertiary mixtures.

The mixture's toxic effect was evaluated according to adaptations of the method presented in NBR 15411-3 (ABNT, 2006). Unlike the test with isolated PhACs, in which several PhACs were tested to determine EC_{50}, the effect of a given concentration of PhACs was tested for mixtures. The concentrations of each PhAC in the mixtures were determined following the methodology proposed by Markovic et al. (2021): $0.5 \cdot EC_{50}$; $1 \cdot EC_{50}$; $2 \cdot EC_{50}$. Thus, the effect could be calculated according to Equations 1, 2, and 3 below.

Equation 1 allows for establishing a correction in the measured light intensities due to the decrease in luminescence that may occur due to external factors during the test.

$$f_{kt} = \frac{I_{kt}}{I_0} \quad (1)$$

where f_{kt} is the correction factor, I_{kt} is the luminescence intensity of the control after the exposure periods (30 min) and I_0 is the bacteria luminescence intensity of the control immediately before the addition of the diluent, in relative unit of luminescence.

Thus, the correction factor was applied to the luminescence values of the bacteria suspension, according to Equation 2.

$$I_{ct} = I_0 \, x \, f_{kt} \quad (2)$$

where f_{kt} is the mean f_{kt} of the controls, I_0 is the mean bacteria luminescence intensity of the control immediately before the addition of the diluent, in relative unit of luminescence, and I_{ct} represents the corrected I_0 value.

Finally, it was possible to calculate the effect of the sample under the bacteria luminescence from Equation 3.

$$E_t = \frac{I_{ct} - I_{kt}}{I_{ct}} \, x \, 100 \quad (3)$$

where E_t is the inhibitory effect of the suspension-test after the exposure periods, expressed as a percentage (%), I_{ct} represents the corrected I_0 value and I_{kt} means the luminescence intensity of the bacteria in the sample evaluated after the exposure periods, in relative unit of luminescence.

For comparing the experimental effects and the toxicity prediction models, the Concentration Addition (CA) and Independent Action (IA) were used. The CA model was applied according to Equation 4.

$$\sum \frac{c_i}{CE_{50i}} = 1 \quad (4)$$

where c_i is the concentration of component i in the mixture and EC_{50i} is the EC_{50} value of component i as a single compound.

The AI model was represented according to Equation 5.

$$E_{(cmix)} = E(c_1 + \ ... \ + \ c_n) = 1 - \prod_{i=1}^{n}[1 - E_{(ci)}] \quad (5)$$

where c_i is the concentration of component i; $E_{(ci)}$ is the effect of component i if applied only at the concentration used in the mixture; $E_{(cmix)}$ is the effect of the total mixture on the concentration equal to the sum of c_i.

Then, the residual effect ratio (ERR) method proposed by Wang et al. (2010) was used to compare the deviations of the experimental effects in the mixture in relation to the models. This method was defined as a proportion of the difference between the effect (E) predicted by a reference model and the observed one. Equation 6 represents the ERR method.

$$ERR = \frac{E_{prd} - E_{obs}}{E_{obs}} x100 \quad (6)$$

where E_{prd} and E_{obs} are, respectively, the effect predicted by the IA or CA models and the observed effect at a certain concentration level.

Finally, synergistic, antagonistic, or additive phenomena were identified by comparing the experimental results of the ecotoxicological tests and the responses predicted by the CA and IA models. Wang et al. (2010) guide the application of a 95% confidence interval about experimental results. Thus, the mixture can be characterized as antagonistic when the value predicted by the models is above the maximum safety interval of the experimental result, synergistic when the prediction of the models is below the minimum

safety interval about the experimental result, and additive when the predictions of the models are among the safety intervals applied to the observed results.

3.2.4 Environmental risk assessment

The acute environmental risk was estimated for toxic PhACs using the risk quotient (RQ), measured by the ratio between the measured concentration (MEC) in the aquatic environment, and predicted no-effect concentrations (PNEC), obtained by the ratio between toxicity value for each PhAC and a correction factor (equal to 1000 for acute toxicity) (European Commission, 1996). For environmental risk, the classification of the European Commission (1996) was used: RQ> 1 (high risk); $0.1 \leq QR \leq 1$ (medium risk); $0.01 \leq QR < 0.1$ (low risk); and $RQ < 0.01$ (negligible risk). This study used the maximum concentration of each PhAC found in surface water to assess the most critical risk scenario. Concentrations of PhACs in surface water were obtained by literature search, using Scopus as the main database, with the following keywords: "name of PhAC + occurrence + surface water"; "name of PhAC + concentration + surface water"; and "name of PhAC + detection + surface water".

Besides, the toxicity values for *A. fischeri* found in the present study and toxicity data obtained in the literature for other aquatic organisms were considered for comparison purposes. The risk of the mixture for each aquatic organism was calculated from the hazard index (HI), which represents the sum of the risks found for PhACs (US EPA, 2000).

3.3 RESULTS AND DISCUSSION

3.3.1 Toxicity of single PhACs

The acute toxicity of the PhACs evaluated for *A. fischeri* is presented in Table 2. Methanol concentrations for the solubilization of PhACs did not exceed the safety value (1% (v/v)) established by Białk-Bielińska et al. (2011). Thus, even with the addition of the solvent, it was impossible to determine the effect concentration of the EE2 and BET due to their low solubility in water. However, it was possible to assess that the EC_{50} is greater than 20 mg L^{-1} for EE2 and 10 mg L^{-1} for BET. Therefore, the TU could be classified as toxic or no toxic. In other studies, it was possible to find the EC_{50} of EE2 for crustaceans (Clubbs and Brooks, 2007) and fish (Pfizer Pharmaceuticals Group, 2011),

with TU values classified as very toxic; and BET for crustaceans, algae, and fish species (Sanderson et al., 2003), with TU classified as toxic (Figure 2).

For FLU, hormesis was observed, representing a positive response of the organism to the medium (Chapman, 2002). The bacteria exposure to the FLU increased the luminescence emission, and this phenomenon may be related as a manifestation of the adaptive nature of organisms to overcome a specific imbalance (Calabresi, 2010). Due to its common occurrence in toxicity tests, causes of hormesis have been explored. For example, Gao et al. (2021) showed that different culture media for *A. fischeri* can regulate the metabolism of bacteria in different ways and, consequently, the growth of bacterial density and luminescence. Therefore, the authors observed that the culture media could influence stimulus or inhibitory actions to trigger hormesis. Drzymała and Kalka (2020) also showed that replacing the diluent medium (NaCl 2%) used in the standard test with synthetic seawater ($MgCl_2$, Na_2SO_4, $CaCl_2$, KCl, $NaHCO_3$, and H_3BO_3), altered the response of organisms to wastewater containing diclofenac and sulfamethoxazole, increasing bacterial sensitivity, and eliminating hormetic effects. These results show that, despite the hormesis results in the present study, FLU can present toxicity to the bacteria under other conditions. Furthermore, FLU was classified as toxic to crustacean and algae species (Kim et al., 2009), as shown in Figure 2.

Table 2 - Acute toxicity of the evaluated PhACs for *A. fischeri*

PhAC	EC_{50} (mg L^{-1})	TU	Classification
EE2	>20[1]	<5	-
BET	>10[1]	<10	-
KET	36.8	2.71	Toxic
FEN	0.32	310.23	Highly toxic
FLU	Hormesis[2]	-	-
LOR	6.15	16.26	Very tóxico
PRE	>100[3]	<1	No toxic

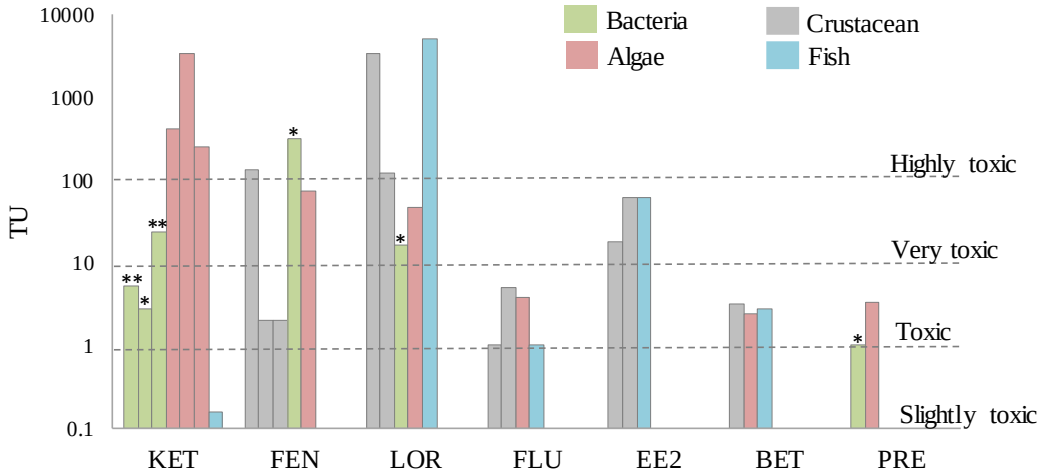
[1]Above the maximum solubilization value.
[2]Positive response of the organism to the medium.
[3]No adverse effect even at the highest sample concentration (100%).

Regarding PRE, the TU value was classified as no toxic for the bacteria (Table 1), even at test concentrations considerably above environmental concentrations. On the other hand, PRE was considered toxic to algae species (Pfizer Pharmaceuticals Group, 2011) (Figure 1). The higher sensitivity to algae may also be related to the longer test time (72

h), while the exposure time for the bacteria was 30 min. Mo et al. (2023) observed that for some antibiotics, the toxicity to *A. fischeri* increased considerably over time; that is, the toxicity was dependent on the exposure time. Thus, future studies with more extended periods of exposure of *A. fischeri* to PRE can be conducted. However, it is essential to emphasize that PhACs act differently in each organism, and the methodologies of acute and chronic testing are different. Besidess, the greater sensitivity of algae may be associated with the mechanisms of action of PRE.

KET was considered toxic to the bacteria, with a TU value of 2.71 (Table 2). As with PRE, higher toxicity values were found for algae (Mennillo et al., 2018; Wang et al. 2020), with TU classified as highly toxic (Figure 1). In contrast, the bacteria were more sensitive to KET than fish, which had slight TU. Wang et al. (2020) studied the toxicity of non-steroidal anti-inflammatories, including KET, to the algae *Scenedesmus obliquus*. The authors noted that these PhACs adversely affected the algae's cellular ultrastructure, causing damage such as cell growth inhibition, chloroplast deformation, disintegration, and decreased photosynthetic and respiratory rates. KET was especially toxic, and according to the authors, this is due to its higher liposolubility, which makes it more easily cross the cell membranes of algae. In addition, algae-based systems are increasingly studied to remove PhACs in aquatic environments due to their ability to adsorb these pollutants (Mojiri et al., 2022). In this way, the intrinsic characteristics of KET, together with the metabolic specificities of algae, provide high toxicity. Regarding bacteria, no studies reported the mechanisms of KET toxicity; however, the higher liposolubility and bioavailability of this PhAC may have contributed to its interaction and increased toxicity to *A. fischeri.*

Figure 1 - Acute toxicity of the evaluated PhACs for *A. fischeri* compared to other aquatic organisms.



*This study
**Results for *A. fischeri*

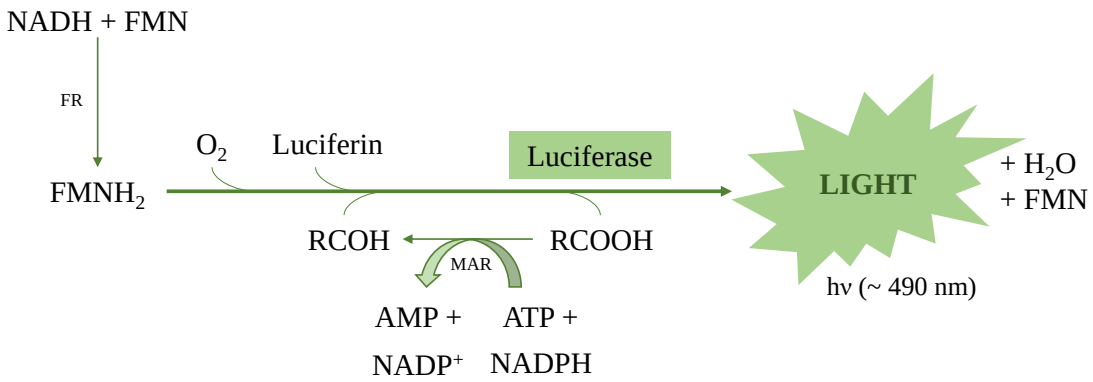
Regarding LOR, TU was classified as very toxic to the bacteria, with a value of 16.26 (Table 2), showing the dangers of this PhAC, which was also very toxic for algae species (Iesce et al., 2019) and highly toxic for crustaceans and fish (Sanderson et al., 2004; Iesce et al., 2019), as shown in Figure 1. According to Coors et al. (2018), one of the side effects of antihistamines is linked to the action of acetylcholine, a neurotransmitter that transmits signals to nerve cells. These PhACs can trigger a blockage in the muscarinic acetylcholine receptor (mAChRs). The mAChRs present in humans are also present in daphnids and fish. Thus, the greatest toxicity to crustaceans and fish may be related to the muscarinic receptor. However, the binding and subsequent inactivation of mAChRs are highly complex processes involving several physiological functions and pathways. Therefore, it cannot be excluded that other mechanisms also contribute to the high toxicity of LOR (Coors et al., 2018).

FEN was the most toxic compound for *A. fischeri*, with a TU of 310.23, and classified as highly toxic (Table 2). This compound was also very toxic for algae (Sanderson et al., 2004) and highly toxic or toxic for crustaceans (Isidori et al., 2009) (Figure 1). In this case, the bacteria was the most sensitive organism to FEN. Sigurnjak Bureš et al. (2021) developed robust models to predict the toxicity of binary mixtures between PhACs and showed variables that play a crucial role in toxicity to *A. fischeri*. According to the authors, the frequency of oxygen and chlorine atoms at a determinate distance in the molecular structure of the compounds evaluated significantly influenced the toxicity to

the bacteria. Dong et al. (2019) also observed greater toxicity to PhAC triclosan due to the presence of Cl and O in its molecular structure. Thus, the higher toxicity to FEN and LOR can be explained by the molecular structure of these compounds, shown in Table 1.

In this context, toxic compounds' mechanism, or mode of action (MOAs) is essential for predicting target molecular pathways. For *A. fischeri*, at short-term exposures, the primary influence of toxicity can occur through interactions with cellular proteins, and luciferase, a vital enzyme that catalyzes the fluorescent reaction in bacteria, is considered the main target of many toxicants (Wang et al., 2017). As shown in Figure 2, for luminescence emission to occur, the Flavin Mononucleotide (FMN) reduces to $FMNH_2$ upon the reaction catalyzed by Nicotinamide Adenine Dinucleotide (NADH):FMN oxidoreductase enzyme in the presence of a reduced NADH and a H^+. Bacterial luciferase then catalyzes the oxidation of reduced $FMNH_2$ to produce oxidized FMN in the presence of long-chain aldehyde (RCHO) and O_2 with light emission. This reaction is very particular, and if affected by harmful environmental factors, it manifests as a reduction in luminescence, and the toxic substance probably penetrates the cell structure (Erzinger et al., 2018).

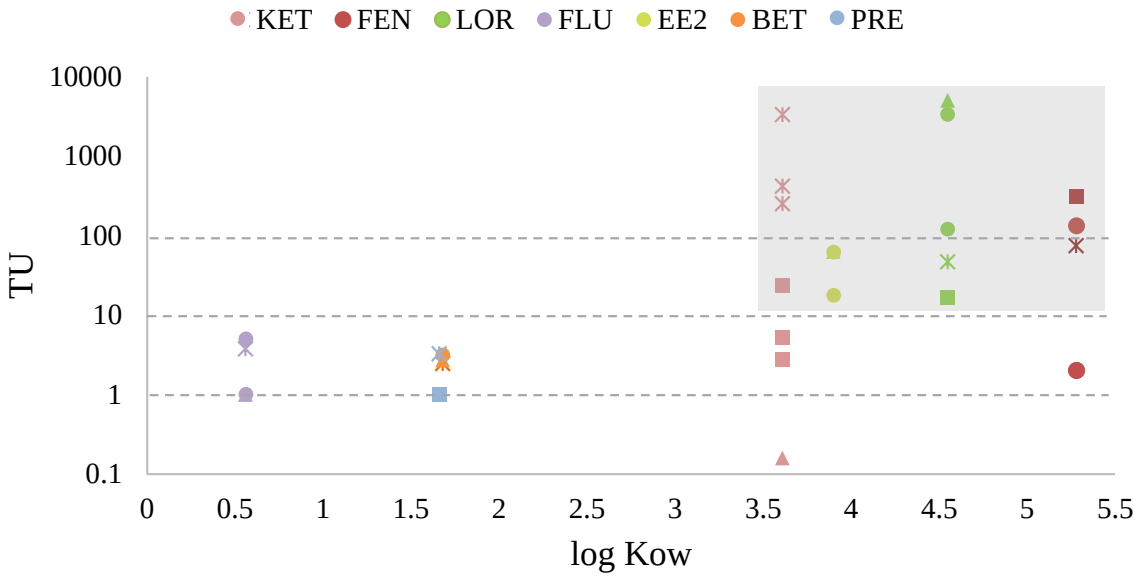
Figure 2 - Scheme of bioluminescence in *A. fischeri*.



In addition, there may be a correlation between acute toxicity to *A. fischeri* and the logarithm of the n-octanol/water partition coefficient (log K_{ow}) for several compounds, with hydrophobic compounds (log K_{ow}>0) generally being more toxic because they interact more easily with the cell membrane. All PhACs evaluated in the present study are hydrophobic (Table 1); however, PRE, the compound that has the lowest log K_{ow} (1.66) among the PhACs whose toxicity could be measured, was classified as no toxic to *A. fischeri*. As shown in Figure 3, the greater the log K_{ow}, the greater the tendency for

PhAC to be very toxic or highly toxic. However, no strong positive correlation (by Pearson correlation) was found between TU and log K_{ow} values. This is justifiable since there are several mechanisms of action and interaction between living beings and toxic compounds, especially in organisms with more complex metabolisms. Thus, more studies on the mechanism of molecular interaction are needed.

Figure 3 - Relationship between the toxic unit (TU) and the log K_{ow} of the evaluated PhACs. Asterisks represent algae, squares represent bacteria, triangles represent fish and circles represent crustaceans.



3.3.2 Synergistic and antagonistic effects of PhACs in the mixture

As shown in Table 3, all mixtures evaluated for the bacteria were toxic, even considering the proportion of $0.5 \cdot EC_{50}$ of the PhACs in the mixture. This result shows that PhACs can be toxic when mixed at concentrations lower than their EC_{50}. In addition, tertiary mixtures were more toxic than binary mixtures in all proportions studied. Therefore, even low, the environmental concentrations of these PhACs can pose a danger to aquatic organisms when interacting with numerous other compounds, as occurs in aquatic compartments.

Godoy et al. (2019) observed similar results for the PhACs metformin-bisoprolol and metformin-ranitidine mixtures. Even at no-effect concentrations when evaluated individually, these PhACs produced toxic effects on *Daphnia similis* in the binary mixtures. Similarly, Thrupp et al. (2018) evaluated five synthetic hormones' individual and mixture toxicity to the fish *Pimephales promelas*. The results showed that for all

individual PhACs, the lowest concentrations tested showed no significant difference from the control and were declared as no observed effect concentration (NOEC). However, this concentration in the mixture produced a very significant effect, with egg production inhibited by more than 50%. The authors termed this phenomenon "something out of nowhere," in which effects not existing for isolated PhACs can produce considerable effects when mixed.

Table 3 – Comparison between the experimental results of mixtures toxicity for *A. fischeri* and the models CA and IA.

Concentration for each PhAC	Mixture	ID	Experimental luminescence reduction (%)	Confidence interval (%)	CA (%)	IA (%)
$0.5 \cdot EC_{50}$	KET + FEN	M1	28.57	27.14–30.00	50	29.13
	FEN + LOR	M2	51.43	48.86–54.00	50	46.16
	KET + LOR	M3	54.00	51.30–56.70	50	42.02
$1 \cdot EC_{50}$	KET + FEN	M4	39.61	37.63–41.60	100	75.00
	FEN + LOR	M5	50.84	48.29–53.38	100	75.00
	KET + LOR	M6	81.11	77.05–86.16	100	75.00
$2 \cdot EC_{50}$	KET + FEN	M7	81.46	77.39–85.54	200	94.14
	FEN + LOR	M8	77.27	73.41–81.14	200	94.73
	KET + LOR	M9	98.05	93.15–102.95	200	91.81
$0.5 \cdot EC_{50}$	KET + FEN + LOR	M10	58.26	55.35–61.17	75	52.96
$1 \cdot EC_{50}$	KET + FEN + LOR	M11	82.00	77.90–86.10	150	87.50
$2 \cdot EC_{50}$	KET + FEN + LOR	M12	98.24	92.38–102.10	300	98.71

Green area: antagonistic effects; pink area: synergistic effects; white area: additive effects.

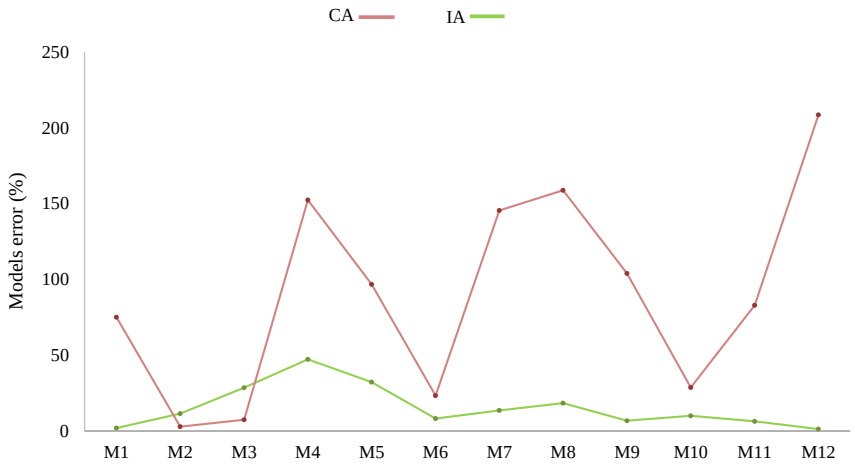
Regarding the effect of the mixtures, those characterized as antagonistic prevailed, especially concerning CA. This is evident for the mixtures between KET and FEN (M1, M4, and M7), in which the experimental results were lower than those predicted by CA and IA for all proportions tested, except for M1 for IA, which had an additive effect. However, for the mixtures between KET and LOR (M3, M6, and M9), the effects were synergistic for CA and or IA showing that the models underestimated the toxicity of this mixture (Table 3). In fact, The KET + LOR mixture has always been the most toxic among binary mixtures. This result shows a contradiction between the toxicity of the isolated PhACs and the mixtures since FEN, the most toxic PhAC alone, did not contribute to higher toxicity in their mixtures. In contrast, binary mixtures containing FEN were the least toxic. In a similar result, Markovic et al. (2021) showed that binary mixtures with diclofenac-17α-ethinylestradiol and diclofenac-fluoxetine, presented for

the duckweed *Lemna minor* growth inhibition lower compared to the individual values of 17α-ethinylestradiol and fluoxetine.

Synergistic effects occurred to a greater extent for $0.5 \cdot EC_{50}$ (Table 2). This indicates that, in this case, the models underestimated the toxicity of the mixture mainly when the PhAC concentrations were lower (compared to $1 \cdot EC_{50}$ and $2 \cdot EC_{50}$). For example, the IA model had a deviation of 28.5% in the tertiary mixture for concentrations of $0.5 \cdot EC_{50}$ (Figure 4); however, this model generally approximated the experimental results better. In contrast, the CA model had high deviations, mainly in the tertiary mixture for concentrations $2 \cdot EC_{50}$, deviating up to 208.5% from the experimental results (Figure 4). According to the statistical tests, there was no significant difference between the experimental results and the IA model, while for the CA model, there was a significant difference ($p < 0.05$).

Godoy et al. (2019), evaluating the toxicity of metformin, bisoprolol, ranitidine, and sotalol, also noted that the CA model overestimates the observed toxicity of the mixture, while the IA may underestimate these values. For the PhACs evaluated, the CA model was closer to the experimental results. In contrast, Ukić et al. (2019) evaluated the effect of mixtures between several PhACs and observed that for diclofenac-azithromycin, diclofenac-erythromycin, oxytetracycline-azithromycin and oxytetracycline-erythromycin the IA model better represents the experimental results with *A. fischeri*. It is worth mentioning that CA and AI do not consider the complexity of the target biological system and the characteristics of the compounds evaluated, which may limit the application of these models.

Figure 4 – Errors of the addition concentration (AC) and independent action (IA) models about experimental results.



3.3.3 Environmental risk assessment

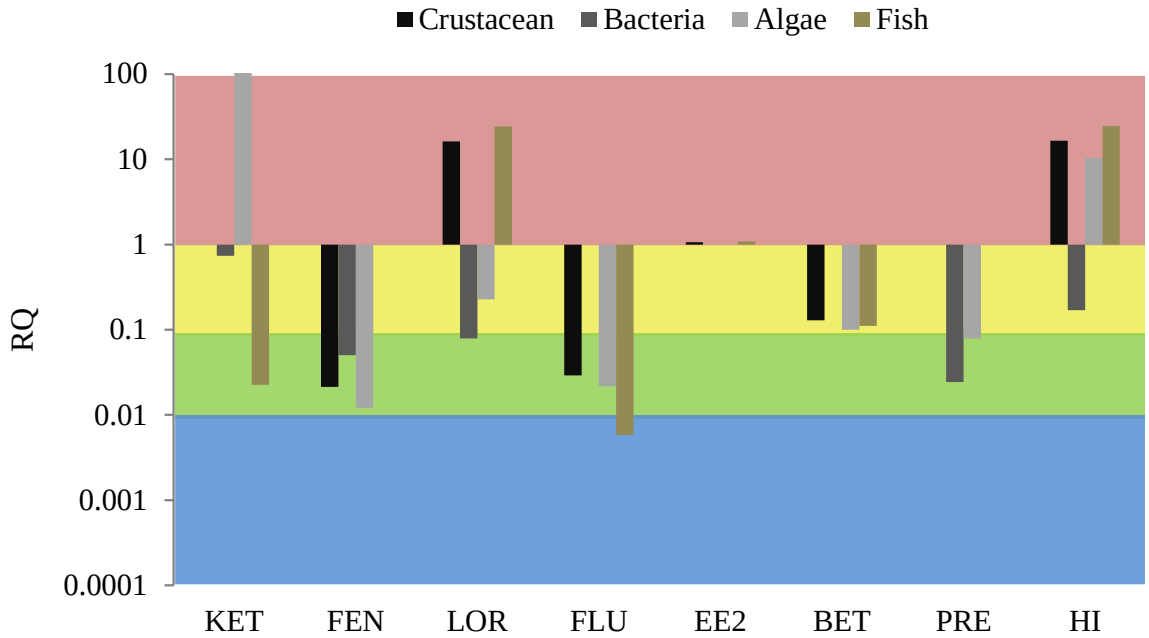
Environmental risks were measured for all selected PhACs and the mixture between them by category of aquatic organism. The concentrations of PhACs in surface water used in risk assessment are shown in Table S1. Environmental risks were assessed for each trophic level, aiming identify the species most susceptible to adverse effects. As observed in Figure 6, the PhACs FEN, FLU, and PRE presented low or negligible risks. The risks of FLU and PRE agree with the toxicity results for *A. fischeri* since PRE did not present toxicity to the bacteria, and hormesis was observed for FLU (Table 2). In addition, crustaceans, algae, and fish species have confirmed that, at the environmental concentrations found and acting alone, these compounds do not pose a potential danger.

In contrast, FEN showed the highest toxicity among the PhACs evaluated for *A. fischeri* (Table 2), and its risks were low for the bacteria and species of crustaceans and algae. This divergence of results occurs due to the low concentrations of FEN detected in surface waters, in the range of ng L^{-1}, while the toxicity measured for aquatic organisms is in the range of mg L^{-1} (dos Santos et al., 2021). Thus, it is crucial to associate toxicity tests with risk assessment so that environmental concentrations are considered. It is important to highlight that few studies report the concentration of this compound in surface waters, and the maximum concentration found in the literature was 16.21 ng L^{-1}, in the district of Évora, Portugal (Palma et al., 2020). Therefore, it is essential to develop studies evaluating the concentrations of this PhAC, especially in underdeveloped countries, where the treatment of wastewater containing toxic compounds may be

inefficient and even non-existent, which adds to the scarcity of monitoring the quality of water and wastewater, may be an aggravating factor of environmental risks.

Besides, some FEN-containing mixtures had synergistic effects (Table 3), showing that the toxic potential of this PhAC can be increased by mixing with other compounds. Consequently, its risks may be more significant. Measuring the risk of mixtures is challenging since there is still an unpredictability of how PhACs can interact in more complex mixtures, such as in natural environments. However, in the present study, an estimate was made from the hazard index (HI). As observed in Figure 5, the risk of the selected PhACs mixture was high for crustaceans, algae, and fish and medium for bacteria.

Figure 5 – Acute environmental risks for selected PhACs by category of aquatic organism.



Blue area: negligible risk; green area: low risk; yellow area: medium risk; Pink area: high risk.

Concerning BET and EE2, it was not possible to measure the toxicity to the bacteria; therefore, the risk to this organism is still unknown. BET presented a medium risk for crustaceans, algae, and fish, and would pose a high risk at concentrations above 41 μg L^{-1}, a value ten times higher than the maximum found in surface waters detected in Brazil (Reis et al., 2019). This value can reference the maximum allowable concentrations so that this PhAC do not promote environmental risks. The importance of monitoring the concentration of compounds with toxic potential in waters and wastewater is highlighted to ensure the protection of the aquatic ecosystem.

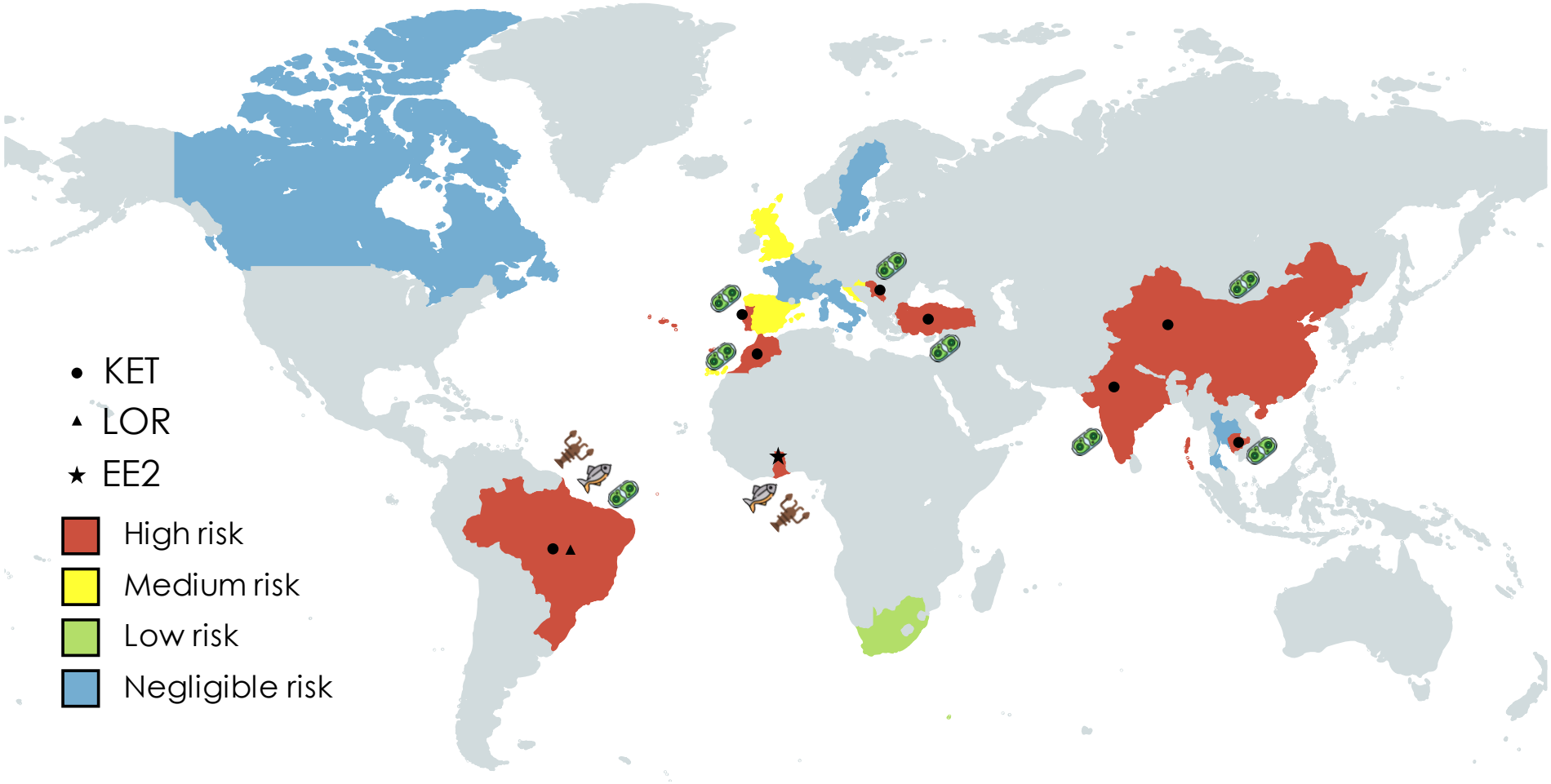
EE2 had a high risk for crustaceans and fish (Figure 5). There is a growing concern about this compound, as EE2 act as an endocrine disruptor. Baekelandt et al. (2023) shows that EE2, in environmentally concentrations, can result in concentration-dependent impacts on fecundity and biomarkers for estrogenic activity, such as induction of vitellogenin, and changes in ovarian gene expression for *Danio rerio*. Likewise, Qin et al. (2023) show that Exposure to EE2 at environmentally concentrations could induce embryo developmental toxicity for *Oryzias melastigma*, such as delayed embryonic developmental processes, reduced embryonic heart rate, delayed hatching time, decreased the hatching rate, and impaired larval behavior.

The PhACs of greatest environmental concern were KET, with a high risk for algae, and LOR, with a high risk for crustaceans and fish (Figure 5). This shows that a PhAC may not present risks to a particular organism, but this does not eliminate the possibility of other compounds causing adverse effects. For the risk of KET to be negligible (RQ <0.01) for algae, the environmental concentrations of this compound must be below 0.3 ng L^{-1}, which represents a value considerably below the maximum value found in surface waters (298 ng L^{-1}) (Reis et al., 2019). Similarly, LOR concentrations must be below 0.3 ng L^{-1} for crustaceans and 0.2 ng L^{-1} for fish for the risk to be negligible. The maximum LOR value detected in surface waters in the studies evaluated was 486 ng L^{-1} (Reis et al., 2019).

These results are worrisome since even KET and LOR present toxicity to *A. fischeri* and other organisms only in concentrations above the environmental ranges (Figure 1); in contrast, the dangers are evident when these compounds are evaluated about the risk quotient. To achieve the necessary concentrations of KET and LOR to reduce risks to negligible, the removal of PhACs by treatment technologies must be high due to the high concentrations of these compounds in raw wastewater. For KET, for example, a value of 28.4 μg L^{-1} has already been detected in wastewater in South Africa (Zunngu et al., 2017), while LOR has already been detected in the range of 8.1 μg L^{-1} in wastewater in Colombia (Serna-Galvis et al., 2019), which represents a high environmental risk. These values are of concern, since removals close to 100% would be required by wastewater treatment technologies to remove risks. In addition, the environmental risk assessment showed that the concentrations of these PhACs already present in surface waters pose a risk, which increases the challenge regarding the on-site remediation of aquatic compartments.

In Figure 6, it is possible to observe the countries whose risk was high, medium, low, or negligible for each aquatic organism. KET was detected in concentrations that pose high environmental risks in China, Serbia, Portugal, India, Morocco, Cambodia, Turkey, and Brazil. At the same time, LOR and EE2 were high risks in Brazil and Ghana, respectively. In most countries, the high risk was related to algae, except for Ghana, where the high risk was related to fish and crustaceans. Brazil showed the most critical scenario, with a high risk for algae, crustaceans, and fish. These results may be a guideline for prioritizing the removal of PhACs in countries with high environmental risk and for more attention to places with medium risk since the legislations establishing concentration limits of PhACs in treated wastewater are still nonexistent. In addition, it is essential to emphasize the importance of studies identifying these PhACs in other countries to measure environmental risks.

Figure 6 - Environmental risk of evaluated PhACs by aquatic organism (fish, crustacean and algae), in countries whose concentration was found.



3.4 CONCLUSION

In this study, the effect concentrations of PhACs still little explored in terms of toxicity, and their synergistic and antagonistic effects in binary and tertiary mixtures were measured. In addition, environmental risks by category of the organism were assessed. FEN, LOR, and KET were, respectively, the most toxic PhACs for *A. fischeri*, and synergistic effects were observed for FEN + LOR, KET + LOR, and KET + FEN + LOR. Besides, the IA model was able to predict the experimental results with greater accuracy, while for the CA model this was not possible. Future studies must explore other available models, such as QSAR. Environmental risks for KET concerning algae, and LOR e EE2 for crustaceans and fish were high. The risk assessment showed that to achieve the concentrations necessary for reducing KET, LOR, and EE2 hazards, high removals by treatment technologies are required so that wastewater treatment plants are not a source of PhAC releases. In addition, studies are necessary for developing advanced removal techniques for these compounds since environmental concentrations presented potential risks in this study. Finally, educational policies to prevent the irregular disposal of PhACs, the constant monitoring of its concentrations in surface waters, and the development of legislation that includes parameters related to these hazardous compounds are essential for the safety of the aquatic ecosystem.

CHAPTER 4

OCCURRENCE, ENVIRONMENTAL RISKS, AND REMOVAL OF BISPHENOL A AND ITS ANALOGUES BY MEMBRANE BIOREACTORS

4.1 INTRODUCTION

Bisphenols (BPs) are organic chemical compounds in the phenols class characterized by two hydroxyl groups (-OH) linked to a benzene nucleus. These compounds are widely used in plastics, resins, and coatings due to their polymerization and resistance properties. Bisphenol A (BPA) was the first BP produced and is highlighted due to its application in several consumer products, such as plastic bottles, food containers, and can coating (Vandenberg et al., 2007). However, the use of BPA has been the subject of debate and regulation due to concerns about its potential adverse effects on human health (Dueñas-Moreno et al., 2023; Silano et al., 2020).

These concerns are mainly linked to the fact that BPA is considered an endocrine disruptor and can interfere with the functioning of the hormonal system of living organisms. Its ability to mimic or block natural hormonal activity can lead to several adverse health effects, especially during sensitive periods of development, such as pregnancy and childhood (Gore et al., 2015). The effects on human health include disorders of the reproductive system, changes in neurological development, increased risk of certain chronic diseases such as diabetes and cancer, and even impacts on obesity and metabolism (Kundu et al., 2024; Qi et al., 2024).

BPA is widespread in the environment and can reach waterbodies through inadequate disposal of industrial and domestic wastewater, inefficient removal at wastewater treatment plants (WWTPs), as well as the degradation of plastic materials over time. Therefore, BPA has been detected in surface waters of several countries in Europe, America, Asia, and Africa (Gil-Solsona et al., 2022; Goeury et al., 2022; Idowu et al., 2022; Kundu et al., 2024; Madeira et al., 2023; Yin and Zhou, 2022). As a result, this compound can negatively affect the ecosystem, causing effects on aquatic organisms such as disturbances in reproductive development, estrogenic effects, damage to the nervous system and negative impacts on survival and growth (Moreman et al., 2017; Park et al., 2019; Yuan et al., 2023; Zhang et al., 2021).

Concerns about BPA have resulted in restrictions or bans on its use in certain countries, in products such as baby bottles and thermal paper, as well as pressure to manufacture “BPA-free” products (Silano et al., 2020). Then, the use of other BPs such as bisphenol AF (BPAF), bisphenol AP (BPAP), bisphenol B (BPB), bisphenol C (BPC), bisphenol E (BPE), bisphenol F (BPF), bisphenol FL (BPFL), bisphenol S (BPS), and bisphenol Z

(BPZ) - with characteristics structurally similar to BPA - have increased. As a consequence, several studies have already verified an increase in the occurrence of these substitute BPs in surface waters (Cunha et al., 2022; Karsauliya et al., 2022; X. Zhang et al., 2024). Additionally, there are concerns about the environmental safety of these substances. Studies have shown that the alternatives to BPA can act as endocrine disruptors and cause toxic effects to aquatic organisms, such as reproduction inhibition, growth inhibition, and mortality similar to or even greater than BPA (Lin et al., 2021; Naderi et al., 2014; Qiu et al., 2021; X. Zhang et al., 2024).

Studies show the release of BPs, particularly BPA, in food-contact plastic and products for children such as food storage containers, water bottles, baby bottles, cups, and toys. For example, Wang et al. (H. Wang et al., 2020) investigated the release of BPs into water from polycarbonate and polyethylene terephthalate bottles. The authors observed that BPA, BPS, BPAP, and BPAF migration occurred. These BPs were found in average concentrations of 1,394.3, 1.9, 1.4, and 1.0 ng/L, respectively, in bottled water. Vicente-Martínez et al. (Vicente-Martínez et al., 2020) determined the concentration of BPA in toys and pacifiers from Spain and found concentrations varying from not detected to 0.30 µg/L. Similarly, Siddique et al. (Siddique et al., 2021) studied the migration of BPs in 20 brands of baby bottles. The average concentration of BPA and BPS in baby bottle leachate was 31.5 ng/L and 2.33 ng/L, respectively, in the water simulant. The authors highlight that although the leaching was low, newborns and children have reduced metabolic capabilities, and the bioaccumulation of these products may be greater and more harmful than adults. In this sense, Brandsma et al. (Brandsma et al., 2022) estimated the migration rate of BPA in toys bought in the European Union and made with recycled polymeric material in artificial saliva simulating 1 h of mouthing. A migration rate of up to 128 ng/cm^2/h and a daily intake of 72.4 ng/kg of body weight per day were found for BPA. Despite being lower than the legislation, attention should be given other plastic additives, such as bis(2-ethylhexyl) phthalate (DEHP), diisobutyl phthalate (DIBP) and tetrabromobisphenol A (TBBPA) were also found in the artificial saliva, migrated from the toys, and the constant and cumulative exposure to this mixture of toxicants may pose risks to children's health. On the contrary, in the study of Souza et al. (Souza et al., 2022), the concentration of BPA in synthetic saliva was below the limit of quantification.

In environmental aquatic matrices, studies about BPs leaching are reduced. Xu et al. (Xu et al., 2011) studied the release of BPA in polyvinyl chloride waste with a BPA content

of 12.1 µg/g in landfill leachate. For 6 days of testing, the authors found that the increment of BPA concentration in fresh leachate, 1.5-year leachate and 10-year leachate were 1.57, 1.02 and 2.03, respectively (Xu et al., 2011). In addition, Sajiki and Yonekubo (Sajiki and Yonekubo, 2003) evaluated the leaching of BPA from polycarbonate tubes in seawater (Pacific Ocean) and river water (Bay from Tokyo). The leaching rate of BPA in seawater was the fastest (11 ng/d), while for river water, it was 4.8 ng/d, at 37ºC. Besides, BPA leached from all samples increased with temperature and time.

Therefore, despite the imminent risks, legislation regarding BPA and its substitutes is still insufficient to prevent the release of these compounds into the aquatic environment. Table 1 shows, in temporal order, milestones in global regulation related to BPs. Until then, regulations were directed at BPA, except for some restrictions regarding the Specific Migration Limit in plastic food contact materials and the concentration in thermal paper for BPS in Switzerland. Furthermore, despite the great advances in regulations, they have focused on the limits of BPs in materials in contact with food, aiming to reduce their intake. However, measurement of BPA in WWTPs is rarely carried out, and no discharge limits of BPs into waterbodies have been found.

Table 1 – Milestones in global regulations related to BPs by temporal order.

Year	Countries or Organizations	Description
2010	Canada	Declaration of BPA as a toxic substance and prohibition of its use in baby bottles by the Canada Consumer Product Safety in the Hazardous Products Act (bisphenol A) (SOR/2010-53)
2010	France	Prohibition of the BPA use in baby bottles by Act 2010-729
2010	Denmark	Prohibition of the BPA use in feeding bottles, feeding cups and materials in contact with food aimed at children aged 0 to 3 years by the Danish Veterinary and Food Administration
2011	European Union	Prohibition of the BPA use in baby bottles and drinking cups by Directive 2011/8/EU
2011	European Union	Establishment of BPS and BPA in plastic food contact materials with a Specific Migration Limit of 0.05 mg/kg by the Regulation (EU) Nº. 10/2011
2011	Brazil	Prohibition of the BPA use in baby bottles by the Resolution RDC Nº. 41/2011
2012	United States	Prohibition of the BPA use in baby bottles and drinking cups by the Food and Drug Administration

2012	Austria	Prohibition of the BPA use in pacifiers and teethers by the Food Satefy and Consumer Protection Act
2012	Japan	Establishment of BPA in plastic food contact materials with a Specific Migration Limit not more than 2.5 µg/ml by the Law 37 of the Food Sanitation
2013	Belgium	Prohibition of the BPA use in contact foods materials intended for children up to 3 years old by the Belgium's Act of 4 September 2012
2015	France	Prohibition of the BPA use in food packaging, with restrictions on products intended for children by the law Nº. 2010-729
2016	European Union	Prohibition of the BPA use in thermal paper at a concentration equal to or greater than 0.02% by weight after January 2, 2020, by the European Chemicals Agency
2016	China	Establishment of BPA and BPS in plastic food contact materials with a Specific Migration Limit of 0.6 mg/kg and 0.05 mg/kg, respectively, by the National Standard for Food Safety - Standard for Use of Additives in Food Contact Materials and Products (GB 9685-2016)
2016	Brazil	Establishment of BPA Specific Migration Limit of 0.6 mg/kg by the Resolution ANVISA/DC Nº 88 of 29/06/2016
2017	European Union	Establishment of BPA Specific Migration Limit as 0.04 mg/L in toys by the Commission Directive (EU) 2017/898
2019	Switzerland	Prohibition of the BPA and BPS use in thermal paper at a concentration equal to or greater than 0.02% after December 15, 2020, by the Reduction of Risks relating to the Use of Certain Particularly Dangerous Substances
2019	Canada	Prohibition of BPA in baby bottles has been expanded to include other baby food products
2020	France	Extension of ban on BPA in food packaging to cover all food containers by 2025

Due to gaps in monitoring in WWTPs and current regulations regarding the concentration of BPA and especially the analogues in treated wastewater and surface waters, tools such as environmental risk assessment are essential to measure and classify the ecological risks of BPs - based on their concentrations and toxic effects - and point out the compounds whose removal should be prioritized by treatment technologies (Ladeia Ramos et al., 2024b). Furthermore, the efficient removal of BPs in wastewater is essential to prevent or reduce continuous releases of them into water bodies, ensuring concentration ranges that do not harm the aquatic ecosystem.

In this sense, membrane bioreactors (MBR) have been efficient in removing several emerging micropollutants, such as pharmaceutical drugs, hormones, and microplastics

(Arcanjo et al., 2022; Ladeia Ramos et al., 2024b; Santos et al., 2023). These technologies can have different configurations and combine aerobic or anaerobic biological treatment with membrane separation processes, such as ultrafiltration (UF), microfiltration (MF), nanofiltration (NF), reverse osmosis (RO), forward osmosis (FO) and membrane distillation (MD). In MBR, membranes contribute to a higher biomass concentration, greater biodiversity, and solid retention time (SRT). Thus, the feed/microorganism ratio is lower, and the efficiency in pollutant removal can be high (Sipma et al., 2010). Besides biological degradation, the high SRT can contribute to the compound's adsorption onto the sludge (Verlicchi et al., 2012). Furthermore, membranes can act as a physical barrier to micropollutants, especially those with high retention. Therefore, this technology can promote greater removal of BPs compared to conventional technologies, such as activated sludge and upflow anaerobic sludge blanket (UASB) reactors, which have shown limited removals for these compounds (Arias et al., 2018; Qian et al., 2021).

That being said, this article aims to provide an overview of the occurrence of BPs in surface water from several locations. Furthermore, the ecological effects of BPs on the aquatic environment are deeply discussed. The discussion relies on data obtained from acute and chronic toxicity tests for different trophic levels, as well as estrogenic activity for BPs. Additionally, environmental risks were calculated for surface water of several countries, and BPs' occurrence was classified as negligible, low, medium, or high risk, thus identifying the priority compounds. Also, the removal of BPA and its analogues was evaluated for several configurations of MBR and the removal of environmental risks related to BPs by these technologies was calculated.

Although other recent review articles deal with the occurrence of BPs in aquatic surface water (Czarny-Krzymińska et al., 2023; Khairul Hasni et al., 2023; Vázquez-Tapia et al., 2022; Xing et al., 2022), no discussions were found focusing on concentrations in surface water by country and for different types of BPs, as discussed in the present article. Furthermore, ecological impacts are also the focus of other review studies; however, most studies assess risks for specific locations or are limited to particular BPs, mainly BPA (Gani et al., 2021; Ladeia Ramos et al., 2024a; Liu et al., 2021); therefore, no publications were found discussing in depth the environmental risks of the various BPs worldwide. Also, this is the first review that evaluates the removal of BPs by MBR and the removal of environmental risks by this technology. Hence, this article contributes to the global understanding of the ecological risks of BPs and highlights the compounds whose removal

should be prioritized by country. Furthermore, the discussions presented here seek to facilitate the choice of MBR configurations with a focus on more efficient removal of BPs, aiming to reduce the release of these compounds into the aquatic environment and reduce their impact on aquatic organisms.

4.2 METHODOLOGY

A systematic literature search in the databases of the Google Scholar, Science Direct, and Scopus was made, using the following keywords for (1) occurrence in surface water: bisphenol AND occurrence AND ("surface water" OR river OR seawater OR lake), bisphenol AND analogues AND occurrence AND ("surface water" OR river OR seawater OR lake); for (2) toxicity: bisphenol AND toxicity, bisphenol AND analogues AND toxicity, bisphenol AND (half maximal effective concentration (EC_{50}) OR half maximal lethal concentration (LC_{50})), bisphenol AND no observed effect concentration (NOEC), bisphenol AND analogues AND (EC_{50} OR LC_{50}), bisphenol AND analogues AND NOEC; for (3) bisphenol removal by MBR: (“membrane bioreactor” OR MBR) AND bisphenol AND removal, (“osmotic membrane bioreactor” OR OMBR) AND bisphenol AND removal, (“membrane bioreactor” OR MBR) AND “membrane distillation” AND bisphenol AND removal, (“membrane bioreactor” OR MBR) AND nanofiltration AND removal, (“membrane bioreactor” OR MBR) AND reverse osmosis AND bisphenol AND removal. Then, studies published from 2003 to 2024 were further selected based on their relevance to the subjects being discussed in this review and critically discussed in the following sections.

Acute and chronic toxicity data, represented by E(L)C_{50} and NOEC, respectively, were converted to toxic unit (TU) values according to the equation: TU = 100 / E(L)C_{50} or NOEC. Then, toxicity data were classified as proposed by Persoone et al. (Persoone et al., 2003): TU < 1 - low toxicity; 1 ≤ TU < 10 - moderate toxicity; TU > 100 - high toxicity.

To assess the acute and chronic environmental risks, measured from the risk quotient (RQ), the concentration of BPs in surface water, found by the systematic literature search, was used (Table S1, Supplementary Material). The RQ values were obtained through the quotient between the BPs concentrations by PNEC. For the calculation of the PNEC, the acute or chronic toxicities for each BP were considered (Table S2, Supplementary

Material), as well as a correction factor: 10 for NOEC from at least three species representing three trophic levels; 50 for NOEC from species representing two trophic levels; 100 for NOEC from only one trophic level; and 1000 for one E(L)C_{50} from each of three trophic levels (European Commission, 1996). Then, the risk of BPs was classified as high risk (RQ≥1), medium risk (0.1≥RQ<1), low risk (0.01≥RQ<0.1), or negligible risk (RQ<0.01) (European Commission, 1996).

Estrogenic activity of BPs was calculated in terms of 17β-estradiol equivalents (EEQ), according to the relative potency (RP) and the measured environmental concentration of each compound. The RP represents the estrogenic activity of the compound in relation to 17β-estradiol and the values were found in the literature. For estrogenic activity risks, the reference compound is 17β-estradiol, and the PNEC values for acute and chronic effects are 5 ng/L and 2 ng/L, respectively (Caldwell et al., 2012). Furthermore, environmental risks were measured for MBR, considering the concentrations of BPs in raw and treated wastewaters.

4.3 RESULTS

4.3.1 Occurrence of bisphenols in aquatic environment

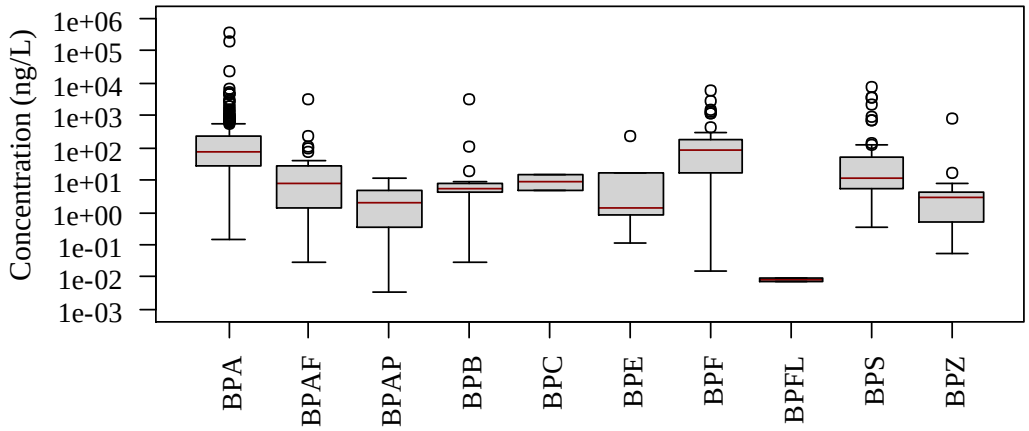
Studies about the occurrence of BPA and its analogues have increased in recent decades, allowing a more precise investigation of their concentrations and global distribution. Occurrence data in surface water for BPA and nine analogues were found in the literature, including BPAF, BPAP, BPB, BPC, BPE, BPF, BPF, BPS, and BPZ, with a total of 450 data and 136 research articles (Figure S1a). Although BPA is the most reported among studies, other BPs, such as BPS and BPF, have been extensively investigated. On the other hand, more studies are needed for BPAP, BPC, BPE, and BPFL. Likewise, for many countries, data concerning the concentration of BPA and its analogues are nonexistent, and for others, such as Australia, Greece, Mexico, Pakistan, Romania, and Switzerland, information is limited (Figure S1b). In contrast, China had the highest reported data, followed by Brazil, India, and Spain.

The average concentrations (ng/L) for these compounds in the aquatic environment were 2,540.7 ± 1,571.4, 144.8 ± 117.8, 3.31 ± 1.5, 222.1 ± 208.8, 9.3 ± 4.7, 40.6 ± 36.6, 399.1 ± 153.1, 0.0082 ± 0.0013, 374.9 ± 164.9 and 68 ± 64.3 for BPA, BPAF, BPAP, BPB, BPC, BPE, BPF, BPFL, BPS and BPZ, respectively. In Figure 1, it is possible to observe the concentration ranges for BPs. The highest average concentrations found in surface

waters, including freshwater and seawater, were for BPA, followed by BPF and BPS. At the same time, these were the BPs with the most data investigated in the literature (Figure S1a). It is essential to highlight that although BPA is still abundant for producing different types of plastics, such as polycarbonates, epoxy resins, paper coatings, and powder paints, its analogues can be used for these applications as substitutes for BPA. For example, BPS can be used as an anticorrosive in epoxy glues (Wong and Durrani, 2017), as a component of plastic substitutes for production of various products, including baby bottles (Siddique et al., 2021), preservative in canned foods and additive in paper products (Liao et al., 2012; Viñas et al., 2010).

Studies indicate that regulations restricting the use of BPA due to its recognition as an endocrine disruptor (Gore et al., 2015), have led to an increasing use mainly of BPF and BPS in applications of industrial and production of "BPA-free" products (Lee et al., 2015; Qiu et al., 2021; Song et al., 2014; Yamazaki et al., 2015). Therefore, the release of these compounds into the aquatic environment is a consequence of their widespread use and growing demand on the global market.

Figure 1 – Concentration of BPA and analogues in aquatic environments. Reference: Table S1 (Supplementary Material).



Furthermore, it was found that for some countries, the concentration of BPs was considerably higher, such as BPA in Taiwan, with an average of 116.4 ± 71.6 μg/L (Figure 2a). Chou et al. (2015) observed an ubiquitous BPA concentration in the <0.01 to 725 μg/L range in several river water samples. The authors suggested that there was a continuous discharge of BPA in the Erren River, where the maximum concentration was found. Similarly, Chen and Chou (2016) detected BPA in all samples evaluated in the Erren River at concentrations ranging from 0.09 to 392 μg/L. According to the authors,

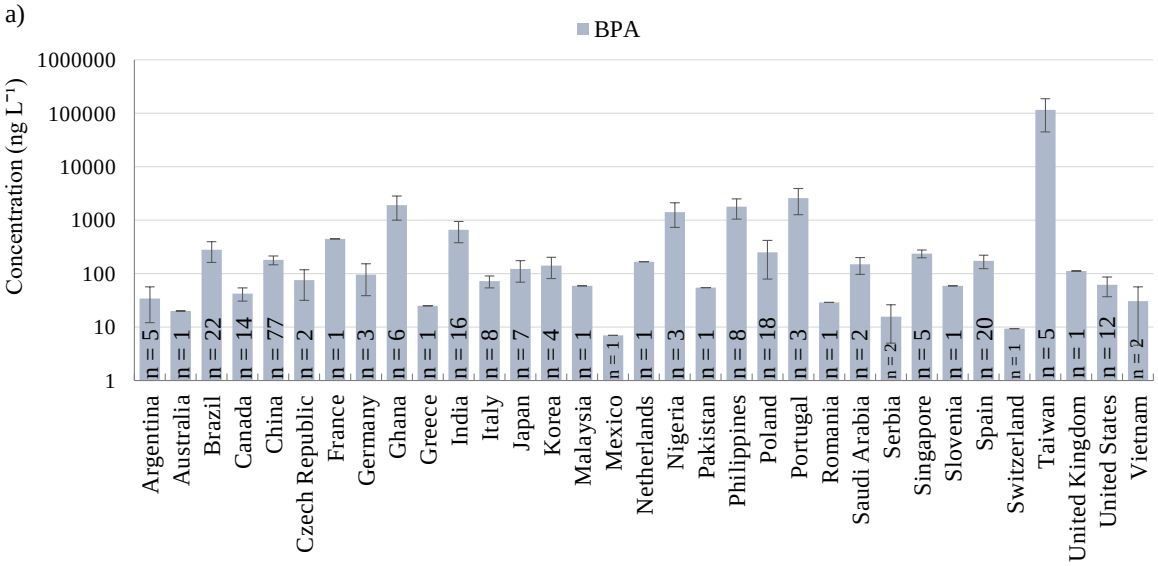
this river has been contaminated with various wastewater sources due to insufficient wastewater treatment. These results show that untreated wastewater or WWTPs with low BPs removals can be a constant source of discharge of these compounds into the aquatic environment.

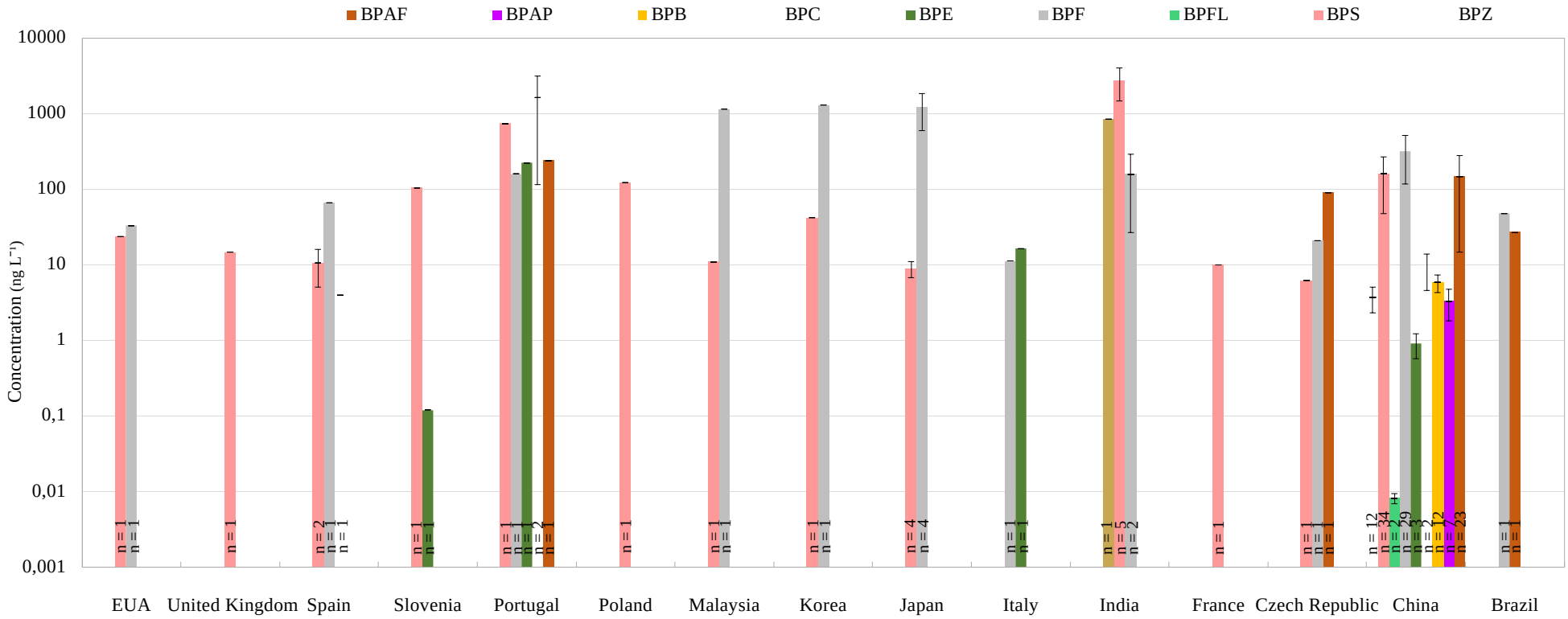
BPA has also been reported in other locations with average concentrations in the μg/L range, such as in Ghana, Nigeria, Philippines, and Portugal (Figure 2a). Adjei et al. (2022) found a concentration of 6.36 μg/L in Chemu Lagoon μg/L, 1.99 μg/L in Densu River, 1.19 μg/L in Ashaiman Lake and 1 μg/L in Fosu Lagoon (Ghana). The authors highlight that Chemu Lagoon is situated along the Tema industrial area and the harbor expansion, the industrial hub of Ghana. Furthermore, increased domestic use and inappropriate disposal of BPA plastic materials may justify the higher concentrations. Similarly, Idowu et al. (2022) observed concentrations between 0.41 and 5.19 μg/L in the Ala River in Nigeria. According to the authors, the sampling point on Ala River with very high BPA concentration had an auto-mechanic workshop and a dumpsite in its proximity; thus, BPA can enter the river at this location. Rotimi et al. (2021) warn that the consumption and import of plastics are not regulated in most African countries; therefore, contaminants in plastics such as BPA are predicted to increase in the environment across Africa.

BPA analogues have also been found in several countries (Figure 2b). The greatest diversities of BPs were reported in China, Portugal, Spain, and India, while the most common BPA analogs in several countries were BPS and BPF. The highest average concentrations were predominantly in Portugal for BPB (1.6 ± 1.5 μg/L) and in India for BPS (2.7 ± 1.3 μg/L). Furthermore, BPF was highlighted in terms of concentration in countries such as Japan, Korea, and Malaysia, with average concentrations of 1.2 ± 0.6 μg/L, 1.3 μg/L, and 1.1 μg/L, respectively (Figure 2b). Yamazaki et al. (2015) highlight that Asian countries are responsible for much global BPA production. Furthermore, the high population density of countries such as China and India directly contributes to greater production and consequent release of BPs into the environment.

Figure 2 – Average concentrations (ng/L) and their respective number of samples (n) for a) BPA and b) its analogues by country. Reference: Table S1 (Supplementary Material).

a)




BPAF
BPAP
BPB
BPC
BPE
BPF
BPFL
BPS
BPZ
Concentration (ng L⁻¹)
10000
1000
100
10
1
0,1
0,01
0,001
EUA
United Kingdom
Spain
Slovenia
Portugal
Poland
Malaysia
Korea
Japan
Italy
India
France
Czech Republic
China
Brazil

Notably, the average concentrations of BPF were higher than those of BPA in Japan, Korea, and Malaysia, which also occurred in countries such as China and India with other BPA analogues. Therefore, restrictive legislation regarding the use of BPA must include its analogues. In Japan, for example, BPA has been banned in thermal receipt paper; however, several analogs, such as BPS and BPF, have been reported as substitutes (Frankowski et al., 2020). Meanwhile, in China, the restriction on BPA concentration in food contact materials has been reduced to 0.6 mg kg^{-1} (Wang et al., 2021); however, China was the place with the greatest variety of other BPs. Likewise, in the European Union, the use of BPA in polycarbonate baby bottles has been prohibited, and its use in thermal paper must be less than 0.02% (Demierre et al., 2024; Silano et al., 2020). On the other hand, other types of BPs have been identified in Spain, Slovenia, Italy, the Czech Republic, France, Poland, and the United Kingdom.

These results consolidate the need for increasing investigations into the occurrence of these BPs in surface waters. Although this study advances the most current overview of the occurrence and global distribution of BPs in surface waters, data are still scarce for many BPs and countries. Furthermore, the ubiquity of BPs in waterbodies in different locations corroborates the importance of studying their environmental risks and efficient technologies aimed at reducing or eliminating the continuous discharge of BPs into the aquatic environment.

4.3.2 Aquatic toxicity and environmental risks of bisphenols

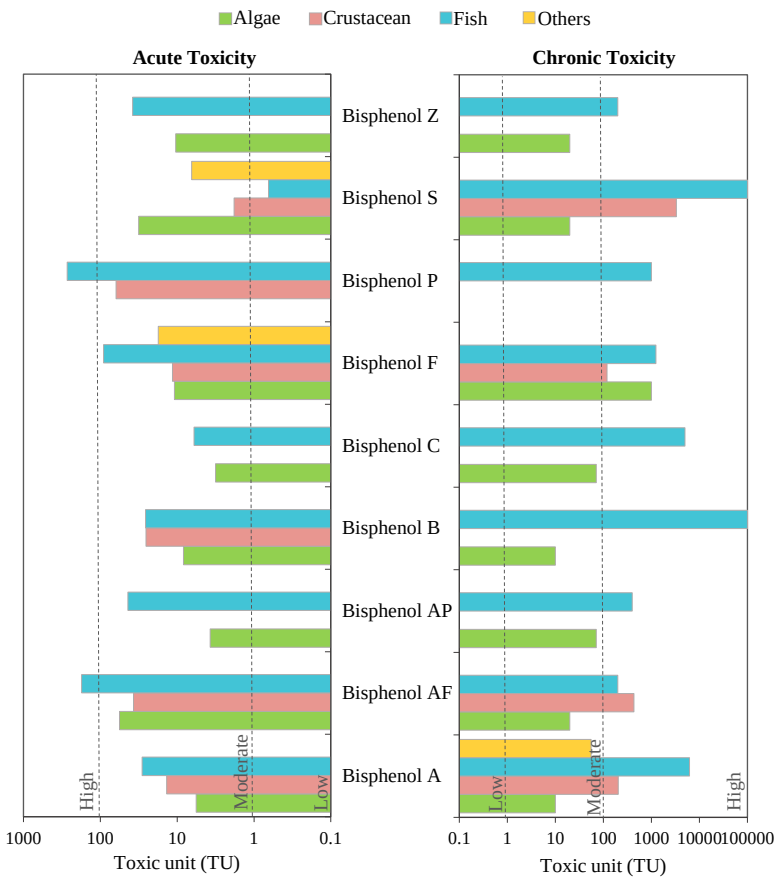
4.3.2.1 Acute and chronic toxicity

Once the presence of BPs in surface waters worldwide has been proven, toxicity tests are essential to determine their adverse effects on aquatic organisms and the concentration that can cause these effects. Despite the importance of the ecotoxicological assays, data regarding the acute and chronic effects of BPA analogues are still scarce for many trophic levels; therefore, the compilation of these data contributes to understanding the extent of the impacts and facilitates the comparison between BPs. Toxicity data were found for BPA, BPAF, BPAP, BPB, BPC, BPF, BPP, BPS, and BPZ (Table S2, Supplementary Material).

In Figure 3 the acute and chronic toxicities (represented in toxic unit (TU)) for BPs are exposed, at different trophic levels found in the literature, as well as their classifications: low concern, moderate concern, and high concern (Persoone et al., 2003). It is possible to see that only BPS presented low concern for algae species, while the other cases were considered of moderate or

high concern for all organisms. Furthermore, for most BPs TU values were considerably higher for fish. These results are concerning since many waterbodies have been consistently contaminated by BPs, as discussed in Section 3. Even at low concentration, they may cause acute or long-term effects on aquatic organisms, due to the high values of TU. Concomitantly, these compounds are generally tricky to degrade, and their in-situ removal is still a challenge (Demierre et al., 2024; Frankowski et al., 2020; Torres-García et al., 2022; L. Wang et al., 2019; Wang et al., 2021; Zhou et al., 2020). Therefore, continuous contact between organisms and BPs is a reality.

Figure 3 – Acute and chronic toxicity of BPs by aquatic organism. Reference: Table S2 (Supplementary Material).



BPA showed high chronic toxicity for crustacean and fish species. Mihaich et al. (2009) evaluated the crustacean *Hyalella azteca* for reproduction for 42 days and found a NOEC of 0.49 mg/L, which corresponds to a TU of 204. In addition, Staples et al. (2011) investigated the effect of BPA on the fish *Pimephales promelas*. The authors found a NOEC of 16 µg/L about the induction of vitellogenin (Vtg) production in male fish. Vtg is synthesized in the female

liver as the precursor to egg yolk; therefore, male fish and juvenile fish do not produce Vtg. However, exposure of fish to estrogenic compounds, such as BPA, can induce the production of Vtg in male fish, characterizing the feminization of fish. Furthermore, these compounds can lead to changes in the reproductive system of organisms, as observed in crustaceans (Mihaich et al., 2009; Staples et al., 2011; Tišler et al., 2016).

When comparing the toxicity of BPs, it is possible to see that the BPA analogues were many times more toxic than BPA, which applied to acute and chronic toxicity, regardless of the trophic level (Figure 3). The most critical toxicity values were for BPB and BPS in fish species. The highest toxicity for BPB was shown by Qiu et al. (2021), with a NOEC of 1 μg/L when evaluating the body length of Zebrafish (*Danio rerio*) *larvae* for 7 days. Similarly, Naderi et al. (Naderi et al., 2014) observed a NOEC of 1 μg/L (reproduction, 7 days) for *Zebrafish*. These values reinforce the concern regarding BPA analogues and the need for more studies about the risks and the technologies capable of removing them.

Furthermore, environmental concentrations of BPs can exceed reported NOEC values (1 μg/L), as happens in the Tagus River in Portugal for BPB (Cunha et al., 2022), in Cooum River, Adyar River and Buckingham Canal in India for BPS (Yamazaki et al., 2015), and in Liuxi River in China for BPS (Huang et al., 2018). The same occurs for BPA, where concentrations reported for several rivers in Taiwan (Chen and Chou, 2016; Chou et al., 2015; Lee et al., 2013) were greater than the NOEC (16 μg/L) for freshwater fish (Staples et al., 2011). In studies evaluating the toxicity of other emerging pollutants, such as pharmaceuticals and microplastics, environmental concentrations are usually lower than the toxicity values presented (Rodrigues dos Santos et al., 2023). Thus, this finding for the cases of BPs shows the potential threat of these compounds to the aquatic ecosystem.

The acute effects were less pronounced compared to the chronic ones, since to realize long-term effects, lower concentrations of BPs are necessary. However, the acute TU for fish species was high for BPAF and BPP (Figure 3). Moreman et al. (2017) found an EC_{50} of 0.92 mg/L (hatching rate, 72 hours) for Zebrafish larvae, while Ren et al. (2023) observed an EC_{50} of 0.4 mg/L for adult Zebrafish and 0.37 mg/L for Zebrafish larvae for mortality in a 96-hour exposure. Therefore, toxicity can be high even in short interactions between BPs and aquatic organisms. It is worth mentioning that no studies were found evaluating the occurrence of BPP in surface waters. Therefore, the assessment of the environmental effects of this compound is still limited.

Further investigation is needed into the presence of BPP in surface waters since it is also used as feedstock for polycarbonate, polyester, and epoxy resins. Therefore, it can reach waterbodies through industrial and domestic wastewater and the degradation of plastic materials.

Another critical issue related to environmental toxicity is the interaction of BPs with each other and with other pollutants present in waterbodies. Studies show that the mixture of toxic or non-toxic compounds can cause an increase or emergence of adverse effects on organisms (Rodrigues dos Santos et al., 2023). For example, Di Paola et al. (2021) evaluated the toxicity of BPA and two heavy metals (Cd and Cr) alone and mixed for Zebrafish. The study showed that in the groups with single exposure to contaminants, there was no significant difference in the content of reactive oxygen species (ROS) compared to the control group. However, in the binary mixtures BPA+Cd and BPA+Cr, the increase in ROS production was significant, which can lead to several diseases, death, and fish aging.

Regarding analogues, Mu et al. (2022) investigated the effect of mixtures between BPA and BPF with polystyrene microplastics on the lethality in Zebrafish larvae and found synergistic effects that is, greater toxic effects on mixture relative to the compounds alone. Similarly, Kwon et al. (2016) found that co-exposure of male Zebrafish to BPAF and sulfamethoxazole significantly increased the thyroid endocrine disrupting effect of BPAF. Despite these demonstrations, more studies are needed to verify the effects of mixing between BPs. The challenge becomes greater in complex samples – such as surface water and wastewater – where the co-existence of several toxic compounds is a fact.

This study's compilation and discussion of data provided an overview of the endpoints and organisms most sensitive to BPs. It also compared their acute and chronic toxic effects, considering concentrations in the aquatic ecosystem. However, a more detailed investigation of the environmental effects of BPs is necessary for a more accurate assessment of the relationship between concentration and toxicity, which can be done based on environmental risk assessment.

4.3.2.2 Environmental risk assessment

Environmental risk assessment, based on the RQ, is an essential method for determining the dangers of pollutants to aquatic organisms at environmental concentrations. To determine the RQ, the values of BPs concentrations in surface waters and the acute and chronic toxicity related to them were considered, as described in Section 2. Figure 4 shows the classification of acute and chronic risks (red: high risk; yellow: medium risk; blue: low risk; green: negligible risk) by

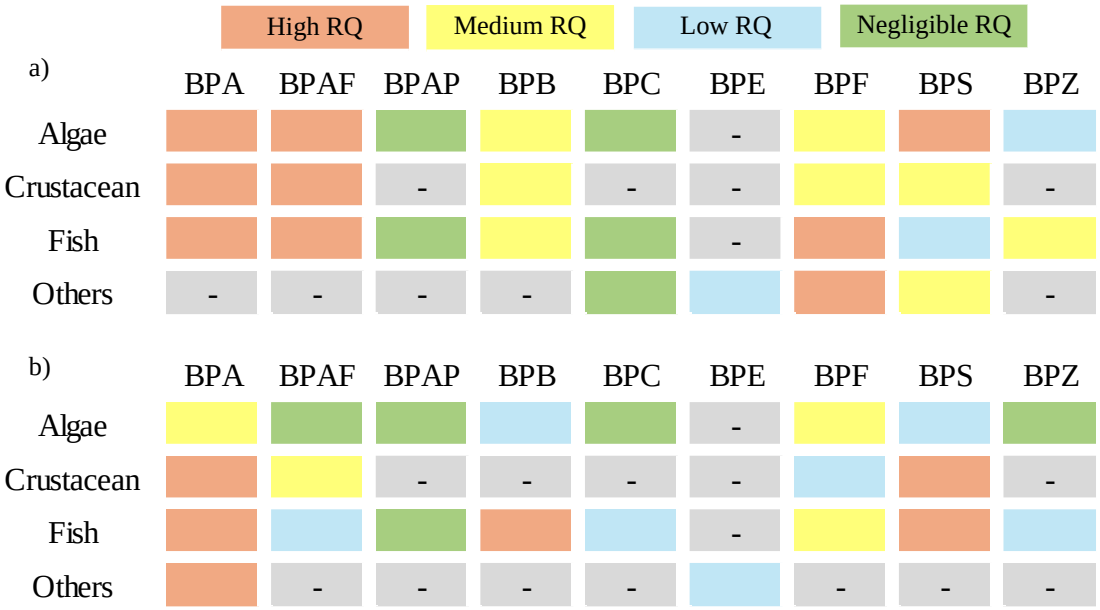
type of BPs and by aquatic organisms. The RQ values calculated for BPs can be consulted in Table S3 (Supplementary Material).

As shown in Figure 4a, acute risks were high for BPA and BPAF (algae, crustaceans, and fish), BPF (fish and bacteria), and BPS (algae). For BPB (algae, crustaceans, and fish), BPF (algae and crustaceans), BPS (crustaceans and bacteria), and BPZ (fish), the risks were considered medium. At the same time, the other BPs had low or negligible risks. Concerning chronic risks (Figure 4b), the RQ was high for BPA (crustaceans, fish, and rotifers), BPB (fish), and BPS (crustaceans and fish), while risks were medium for BPA (algae), BPAF (crustaceans) and BPF (algae and fish).

This assessment clarifies that the environmental risks related to analogues can be equivalent or even higher than those of BPA. BPAF, for example, had a high acute risk for the same trophic levels as BPA, even though it was present in surface waters at lower concentrations (Figure 1). This also occurs with BPF, BPS, and BPB, which, at lower concentrations than BPA, also present high risks due to their high toxicity. Gao et al. (2023)assessed the punctual risk of BPA, BPAF, and BPS in Beibu Gulf, China. According to the authors, all evaluated BPs presented low risks at all sampling sites in the Beibu Gulf. However, the highest average concentration of these compounds in the Gulf was 7.96 ng/L for BPA, while BPA concentrations in waterbodies in China ranged from 0.152 ng/L to 1.573 ng/L (Figure 2a). Therefore, a more comprehensive assessment of risks in different locations is necessary.

In addition, Tišler et al. (2016) evaluated – in a review article – the chronic RQ of BPA and BPF for the crustacean *Daphnia magna* and showed that these compounds are not potentially dangerous for crustaceans, with RQ lower than 1. However, it is essential to highlight that the authors reported the maximum concentrations of BPA and BPF found in surface waters equal to 28 μg/L and 0.180 μg/L, respectively. The most recent maximum concentrations reported in the present study for BPA and BPF are approximately 13 times and 32 times higher than those found in the study mentioned above, carried out in 2016 (Chou et al., 2015; X. Zhang et al., 2024). Therefore, the increased concentrations of BPs in the aquatic environment over time make environmental risk an increasing variable and even more concerning.

Figure 4 – Classification of a) acute and b) chronic risk quotient (RQ) by type of BPs and by aquatic organisms.



In addition to knowing the critical risks related to the types of BPs and aquatic organisms, it is crucial to consider the risks by region since the RQ may vary according to the concentration detected in certain waterbodies. Figure 5 shows that of the 33 countries evaluated, 24 locations presented medium or high risks. In this sense, high risks were observed in surface water from Brazil, Ghana, Nigeria, Philippines, and Taiwan (BPA), China (BPB, BPF and BPS), India and Poland (BPA and BPS), Japan, Korea and Malaysia (BPF), Portugal (BPA, BPS and BPB) and Slovenia (BPS). The BPs with the highest incidence of high risk in several locations were BPA, BPS, and BPF, respectively. At the same time, in most countries, the high RQ was for fish species, except BPS in China and India, which had a high risk for fish and algae (Table S3, Supplementary Material).

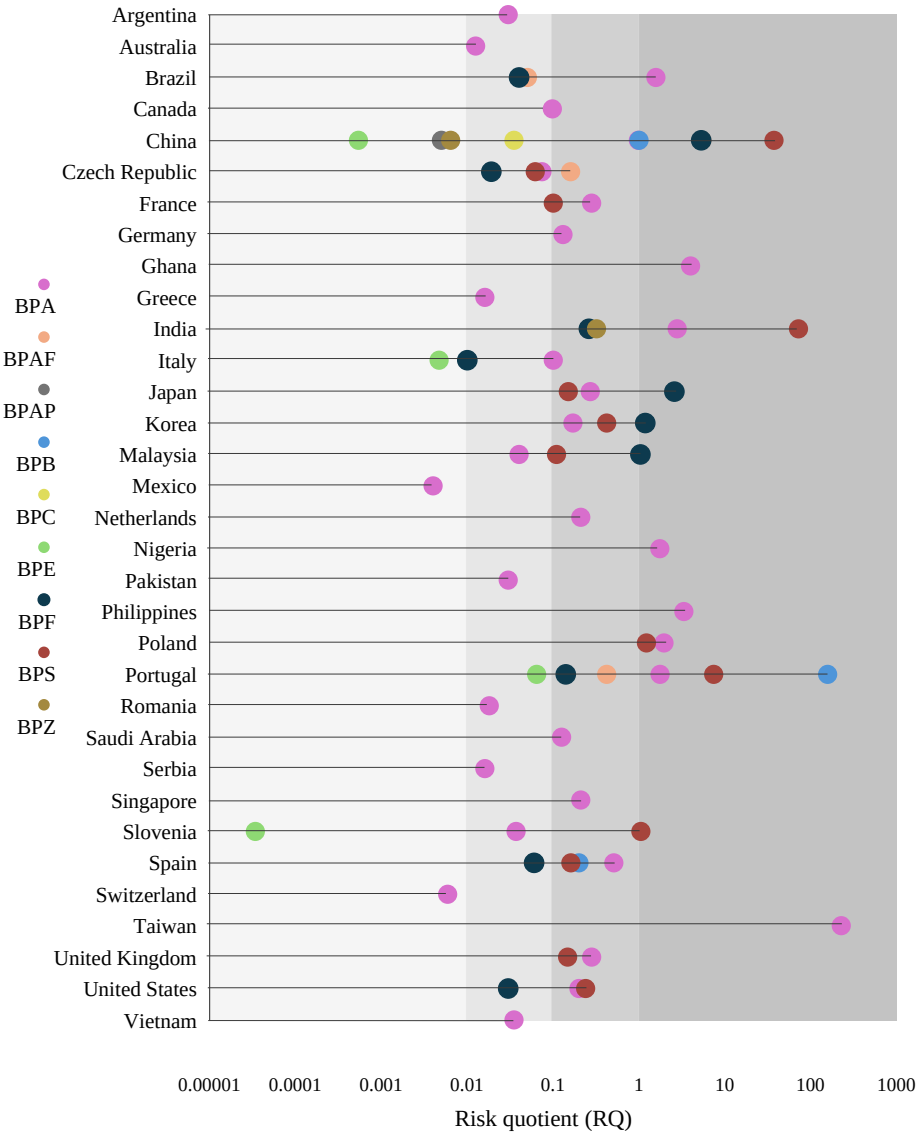
Among these countries, China and Portugal had high risks for a greater diversity of BPs, and together with India and Taiwan, presented the most worrying environmental risk scenarios. The chronic RQ for BPS in China was 37.2 for the Liuxi River, an urban river in Guangzhou, southern China. According to Huang et al. (2018), Liuxi River is located where domestic or industrial wastewater is discharged directly into rivers without any treatment. The BPS also presented the worst-case scenario for chronic RQ in India, with a value of 72.04 in the Adyar River, located in Chennai. Yamazaki et al. (2015) state that BPS is widely produced in India, which can lead to a greater concentration of this compound in waterbodies and, consequently, increase its risks. Along with this, it is known that a large part of construction debris and

municipal and industrial waste from Chennai has been thrown into the Adyar River, considered a dead river.

The most critical scenario for Portugal occurred for BPB in the Tagus River, with an RQ of 157.2. In addition to BPB, pesticides such as alachlor, α-HCH, and bifenthrin were detected in the Tagus River at concentrations with average levels of 2.5 μg/L (Cunha et al., 2022). According to the authors, the Tagus estuary, one of the largest in Europe, suffers contamination mainly due to two industrial zones located on the north and south banks and by domestic effluents from the Lisbon metropolitan area. Therefore, the occurrence of other dangerous compounds and the continuous release of pollutants make the environmental risk even more worrying in this waterbody of water since the risks can increase with the mixture and interaction of these compounds.

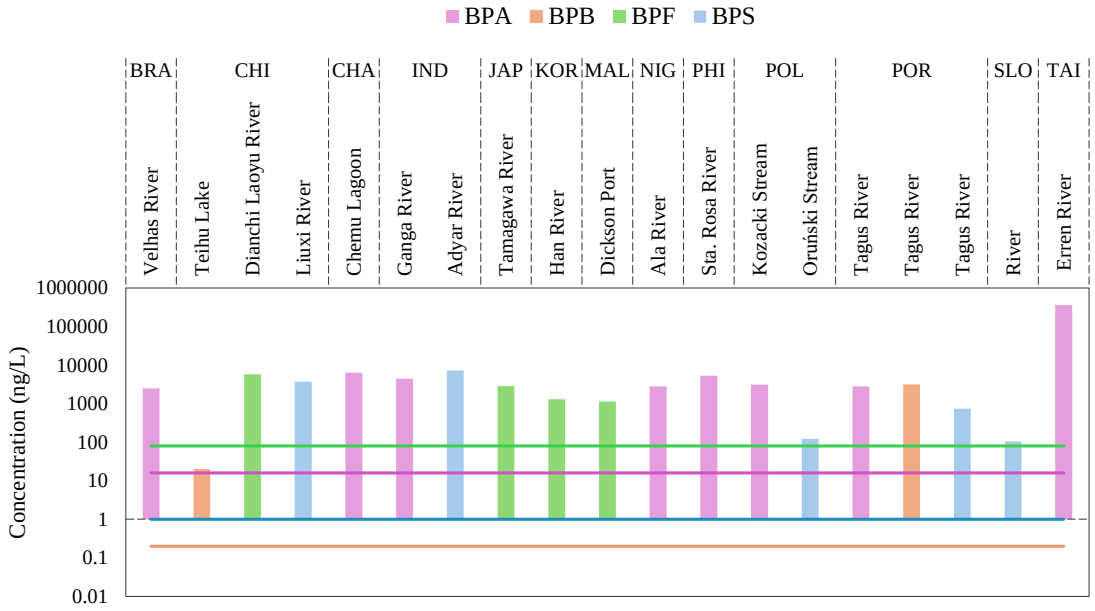
Concerning Taiwan, the most critical risk for BPA occurred in the Erren River, with an acute RQ of 103.6 and a chronic RQ of 226.57. High concentrations of BPA have been reported for this waterbody (Chou et al., 2015; Lee et al., 2013). For example, Chou et al. (2015) found BPA in 100% of samples from the Erren River in dry and rainy seasons, with concentrations ranging from <0.01 to 725 μg/L. The highest concentrations of BPA were identified near the confluence of tributary San–Yeh–Kung Creek, where eight industrial areas are located nearby. In addition, other compounds were found, such as nonylphenol, estrone, 17β-estradiol, estriol, and 17α-ethinylestradiol – all known as endocrine disruptors with estrogenic effects.

Figure 5 – Environmental risk for BPs by country. The gray color scale represents from lightest to darkest: negligible, low, medium, and high risk.



In the absence of regulations regarding the limit concentrations permitted in surface water, the maximum concentration limits of BPs were calculated in each location with a high RQ (>1) so that the RQ became negligible (≤ 0.01), considering the values already established of toxicity. Figure 6 shows that the difference between the concentrations detected and those expected for negligible risk is large in all locations, with the former being 14 to $2.3 \cdot 10^4$ times greater than the latter.

Figure 6 – Difference between the detected concentrations for BPs (bars) and those expected for negligible risk (lines) by waterbody.



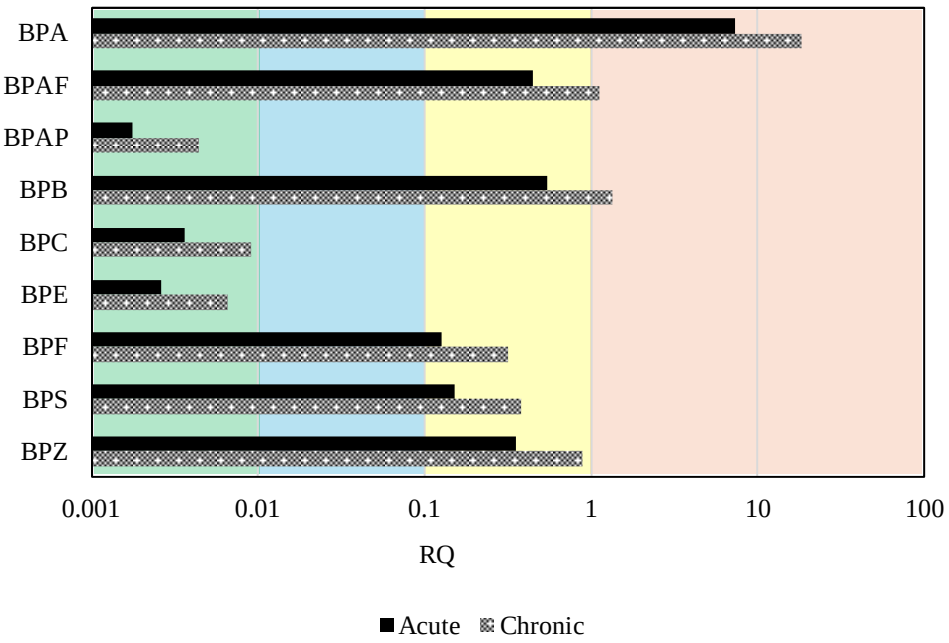
These results show that measuring the estrogenic risk of BPs is of great relevance for the scientific community. Therefore, the present study also assessed the environmental risk of the estrogenic activity for the highest concentration BPA and its analogues in surface waters (Figure 7). All BPs have RP values below $1.29 \cdot 10^{-3}$ (Table S4, Supplementary Material), indicating low estrogenicity compared to 17β-estradiol. However, due to the high concentrations measured in the environment, some BPs still pose high chronic risks related to estrogenic activity, which is the case for BPA, BPAF and BPB. BPA also presents high acute estrogenic activity risk. For BPF, BPS and BPZ concentrations, the risks of estrogenic activity were classified as medium. The BPs with negligible estrogenic activity risks were BPAP, BPC and BPE, considering both acute and chronic effects, showing that they could be the best substitutes for BPA. This result is in accordance with environmental risks for BPA, BPC and BPE, that were classified as low or negligible (Figure 4).

Intensive research has shown the impact of estrogenic compounds to the human beings, such as decline in male fertility, development of prostate, lung, endometrial and breast cancer (Henderson and Feigelson, 2000; Jørgensen et al., 2012). For aquatic organisms, the presence of estrogenicity is associated to fish feminization of male species, changes in primary and secondary sexual characteristics, disturbance in the production and egg quality of female fish (Karki et al., 2021; Thorpe et al., 2009). Other species that have part of their lifecycle in aquatic

environment are also affected by estrogens. For example, amphibian female population have been dominated by female individuals, which may be related to the exposure to estrogenic compounds in their habitats (Lambert et al., 2015). Also, birds neuroendocrine, behavior and immune systems are negatively affected by the endocrine disruptors such as BPA and its analogues (Heimovics et al., 2015; Ottinger et al., 2008). With the risk analysis of the present research, the concern with BPs and its potential effects in aquatic environment has increased.

Therefore, these results show the urgency of efficiently removing BPs in wastewater for safe release into the aquatic environment and in situ removals in surface waters. Furthermore, limiting the use of analogues – and not just BPA – in industry and developing protective legislation regarding the concentrations of BPs in the environment are essential.

Figure 7 – Environmental risk of the estrogenic activity of BPA and its analogues. Red: high risk; yellow: medium risk; blue: low risk; green: negligible risk.



The discharge of wastewater without proper treatment or even WWTPs are an important source of BPA and analogues to the waterbodies. Conventional WWTPs are designed to remove organic matter and nutrients and have little or no removal of recalcitrant compounds like BPs (Gu et al., 2021). Indeed, as can be seen by the many concentration reports found in Section 3, the occurrence of BPs in the surface waters is a result of their constant release due to insufficient wastewater treatment. Zhang et al. (2024) showed that the concentration of BPs in Qinhuai River Basin (China) downstream of WWTPs was up to 2.4 times higher than upstream,

highlighting the impact of the treatment technologies in introducing micropollutants to surface waters. In a recent review, the maximum concentration of BPs in raw municipal wastewater was as high as 16.6, 20.9 and 68.9 μg/L for some countries (Czarny-Krzymińska et al., 2023).

In other matrices - such as landfill leachate - these concentrations may be higher due to the large amount of plastic waste (sources of BPA leaching) present in these locations. Chamanee et al. (2024) found 158 ± 84.4 μg/L of BPA in landfill leachate in Sri Lanka. In addition, Narevski et al. (2021) observed high concentrations - 2.78 mg/L - at the Sanitary landfill Gigoš in Jagodina, Serbia. Huang et al. (2021) also evaluated the concentration of BPs in municipal wastewater, hospital wastewater, and landfill leachate and found concentrations around 30 times higher in landfill leachate. Furthermore, industrial wastewater may have higher concentrations of BPs due to the widespread use of these compounds in their processes. For example, Hernández-Fernández et al. (2022) investigated industrial wastewater treatment plants in the production processes of polypropylene and polyethylene terephthalate in South America and found a BPA concentration of up to 12.5 μg/L. Therefore, it is extremely important to implement technologies capable of removing BPA and analogues in WWTPs, to reduce the adverse effects on aquatic communities. MBR have been shown great results in removing different classes of micropollutants, like pharmaceutical active compounds, pesticides, microplastics and phenolic compounds (Ladeia Ramos et al., 2024a; Sengupta et al., 2021; Wijekoon et al., 2013). Therefore, the present review also evaluated the removal of BPs by MBR.

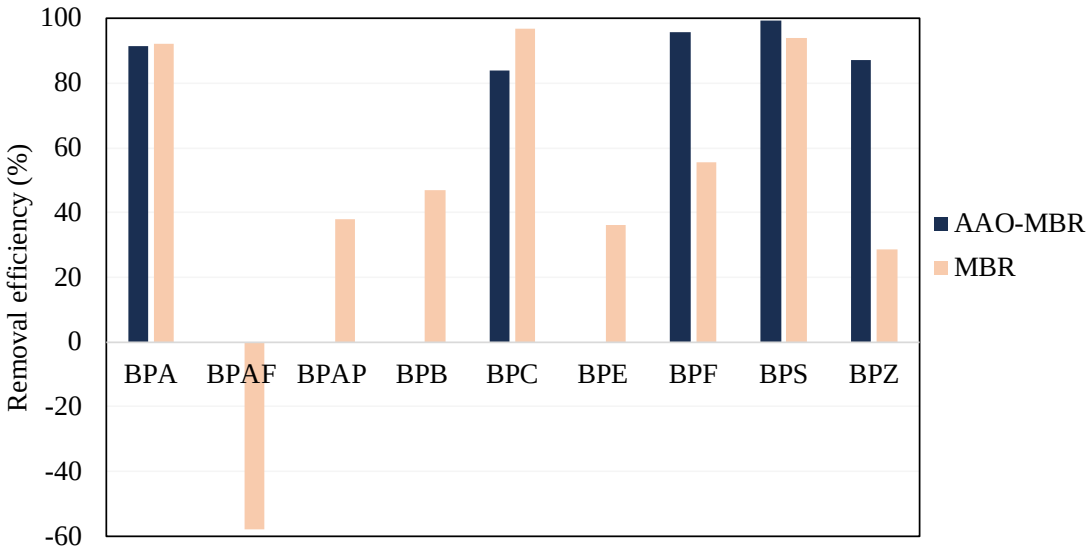
4.3.3 Removal of bisphenols and environmental risks by membrane bioreactors

4.3.3.1 Removal of bisphenols by MBR

MBR combine biological treatment with membrane separation process (MSP) and have been used as an advanced wastewater treatment technology, producing high quality water (Liu et al., 2020; Simon Judd, 2006). MBR have attracted the attention for the removal of micropollutants because they operate with a higher SRT and biomass concentration than conventional activated sludge process, increasing their ability to remove recalcitrant micropollutants (S. Wang et al., 2020). Figure 8 presents the removal of BPA and analogues by full-scale MBR and their variation. Lab-scale and pilot-scale MBR have been studied only for BPA removal, and all the data found in literature is presented in Table S5 (Supplementary Material). A significant part of the data is reported for BPA. The removal of analogues is still poorly investigated in MBR and just a few numbers of studies were found.

Comparison of the average removal between all BPs analogues were considered for full-scale aerobic MBR and anaerobic-anoxic-oxic MBR (AAO-MBR) (Figure 8). For AAO-MBR, the higher removal efficiency was found for BPS (99.5%, n = 1) > BPF (95.8%, n= 1) > BPA (91.4%, n = 3) > BPZ (87%, n = 1) > BPC (84%, n = 1). While for MBR, the higher removal efficiency was found for BPC (97%, n = 2) > BPS (94%, n = 1) > BPA (92%, n = 1) > BPF (55.7%, n = 2) > BPZ (28.5%, n = 2) > BPB (47%, n = 1) > BPAP (38%, n = 1) > BPE (36%, n = 1) > BPAF (-58%, n = 1). AAO-MBR presented higher removal efficiency for BPS, BPS and BPZ, despite no data being found for some BPs (BPAF, BPAP, BPB and BPE). On the other hand, the removal of BPC was higher for MBR, showing that different mechanisms act on the degradation of BPs.

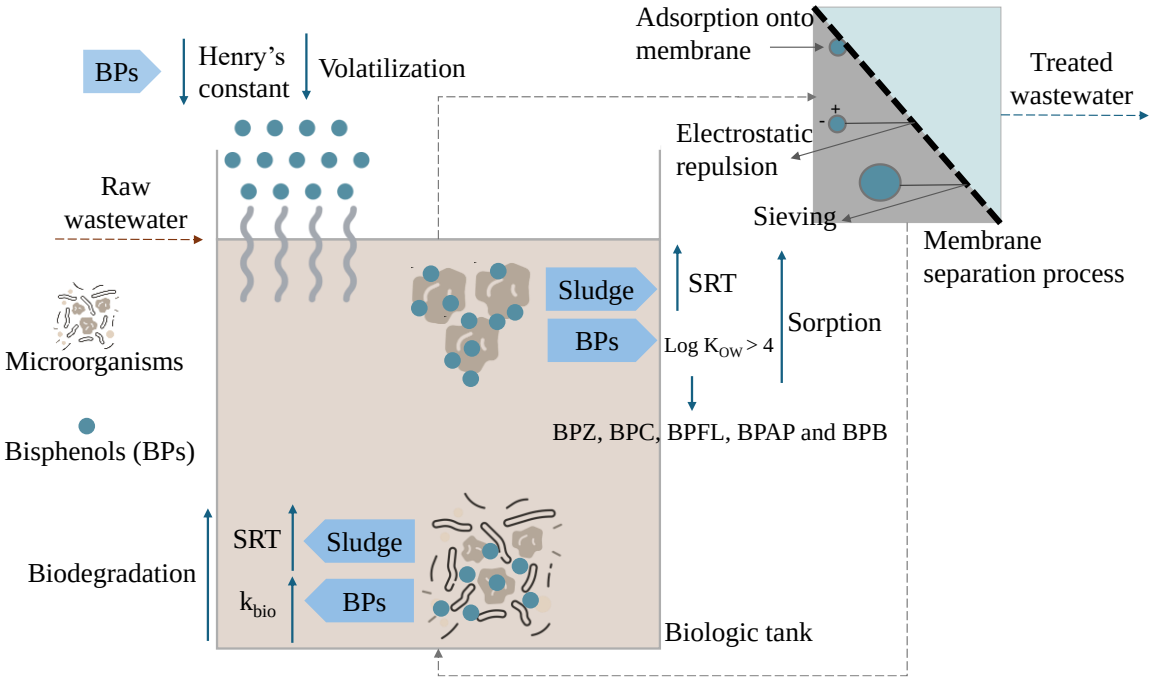
Figure 8 – BPA and its analogues removal efficiency by Full-scale AAO-MBR and MBR. Reference: Table S5 (Supplementary Material).



In the biological treatment, removal pathways of trace organic contaminants include biodegradation, sorption onto the sludge and volatilization (Abegglen et al., 2009; Ferrer-Polonio et al., 2021; Min et al., 2018). Figure 9 shows the pathways of BPs removal in MBR. Biodegradation is related to biochemical reactions, during metabolism of biodegradable organic compounds, when microorganisms produce enzymes that may be capable of degrading BPs analogues (Xue et al., 2010). The most important enzymes involved in BPA degradation are P450 cytochrome, P450 monooxygenase, ammonia monooxygenase, and laccase (Mahesh et al., 2022). They are produced by a bacterial consortium, formed by bacteria that has BPA as a carbon source in metabolic routes, who are called BPA-degraders, and by non-BPA-degraders,

that help to remove BPA by co-metabolism, because they are not capable of degrading BPA (Noszczyńska and Piotrowska-Seget, 2018). Ammonium-oxidizing bacteria, for example, express ammonia monooxygenase to oxidize ammonia, but the enzyme is known to also catalyze the oxidation of aromatic hydrocarbons like BPA (Keener and Arp, 1994; Kim et al., 2007). Some studies have identified the oxidation to intermediates of BPA like 1,2-bis(4-hydroxyphenyl)-2-propanol, 4,4'-dihydroxy-methylstilbene, 4-hydroxyacetophenone, 4-hydroxybenzaldehyde, until mineralization, forming CO_2 and H_2O (Fischer et al., 2010; Ike et al., 2006; Noszczyńska and Piotrowska-Seget, 2018).

Figure 9 – Pathways of BPs removal in biologic tank and membrane separation processes in an MBR.



As shown in section 4, BPs are toxic to aquatic organisms and humans, but attention should also be paid to the toxicity in microbiological communities, especially during biological treatment. Rasheed et al. (2013) investigated the inhibition of bacteria by BPA. They found that BPA was more toxic to gram-positive bacteria *Staphylococcus aureus*, *Bacillus subtilis*, but antibacterial activity was found for the gram-negative *Proteus vulgaris* and *Escherichia coli*. The presence of BPA was correlated with the reduction in microorganisms' diversity in the study of Cydzik-Kwiatkowska et al. (2017). The most abundant phyla were Proteobacteria, Bacteroidetes and Verrucomicrobia. However, the order Pseudomonadales, from the phylum Proteobacteria, was the most sensitive to the compound, reducing its number by almost 100

times. Proteobacteria, represented by the genera *Pseudomonas, Azospira, Hydrogenophaga, Devosia, Delftia, Acidovorax* and *Rhodobacter*, was also significantly related to BPS degradation by activated sludge in the study of Huang et al. (2019). On the other hand, *Ferruginibacter* sp., *Zoogloea* sp., *Flavobacterium* sp., and *Aquicella* sp. were inhibited by BPS, which suggests that these species are sensitive to BPS and/or its degradation byproducts. Zhao et al. (2014) evaluated the mechanisms of toxicity formation in activated sludge treating synthetic wastewater with BPA. They observed that the higher the BPA concentration, the higher toxicity. Also, BPA degradation was the main cause of toxicity to the sludge rather than the adsorption of BPA. Therefore, toxicity to microbial communities was caused by BPA degradation byproducts and secretion produced by the microorganisms themselves (Zhao et al., 2014).

Tian et al. (2022) studied the toxicity resistance in *Rhodococcus* equi when degrading BPA and found downregulation in the genes related to glycolysis/gluconeogenesis, pentose phosphate metabolism, and glyoxylate and dicarboxylate metabolism. On the other hand, the bacteria strain mitigated the impact of BPA by regulating the genes responsible for excisional repair, energy metabolism, osmoprotection, and the iron complex transport system. In the same way, some microorganisms can be diminished by the presence of toxic compounds, due to the interference in their metabolic activities, while other communities could be capable of adapting to new conditions.

BPs may impact the removal of organic matter and nutrients in biological treatment since microbial activity is compromised. Seyhi et al. (2013, 2012) operated a submerged MBR with synthetic wastewater, which achieved 99% removal of COD. After 75 days of operation, they spiked BPA (1 mg/L), and the COD in the permeate increased, until day 90, when COD removal stabilized again in 99% after biomass acclimatation. In spite of that, when the influent concentration of BPA was gradually increased (1 to 15 mg/L), a change in COD removal was observed, specifically for BPA higher than 5 mg/L. Nevertheless, BPA removal was maintained at 99%. Zielinska et al. (2014) and Ouarda et al. (2018) also concluded that the increasing concentration of BPA in wastewater decreases COD removal efficiency and nitrification activity of the biomass, justified by the biomass state of stress caused by BPA and competition of ammonia monooxygenase for the oxidation of BPA. However, for the study of Ouarda et al.(2018) , the concentration of NH_4^+ and COD started to decrease after a period of adaptation, and even at concentrations of BPA higher than 40 mg/L, its removal increased again to 97%.

As shown by Ferrer-Polonio et al. (2021), previously biomass adaptation with BPA can be positive to improve its biodegradation and reduce the toxicity to sludge. Thus, biomass adaptation to BPA and analogues could prevent sludge change in wastewater treatment, favoring their removal in biological treatment and in MBR.

BPA and its analogues have very low Henry's constant values, and they would not be removed by volatilization pathway (Ferrer-Polonio et al., 2021; H. Wang et al., 2019). As MBR increase SRT, sorption is improved, depending on micropollutants properties, i.e. hydrophilicity, represented by Log K_{OW}. The higher the Log K_{OW}, more hydrophobic the compound is. Usually compounds with Log $K_{OW} > 4$ are considered more hydrophobic and have high affinity to organic matter and sludge phase, which is the case of BPZ, BPC, BPFL, BPAP and BPB. For those with Log K_{OW} between 2.5 and 4, hydrophobicity is moderate, as for BPA, BPE, BPF and BPAF. BPS, with Log $K_{OW} < 2.5$ is hydrophilic and has low sorption tendency. Sorption is dependent on physico-chemical properties and concentration, and when sludge maximum sorption capacity is reached, micropollutants cannot be removed (Arcanjo et al., 2022). Also, if sewage sludge is applied in agriculture soil to enhance its fertility, BPs and other contaminants removed by sorption remaining in the sludge are a big problem (Ferrer-Polonio et al., 2021). Thus, biodegradation is substantial in the elimination of BPs and must be improved in WWTP. As stated before, MBR can increase the ability of microorganisms in removing micropollutants when compared with conventional activated sludge systems.

Furthermore, another mechanism is responsible for BPs removal in MBR. Although MF and UF membrane pore sizes are usually higher than BPs, the BPs associated with particulate material and adsorbed to the membranes can be retained. Also, the presence of the fouling layer on the membrane surface, formed in MBR operation, can affect the rejection of the contaminants by size exclusion (Hajibabania et al., 2012).

Therefore, it is expected that MBR would have an improvement compared to conventional wastewater treatment. Wang et al. (2019) carried out a review about the removal mechanisms of BPA and its analogues in municipal wastewater treatment plants and found average removal of BPAP (97.8%), BPF (86.4%), BPZ (85.5%), BPC (83.3%), BPS (81.2%), BPB (72.9%), BPA (69.3%), BPE (−19.5%), and BPAF (−52.5%). Compared to the present review, MBR presented lower removal for BPAP, BPF, BPZ and BPB. The justification for the worst results is difficult to understand, since all the data are related to full-scale WWTP and operational conditions

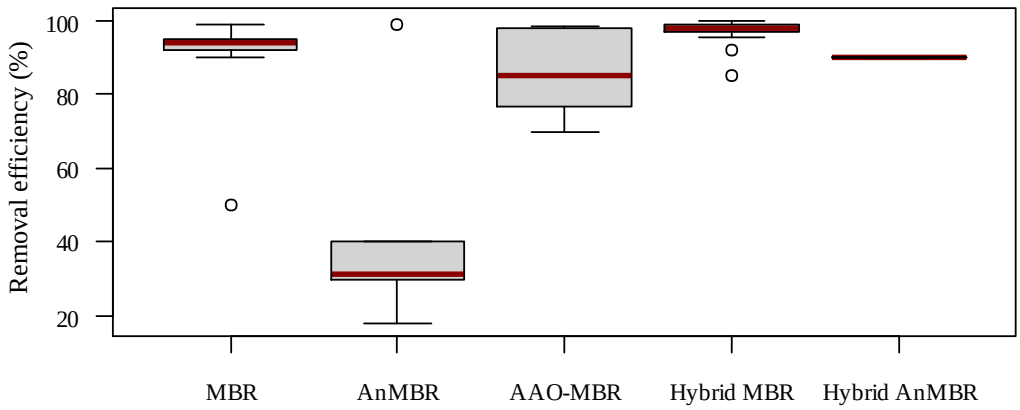
significantly impact treatment efficiency. It is emphasized the importance of more studies investigating BPs analogues, especially in a long-term operation to understand the factors that may reduce their removal.

Attention must be paid to BPAF, that is more recalcitrant in environmental than other BPs analogues (Chen et al., 2016a). Therefore, it is expected that BPAF would have the low removal efficiency in biological treatment, since sorption would be the only mechanism responsible for it. Indeed, negative removal was found for BPAF and BPE, which is a result of their concentrations in the effluent being higher than influent. The same has already been observed by Sun et al. (2017), in WWTP in China. The WWTP techniques were not MBR but composed of biological treatment. The negative results can be justified by the lack of degrading bacteria in the WWTP and the release from conjugated forms. When considering the results for BPAF, MBR with MF or UF membranes were not capable of improving the performance, but for BPE, MBR removal increased to 36.0%, much higher than the average values found by Sun et al. (2017) (-82.5%) and Wang et al (2019) (-19.5%) for other biological WWTP (Table S5, Supplementary Material).

Nevertheless, further studies on BPs analogues in full-scale WWTP with MBR need to be carried out to understand the mechanisms affecting their removal.

Figure 10 shows the removal of BPA by the different kinds of MBR, in lab, pilot and full-scale operation. For MBR, it was considered conventional MBR, with aerobic biodegradation and MF or UF membrane, including hybrid moving bed biofilm reactor–membrane bioreactor (MBBR–MBR), and sequencing batch membrane bioreactor (SBR-MBR). Hybrid MBR were the MBR followed by another membrane, such as NF, RO, MD or FO, or osmotic membrane bioreactor (OMBR). For anaerobic MBR (AnMBR), it was considered anaerobic MBR itself. On the same way, the hybrid AnMBR were any AnMBR that used NF, RO, MD or FO membranes. Another class of MBR were the AAO-MBR. No study was found for lab or pilot scale MBR regarding the removal of BPA analogues.

Figure 10 – Removal efficiency of BPA by several configurations of MBR. Reference: Table S5 (Supplementary Material).



In general, conventional MBR, with UF or MF membrane, present BPA removal of 91.5%, while in AnMBR, BPA removal is only 43.6%. It is well known that biodegradation of micropollutants is lower under anaerobic conditions, when compared to aerobic conditions. Wang et al. (2019) and Zhou et al. (2012) estimated the biodegradation constant for BPA (k_{bio}), that in aerobic condition was 0.30 L/gSS/h, while in anaerobic condition the constant decreased to 0.23 L/gSS/h. An exception was found in the work of Wijekoon et al. (2015), when BPA removal was 99%, possibly due to extended hydraulic retention time (HRT) and SRT of 96 h and 180 d, respectively, which may not be feasible in WWTP.

Removal of BPA by AAO-MBR was slightly lower than in MBR, with an average of 86.0%, despite 3 of the 5 WWTP present removal higher or equal to 98%. Nevertheless, AAO has been reported to have lower removal of BPA than aerobic process (H. Wang et al., 2019). The justification relies on the biodegradation constants, that for anoxic condition are even lower than aerobic and anerobic (0.079 L/gSS/h) (Zhou et al., 2012).

The substitution of MF and UF for more selective membranes like NF, RO and FO, or the combination of conventional MBR with the latter, increased BPA removal from 91.5% to 97.1%. Besides all the factors affecting BPA removal, size exclusion and electrostatic interactions now play an important role in rejecting the contamination. Therefore, contaminants retention time in hybrid MBR is higher, leading to enhanced biodegradation (Alturki et al., 2010). For illustration, Zhu and Li (2013) compared two lab-scale MBR for the removal of BPA, one with MF and one OMBR. Global removal of BPA in conventional MBR was 93.9% and increased to 98% in OMBR. The authors found out that the rejection of BPA by FO membrane was 70%, while MF membrane rejected only 10% (Zhu and Li, 2013). But it is

important to emphasize that even with a low removal by MF, the MBR had a high removal which shows the importance of the combination of removal mechanisms in MBR (biodegradation, sorption, membrane rejection).

As stated for hybrid MBR, significant improvement in AnMBR efficiency could be achieved by using high retention membranes and overcome disadvantage over aerobic treatment. Unfortunately, only one paper was found in literature investigating BPA removal in hybrid AnMBR. Song et al. (2018) integrated membrane distillation in an AnMBR and reached an average BPA removal of 90%, while AnMBR could removal only 17% of BPA. Despite the lack of studies showing that hybrid AnMBR may be a feasible alternative to WWTP, dealing with the removal of BPA, other research has proven that they are indeed very effective in removing trace organic compounds, estrogenic activity and toxicity, producing higher quality permeate water, reducing even human health risks (Arcanjo et al., 2022; Caroline Ricci et al., 2021; Santos et al., 2023).

Other types of MBR were also investigated in literature for BPA removal in municipal wastewater, as presented in Table S5 (Supplementary Material). The enzymatic MBR (EMBR) use laccases, that are oxidoreductase enzymes capable of oxidizing a wide range of aromatic compound, like phenols (Nguyen et al., 2016). Two EMBR, catalyzed by laccase, obtained only 18% and 42 % of BPA removal (Asif et al., 2020; Nguyen et al., 2016), despite being an ecofriendly alternative to activated sludge systems, since it produces less sludge and fungal enzymes can degrade trace organic compounds. On the other hand, when syringaldehyde, a redox mediator, was introduced in EMBR, as in the study of Nguyen et al. (2016), the removal reached 98%. This was a result of reactive radical species generated by laccase-redox-mediator system. However, excess of radicals and syringaldehyde increased effluent toxicity, compromising EMBR applicability.

Granular activated carbon (GAC) was used in a fluidized bed membrane bioreactor (GAC-FAnMBR) and the removal of BPA was near 100% (Lee et al., 2021). GAC is used as a support for biofilm growth and the adsorption of BPA can also increase the contaminant retention time in the system. Also, the recirculation of GAC can promote a scouring effect on the membrane, contributing to cleaning and reducing the fouling (Dutta et al., 2014). Biogas sparging was also used in a fluidized bed membrane bioreactor (GAnMBR) and BPA was not detected in the

permeate, showing that somehow, biogas transports contaminants away from the membrane, reducing their accumulation and passage to permeate (Lee et al., 2021).

It could be inferred that, since BPA and analogues have similar molecular structures, the fate of BPs in WWTP may have the same pattern. Thus, hybrid MBR, hybrid AnMBR, and modification in biological MBR can be effective alternatives for BPs analogues removal, but, as shown in this review, it still needs to be investigated.

4.3.3.2 Environmental risk reduction by MBR

In addition to removing or reducing the concentrations of BPs in wastewater, treatment technologies must guarantee the reduction of environmental risks since even achieving high removals, the remaining concentrations can still cause risks to the ecosystem (dos Santos et al., 2022). Thus, the acute and chronic RQ were measured considering the concentrations of BPs in raw and treated wastewater by several configurations of MBR, explained in Section 5.1. In Table 2, it is demonstrated that, for the most part, raw wastewater (RWW) presents high or medium risks, regardless of the types of wastewaters (specified in Table S5, Supplementary Material). In contrast, treated wastewater (TWW) risks were low or negligible in most cases, which indicates that MBR, in general, were effective in reducing environmental risks.

Table 2 – Acute and chronic environmental risks for raw wastewater and treated wastewater by membrane bioreactors (MBR). Red: high risk; yellow: medium risk; blue: low risk; green: negligible risk.

BPs	MBR configuration	Raw wastewater		Treated wastewater	
		Acute RQ	Chronic RQ	Acute RQ	Chronic RQ
BPA	SBR-MBR	857.14	187.50	34.29	7.50
	Submerged aerobic MBR	57.14	12.50	1.14	0.25
	Gas-sparged anaerobic MBR	285.71	62.50	0	0
	Anaerobic fluidized bed MBR	285.71	62.50	0	0
	UASB-MBR	0.58	0.13	0.40	0.09
	Anaerobic MBR	0.57	0.13	0.34	0.08
	Anaerobic MBR	0.57	0.13	0.47	0.10
	Enzymatic MBR	2.06	0.45	1.69	0.37
	Enzymatic MBR	2.06	0.45	0.04	0.009
	Aaerobic MBR	1.43	0.31	0.09	0.02
	Anaerobic MBR	1.43	0.31	1.00	0.22
	Hybrid MBBR-MBR	1.43	0.31	0.14	0.03
	MBR	1.43	0.31	0.71	0.16

Anaerobic-Anoxic-Oxic-MBR	0.18	0.04	0.04	0.009
Anaerobic MBR with MD	0.57	0.13	0.06	0.01
MBR	1.43	0.31	0.14	0.03
Aerobic MBR with ceramic membrane	0.21	0.05	0.004	0.001
Enzymatic bioreactor with MD	5.71	1.25	0.06	0.01
Anoxic-aerobic MBR	1.43	0.31	0.03	0.006
Aerobic MBR	0.27	0.06	0.01	0.003
MBR-Aerated Biofilm Reactor	14.29	3.13	0.44	0.10
SBR-MBR	5.71	1.25	0.06	0.01
Enzymatic MBR	1.43	0.31	0.83	0.18
Enzymatic MBR with redox mediators syringaldehyde	1.43	0.31	0.09	0.02
Aerobic MBR	0.68	0.15	0.005	0.001
Aerobic MBR	285.71	62.50	1.20	0.26
Aerobic MBR	0.04	0.009	0.003	0.001
Submerged aerobic MBR with NF	0.03	0.006	0.001	0.0003
Submerged aerobic MBR with RO	0.03	0.006	0.0009	0.0002
Aerobic MBR	0.79	0.17	0.04	0.009
Aerobic OMBR	0.79	0.17	0.11	0.03
Aerobic MBR	57.14	12.50	3.49	0.76
Aerobic OMBR	57.14	12.50	1.14	0.25
Aerobic MBR	0.29	0.06	0.02	0.004
Aerobic MBR	0.29	0.06	0.02	0.004
Aerobic MBR	1.43	0.31	0.07	0.02
Anaerobic-Anoxic-Oxic- MBR	1.06	0.23	0.31	0.07
Anaerobic-Anoxic-Oxic- MBR with RO	1.06	0.23	0.01	0.003
CAS-MBR	1.06	0.23	2.03	0.44
Aerobic MBR	1.06	2.03	0.11	0.01
Aerobic MBR with NF	0.49	0.11	0.01	0.003
Aerobic MBR with NF	0.49	0.11	0.005	0.001
Aerobic MBR with NF and RO	0.49	0.11	0.005	0.001
Aerobic MBR with NF and RO	0.49	0.11	0.01	0.002
MBR with salinity build-up	1.43	0.14	0.31	0.03
Anaerobic-Anoxic-Oxic-MBR	0.08	0.02	0.001	0.0003
Anaerobic-Anoxic-Oxic-MBR	0.11	0.03	0.002	0.0004
Anaerobic MBR	1.43	0.31	0.01	0.0031
Anoxic-Aerobic MBR	0.09	0.02	0.02	0.005
Anoxic-Aerobic OMBR	0.09	0.02	0.02	0.0042
Anoxic-Aerobic OMBR with RO	0.09	0.02	0.007	0.0015
Aerobic OMBR with RO	1.43	0.31	0	0
Aerobic OMBR with RO	1.43	0.31	0	0
Aerobic OMBR	1.43	0.31	0	0
Anaerobic-Anoxic-Oxic-MBR	5.71	1.25	0.86	0.19

	Aerobic OMBR with MD	1.43	0.31	0.11	0.03
BPS	Anaerobic-Anoxic-Oxic-MBR	0.01	0.32	4.75E-05	0.002
	Aerobic MBR	0.02	0.62	0.001	0.03
BPF	Anaerobic-Anoxic-Oxic-MBR	0.02	0.0025	0.0008	0.0001
	Aerobic MBR	0.01	0.0008	0.0004	0.0001
	Aerobic MBR	0.24	0.03	0.19	0.03
BPAF	Aerobic MBR	0.12	0.001	0.19	0.002
BPAP	Aerobic MBR	0.09	0.04	0.06	0.03
BPB	Aerobic MBR	0.08	15.00	0.04	7.95
BPZ	Anaerobic-Anoxic-Oxic-MBR	0.0004	0.0001	4.94E-05	0.00001
	Aerobic MBR	0.002	0.0005	0.0005	0.0001
	Aerobic MBR	0.10	0.02	0.11	0.03
BPC	Anaerobic-Anoxic-Oxic-MBR	0.001	0.02	0.00018	0.004
	Aerobic MBR	0.001	0.03	4.42E-05	0.001
BPE	Aerobic MBR	0.02	0.006	0.01	0.004

MBR conjugated with more selective membranes, such as NF, RO, and MD, achieved low or negligible risks in TWW for all cases due to higher removal efficiency (Asif et al., 2018; Sahar et al., 2011). In contrast, despite the low removal efficiencies observed in some cases of conventional MBR (using UF/MF (ultrafiltration/microfiltration) membranes), the risks in TWW were considered low due to the concentrations detected in RWW. For example, Qian et al. (2021) used an aerobic MBR to treat municipal wastewater containing BPs and obtained removal efficiencies of 19%, 47%, 36%, and 38% for BPF, BPB, BPE, and BPAP, respectively, as discussed in Section 5.1. Even so, post-treatment risks were low due to the low concentrations of these BPs detected in RWW (Table S5, Supplementary Material).

In other cases, high risks were found in TWW, as occurred with the enzymatic MBR with flat-sheet UF membrane studied by Asif et al. (2018), whose BPA removal was 18%. In this case, the acute risk in RWW was high and continued to be classified as high in TWW (RQ = 1.69). Similarly, Liu et al. (2020) evaluated an anaerobic MBR with ceramic MF membrane. They observed a BPA removal of 30%, with a remaining concentration in TWW of 3.5 µg/L, which promoted a high acute risk, while chronic risks were medium in raw and treated wastewater (Table 2).

On the other hand, in some scenarios, the risks in the TWW were high, even with high BPs removal efficiencies. Wang et al. (2023) used a submerged aerobic MBR to remove BPA in wastewater and achieved 98% removal; in contrast, the acute RQ was high (1.14) for TWW.

The same occurred with Zhu and Li (2013), who studied an aerobic OMBR for BPA removal and achieved high removal (98%); however, the remaining concentration in TWW water (4 μg/L) triggered high environmental risks. It is important to consider that this study used synthetic wastewater with a concentration of 200 μg/L of BPA. This value is 2 to 10 times higher than concentrations already detected in municipal wastewater (Chen et al., 2016b; Hajibabania et al., 2012; Sun et al., 2017; H. Wang et al., 2019).

For BPs with high risk in TWW (BPS and BPB), the minimum removal efficiencies of the technologies were calculated so that acute and chronic risks were classified as negligible (RQ ≤ 0.01). In all cases, removal efficiencies should be above 99.99%. This direction shows that removing environmental risks related to BPs may require highly efficient technologies. Furthermore, the need to monitor WWTPs regarding the concentration of BPs in the TWW is an environmental urgency.

4.4 FINAL CONSIDERATIONS AND FUTURE PERSPECTIVES

The present review presented unprecedented contributions regarding the occurrence of BPs in several locations, their toxicity, estrogenic activity, environmental risks, and their removal by MBR. The findings of this study can direct future actions related to the presence of BPs in surface waters and support the choice of the best configuration of MBR to reduce the release of BPs into the aquatic environment and the related risks. The main findings and conclusions and their implications are listed below:

(1) The highest average global concentrations found in surface waters were for BPA (2,540.7 ng/L), BPF (399.1 ng/L), and BPS (374.9 ng/L). This finding indicates that, in general, the reduction of releases into the aquatic environment should be directed mainly to these BPs;

(2) The concentrations of analogues were greater than BPA for surface waters of several locations. Therefore, the increasing use of these compounds to replace BPA has already shown their environmental impacts;

(3) The toxicity data was most investigated in the literature for BPA, although its substitutes also presented high acute or chronic toxicity for several aquatic organisms;

(4) High environmental risks in surface waters were found for BPA, BPAF, BPB, BPF, and BPS, while high estrogenic risks were found for BPA, BPAF, and BPB. This

corroborates the need for more attention to BPs analogues and the urgent need for their removal from wastewater;

(5) Surface waters from countries such as China, India, Poland, and Portugal were highlighted, as they had high environmental risks for more than one BP. Thus, reducing the release of these priority compounds into the aquatic environment is unpostponable;

(6) Hybrid MBR and AnMBR (followed by NF, RO, MD, or FO membranes) and OMBR are promising alternatives for BPs and risk removal in wastewater treatment.

Despite these knowledge advances, some critical gaps were identified in these areas. Therefore, future research and actions were suggested below:

(a) Studies about occurrence in surface water were still scarce for many analogues such as BPC, BPFL, BPE, and BPAP. Thus, more studies are needed to conclude about the presence of these compounds in surface waters more comprehensive;

(b) In the present study, it was impossible to estimate the acute or chronic environmental risks of BPAP, BPB, BPC, BPE, and BPZ for three trophic levels due to the lack of ecotoxicological data. Therefore, ecotoxicological assessments must move towards including more BPs;

(c) This study was limited to surface waters for which BPs concentration data have already been reported. Thus, it is suggested that future studies and monitoring of the BPs concentration be carried out in places not covered, mainly developing countries;

(d) Although some MBR configurations are promising for the BPs removal, more investigations are needed for analogues since only 14 studies were found (for all types of BPs) regarding removal by MBR;

(e) This study shows the urgency of developing legislation and more significant restrictions regarding the presence of these compounds in surface water and the standards for releasing wastewater containing BPs into the aquatic environment.

CHAPTER 5

GRANULAR ANAEROBIC MEMBRANE BIOREACTOR COUPLED HYBRID FORWARD OSMOSIS - MEMBRANE DISTILLATION FOR ORGANIC MATTER, NUTRIENT AND BISPHENOL A REMOVAL: INTEGRATED ASSESSMENT OF PERFORMANCE, COST, TOXICITY, AND RISKS

5.1 INTRODUCTION

The intensity and speed of industrialization have contributed to several environmental impacts whose reversal is a major challenge. Among them, the increasing occurrence of endocrine disrupting compounds (EDCs) in wastewater, surface water, and drinking water worldwide has been the subject of several studies (Czarny-Krzymińska et al., 2022; Santos et al., 2024a). EDCs can be classified as polymeric, naturally occurring compounds, and synthetic chemicals such as bisphenol A (BPA) (Al Sharabati et al., 2021). BPA is one of the most produced and consumed industrial compounds globally, which results in its presence in several aquatic compartments (Santos et al., 2024a), posing serious health risks, including cancer, diabetes, brain function disorders, hormonal changes, immunodeficiency, among others (Huang et al., 2018; Prins et al., 2014). Besides, BPA can be highly toxic for aquatic organisms, affecting fish (Moreman et al., 2017; Staples et al., 2011), crustaceans (Jung et al., 2020; Mihaich et al., 2009), and algae (Czarny-Krzymińska et al., 2022; Ding et al., 2020).

Concern about human and environmental risks has led to regulations on BPA production and use, mainly in the European Union, stimulating the use of alternative substances to replace BPA. For many countries, the monitoring and legislation for BPA focus on its limits in materials in contact with food, aiming to reduce the intake; however, no regulations exist for its concentration in surface water and treated wastewater (Santos et al., 2024a). This is problematic because conventional wastewater treatment plants (WWTPs), which are inefficient at removing recalcitrant compounds, are major sources of BPA discharge into water bodies (Czarny-Krzymińska et al., 2022).

The release of BPA into the aquatic environment can be reduced by employing advanced treatment methods, like membrane bioreactors (MBRs), which have been applied to the treatment of wastewater containing TrOCs with satisfactory performances (Asif et al., 2019; C. V. Faria et al., 2020a). For example, anaerobic osmotic membrane bioreactors (AnOMBRs), which associate anaerobic biological treatment with forward osmosis (FO) membranes has demonstrated high removal efficiencies for TrOCs in sewage treatment (Arcanjo et al., 2022; Caroline Ricci et al., 2021; Santos et al., 2023a), overcoming the challenges of removing some recalcitrant compounds in anaerobic systems. FO is a membrane technology driven by the difference in osmotic pressure between the feed and the draw solution (DS) (Zhao et al., 2014). As water passes into the DS during the FO filtration process, the DS dilution occurs, reducing

the osmotic pressure gradient. Thus, membrane distillation (MD) - in FO-MD hybrid systems - has shown potential for water recovery and DS regeneration in AnOMBRs (Ibrar et al., 2022).

FO-MD membranes offer benefits such as lower energy consumption, the possibility of using residual heat, and high separation efficiency (Baker et al., 2012; Holloway et al., 2016; Ricci et al., 2019). Anaerobic degradation systems require less energy and nutrient addition, produce less sludge, and are more compact (Zieliński et al., 2023). Combining these in the AnOMBR-MD presents a promising technology for wastewater treatment, particularly for removing risks related to the TrOCs (dos Santos et al., 2022a). For example, Arcanjo et al. (2022) and Caroline Ricci et al. (2021) achieved removals above 96% for the evaluated PhACs (17α-ethinylestradiol, ketoprofen, fenofibrate, fluconazole, loratadine, prednisone, and betamethasone) in sewage treatment.

However, some gaps must be overcome. Organic nitrogen is converted to ammonia in anaerobic treatment, which is difficult to remove due to its volatility (Arcanjo et al., 2022). Caroline Ricci et al. (2021) evaluated the AnOMBR-MD for sewage treatment, and ammonia was the only parameter above the potability limits established in the Brazilian legislation due to its passage through the MD membranes. Additionally, issues with low permeate flux in the hybrid FO-MD module hinder large-scale application and increase costs. Caroline Ricci et al. (2021) and Arcanjo et al. (2022) shown a stabilized flux of approximately 0.5 L m^{-2} h^{-1} after 30 days of operation, highlighting the need to increasing the permeate fluxes in FO and MD to reduce overall treatment costs.

Seeking to address these challenges, granular sludge (GS) has been widely applied in other MBRs configurations (Chu et al., 2005; Faria et al., 2020a; Sheldon & Erdogan, 2016). Compared to floccular sludge, the larger size of GS promotes a denser structure, greater sedimentation characteristics, and greater filtration capacity (Jing-Feng et al., 2012). Kang et al. (2023a) showed that the particle size of anaerobic sludge is directly related to ammonia removal efficiency by ANAMMOX. The authors achieved 100% ammonia removal by adjusting the granule size from 0.6 to 1.6 mm for an influent NH_4^+-N concentration of 55 mg L^{-1}. In addition, Lin et al. (2023) observed that adding a calcium source in the anaerobic sludge feed can stimulate the formation of GS in a short period, increasing the biomass capacity in ammonia removal.

Granular sludge (GS) has been effective in reducing membrane biofouling in MBR. Smaller sludge granules enhance specific interaction energy in contact, facilitating the adhesion of the small granules in suspension to the membrane surface, and consequently, reducing the water flux (Shen et al., 2015). Wang et al. (2013) used an MBR with aerobic GS to treat synthetic wastewater. They achieved a long and stable operation with a high permeate flux (20 L m^{-2} h^{-1}) compared to flocculent sludge. Besides, Faria et al. (2020a) showed that the combination of membrane with expanded granular sludge bed reactors (EGSB) reduced the fouling potential since the contact of the submerged membranes occurred only with the EGSB supernatant. It is also noteworthy that the formation of the GS is facilitated with the EGSB configuration since this reactor allows the expansion of the sludge bed, improving the biomass-feed contact (Sheldon & Erdogan, 2016)

Given the above, the objective of the present study was to evaluate the performance of a granular anaerobic membrane bioreactor associated with a hybrid module of forward osmosis – membrane distillation (G-AnOMBR/MD) – using an EGSB as granular reactor - for the treatment of domestic sewage, focusing on BPA, COD, P-PO_4^{3-}, and N-NH_4^+ removal. Additionally, ecotoxicological tests, risk assessment, and cost evaluation were performed, seeking a holistic investigation of this MBR configuration to facilitate scaling for large-scale applications. Previous studies have not yet reported this MBR configuration. Therefore, this study impacts the advancement of several lines of research, such as (1) the evaluation of a hybrid module of FO-MD membranes associated with an EGSB reactor, as a new technology for the advanced treatment of wastewater; (2) the search for efficient technologies for removing recalcitrant micropollutants, such as BPA; (3) the investigation on the increase in nutrient removal by anaerobic MBRs, from GS; (4) integrated analyses – and not only regarding removal efficiencies – of wastewater treatment technologies, such as assessment of toxicity, environmental and human health risks and costs.

5.2 MATERIALS AND METHODS

5.2.1 Granulation of anaerobic sludge

The sewage sludge was collected in an upflow anaerobic sludge blanket (UASB) at the Ribeirão do Onça WWTP, located in the metropolitan region of Belo Horizonte, Minas Gerais, Brazil. The sludge was inoculated to an upflow anaerobic reactor for preliminary granulation to ensure the granulation of anaerobic sludge in EGSB reactors (used in the next steps), since it was

essential that the sludge already showed good sedimentability so that the ascensional velocity, potentiated by the wastewater recirculation, did not interfere with the maintenance of the sludge granulation process or cause the elimination of granular biomass from the reactor (Faria et al., 2020a).

For the preliminary granulation, the feed was composed of synthetic sewage, prepared according to the modified methodology of Mockaitis et al. (2014), presented in Table 1. Calcium chloride ($CaCl_2$), a granulation precursor, was added to the synthetic sewage at 400 mg L^{-1} (Faria et al., 2020a) to aid in granulation by neutralizing the negative charges on microbial surfaces, reducing electrostatic repulsion and favoring granulation (Y. Liu et al., 2002). The granulation process followed the methodology proposed by Faria et al. (2020a) to optimize the granulation of sludge, and operated with a specific organic loading rate (SOLR) of 126.5 mgCOD $gVSS^{-1}$ d^{-1}; a hydraulic retention time (HRT) of 15.7 h; a recirculation flow + feed equal to 10.7 L h^{-1}; and an ascensional velocity of 3.8 m h^{-1}.

Table 1 - Composition of synthetic sewage.

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

During the granulation step, the sludge was evaluated for particle size in a laser dispersion particle size distribution analyzer (Model LA-950, Horiba) and by observations under an Olympus CX31 microscope. Sludge can be considered granular when 10% of the granules have a diameter greater than 2 mm (Yu, 2001). The resistance test of the granules was performed from the adapted ultrasound method: 10 mL of sludge was added in to Erlenmeyer (25 mL), completing the volume with deionized water. The sample was homogenized and its turbidity read in a spectrophotometer at 600 nm. After this step, the sample was placed in an ultrasound bath at 20–25 kHz, 65 W, and turbidity is re-evaluated after 5, 10, 15, 20, and 25 minutes in an ultrasound bath. In this way, the resistance of the granules was evaluated from the disintegration

of the sludge over time (Wan et al., 2013). Sludge was also evaluated for volatile suspended solids (VSS), and its capacity to remove chemical oxygen demand (COD) from feed, according to the Standard Methods for the Examination of Water and Wastewater (APHA, 2017), as shown in Table 2.

To assess the relative abundance and taxonomic classification of the sequences in the GS, DNA was extracted from 0.5 g of sludge using DNA Power Soil Kit (Mobio Laboratories, Inc., Carlsbad, CA, USA) following the manufacturer's instructions. Quantitative PCR (qPCR) was used to estimate the number of copies of 16S rRNA gene (16SV4 region) using primers 505F 806R, synthesized with pre-adapters compatible with the Illumina platform. The products of this amplification were visualized on 1.5% agarose gel. This PCR product was purified with AMPure XP Beads (Beckman Coulter, Life Sciences). After this step, the Illumina adapters were ligated in a PCR reaction (index Nextera XT Index Primer 1 (N7xx) and Nextera XT Index Primer 2 (S5xx). Then, another purification of the PCR product was performed with AMPure XP Beads (Beckman Coulter, Life Sciences). After purification, the products of this amplification were visualized on 1.5% agarose gel. The PCR products from the ligation of the adapters were quantified in NanoDrop (Thermo) and then normalized to the same concentration. Then, an equimolar pool was made with all samples, quantified by qPCR to validate and determine the final concentration of the pool in nM. The KAPA Library Quantification kit for Illumina (Roche) was used, and sequencing was performed on the Illumina NextSeq2000 equipment in 2x300 bp runs.

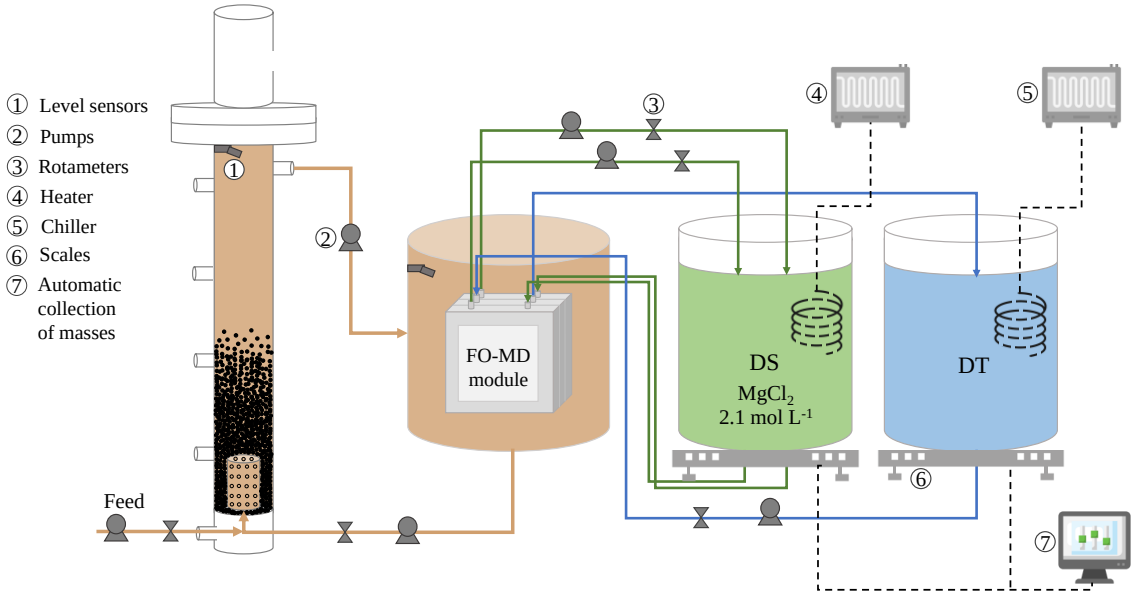
5.2.2 G-AnOMBR/MD experimental setup and operational conditions

As feed solution (FS) for G-AnOMBR/MD, synthetic sewage simulating real domestic sewage was prepared according to Table 1. Also, it was fortified with BPA in concentration of 20 μg L^{-1}, determinate based in concentrations of BPA in raw sewage (Santos et al., 2024a). BPA (purity > 97%; product number: 133027) was purchased from Sigma-Aldrich® and the stock solution (100 mg L^{-1}) was prepared in methanol. For draw solution (DS), $MgCl_2$ concentration of 2.1 mol L^{-1} was used as solute. $MgCl_2$ was pointed out by Arcanjo et al. (2020) as the ideal solute for this system, mainly due to the reduced reverse salt flux (J_s).

The sludge previously granulated was inoculated in an EGSB reactor, following the same operating conditions of the granulation step, and an applied SOLR of 58.6 mgCOD $gVSS^{-1}$ d^{-1}. 900 mL of GS (55 g L^{-1} VSS) was added to the EGSB (2.7 L), resulting in a VSS concentration

equal to 18.3 g L^{-1} in EGSB. The mixed liquor (ML) from the EGSB reactor was pumped into the membrane tank with a submerged FO-MD hybrid module and the recirculation of ML occurred in EGSB reactor, as shown in Figure 1. The HRT and solid retention time (SRT) in EGSB reactor were 15.7 h and 31 d, respectively.

Figure 1 - Experimental setup of granular anaerobic membrane bioreactor associated with a hybrid module of forward osmosis – membrane distillation (G-AnOMBR/MD).



The flat-sheet FO membrane (Hydration Technologies, Albany, USA) used in this study has a thickness of 50 µm, a water permeability coefficient of 1.29 × 10^{-12} m s^{-1} Pa^{-1}, and a structural parameter of 481 µm. The FO membrane had an asymmetric structure and was composed of cellulose triacetate with an embedded polyester screen support. The flat-sheet MD membrane (Sterlitech, USA) composed of polytetrafluoroethylene (PTFE) in a non-woven polypropylene with an average pore size of 0.2 µm. Also, has a thickness in the range of 76 - 152 µm, water entry pressure > 37 psi, and air permeability of 0.26 - 0.55 L min^{-1} cm^{-2}. All experiments were conducted with the FO membrane active layer facing the FS, and MD tests were carried out in the direct contact configuration (DCMD).

The FO-MD module consists of a plate-and-frame system with three compartments. The compartments were separated and sealed by four membranes, with an area of 132 cm^2 each. FO membranes were placed on the outer faces, while the MD membranes were placed on the inner ones. The heating DS was recirculated in the outer compartments, while the cooled distillate

(DT) was recirculated inside the middle compartment. Furthermore, the DS and the DT flowed counter-currently (Ricci et al., 2021). Counter-current flow was preferred in this system because it leads to better water vapor flux and reduced fouling compared to the co-current flow (Francis et al., 2014; Lee et al., 2014).

DS temperature was maintained by a heating element (electric resistance) and a thermostat controller (MT520E fast, Full Gauge Controls, Canoas, Brazil), and DT cooling was maintained by a chiller (Chiller Gelaqua 1/8 hp., Santos, Brazil). The circulation rate and temperature for DS were set up at 75 L h^{-1} and 45 °C, respectively. For DT, these values were 80 L h^{-1} and 25 °C. The system was operated under continuous flow and a computer recorded the weight of the DS and DT every 5 min. The conductivity, pH and temperature of samples were monitored daily. In addition, samples from FS, $EGSB_{eff}$, membrane tank (MT), and DT were collected weekly for physicochemical characterization.

5.2.3 Analytical methods

5.2.3.1 Physicochemical analyses

The physicochemical analyses were performed following the methodologies of the Standard Methods for the Examination of Water and Wastewater (APHA, 2017), as shown in Table 2.

Table 2 - Analytical methods

Parameter	Method
pH	4500-H^+
Conductivity	2510
Chemical oxygen demand (COD)	5220
Total suspended solids (TSS)	2540 D
Volatile suspended solids (VSS)	2540 E
Total phosphorus ($P-PO_4^{3-}$)	4500-P D
Ammoniacal nitrogen ($N-NH_4^+$)	4500-NH3 B e C

5.2.3.2 BPA identification and quantification

Extraction of BPA from samples was performed according to Wang et al. (2005). Before extraction of BPA, the pH of samples was adjusted for a range of 2 to 3 using H_2SO_4 solution. The C_{18}-E cartridges were conditioned twice with 5 mL each of ethyl acetate, methanol, and deionized water. The extraction used a vacuum manifold (Phenomenex, California, USA). 600 mL of permeate (15th and 30th day of operation) and 250 mL of EGSB effluent (15th and 30th

day of operation) were used for BPA extraction. The samples were passed through the cartridge at a 5 mL min^{-1} flow rate and vacuum dried. In sequence, the analyte was eluted with 4 mL of ethyl acetate, transferred to glass vials and immediately analyzed.

Determination of BPA was performed by gas chromatography with mass spectrometry (GC-MS) Shimadzu GCMS-QP2010, according to the modified methodology by Kiejza et al (2022). The separation was achieved by a DB-5MS column with dimensions of 30 m × 0.25 mm × 0.25 µm film thickness. Helium (99.999%) was used as a carrier gas at a constant flow rate of 1.0 mL min^{-1}. The injector worked in splitless mode at a temperature of 250 °C. The oven operated using a starting temperature of 130 °C for 3 min; then, the temperature was raised by increments of 30 °C min^{-1} until reaching 250 °C after 4 min; after, the temperature was raised at a rate of 20 °C min^{-1} until reaching the final temperature of 310 °C. The system operated at this final temperature for 5 min, making the total analysis 19 min. The electron impact source temperature was 230 °C, with an electron energy of 70 eV. The quadrupole temperature was 150 °C, and the GC interface temperature was 280 °C. The MS detector was set to work in selected ion monitoring (SIM) mode. The compound was identified based on retention time (RT) and mass spectra obtained from scan acquisition mode. The BPA calibration curve was performed in the linear range of 0.2 - 20 ng mL^{-1}.

For quality assurance and quality control, samples were spiked separately with 5 ng mL^{-1} of BPA standards, then extracted, derivatized, and quantified as mentioned above. Thus, obtained linearity, mean recovery, precision (% RSD), limit of detection (LOD), and limit of quantification (LOQ) were calculated. The LOD and LOQ were estimated from slope of the standard curve, and standard deviation of standard solution at a concentration of 0.2 ng mL^{-1} of BPA (Selvaraj et al., 2014).

5.2.4 Permeate fluxes and removal efficiencies

Permeate fluxes in MD (J_{MD}) and FO (J_{FO}) membranes were calculated by Equation 1 and Equation 2:

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

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

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

The overall removal efficiency of the AnOMBR-MD was calculated by Equation 3.

$$R_{AnOMBR-MD} = \frac{C_{FS} - C_{p,MD}}{C_{FS}} \text{ x } 100 \quad (3)$$

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

5.2.5 Ecotoxicological tests

Ecotoxicological tests were carried out for FS, EGSB effluent, membrane tank (MT), and DT. Acute toxicity tests with the luminescent marine bacteria *Aliivibrio fischeri* were carried out using the MICROTOX® model 500 Analyzer (SDI) equipment, following ABNT NBR 15411-3 (2021) and the protocol established by the software (MICROTOX® Omni Software, version 4.1) of MICROTOX®. The effect concentration (EC_{50}) was determined from the MICROTOX® 81.9% Basic Test with 9 concentrations for each sample (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 for 30 minutes. The software makes a comparison of bacteria luminescence with samples and the control. The lower the 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., 2022).

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 (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. The results obtained in toxicity tests were transformed into values of toxic unit (TU), dividing 100 by the EC_{50}, to facilitate discussion of the results. In addition, the toxicity was classified as proposed by Persoone et al. (2003): class I (TU < 1) - non toxic; class II (1 < TU < 10) - toxic; class III (10 < TU <100) - very toxic; class IV (TU > 100) - highly toxic.

5.2.6 Human health and environmental risk assessment for BPA

To assess the acute and chronic environmental risks for BPA, expressed as the risk quotient (RQ), the concentration of BPA in FS, EGSB effluent, and DT on the 15ht and 31ht day (last day) of operation was considered. The RQ values were obtained through the quotient between the concentrations of BPA by predicted no-effect concentration (PNEC). For the calculation of the PNEC, acute or chronic toxicities for BPA were considered, 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 toxicity values of BPA, the more critical E(L)C_{50} and NOEC, reported for several trophic levels by Santos et al. (2024a), were considered.

Human health risk, estimated as the hazard quotient (HQ), was calculated to determine possible chronic non-carcinogenic health effects by consuming water with BPA. For this, were used the BPA concentration in FS, $EGSB_{eff}$, and DT divided by drinking water equivalent level (DWEL), calculated according to established values from U.S. EPA (U.S. EPA, 2011). DWEL considers tolerable daily intake for BPA (4 μg kg bw^{-1} day^{-1}) recommended by the European Food Safety Authority, the body weight for adult (60 kg for > 10 years of age) and children (10 kg for < 10 years of age), the relative contribution of water exposure (equal to 0.2), and the daily water intake for adult (2 L d^{-1}) and children (1 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 ≤ R(H)Q ≤ 1, the risk was considered medium; for 0.01 ≤ R(H)Q <0.1 the risk is low; and if R(H)Q <0.01 the risk is negligible (European Commission, 1996).

5.2.7 Preliminary cost evaluation

Preliminary cost evaluation of the G-AnOMBR/MD was carried out through capital expenditures (CAPEX) and operating expenditures (OPEX), based on the experimental results. For direct and indirect CAPEX, the cost of civil work, intake and pretreatment, pumps, membrane acquisition, anaerobic tank, membrane tank, mixers, and heat exchangers were considered (Osipi et al., 2018). Table 3 shows the general parameters considered for the CAPEX and OPEX estimation of large-scale system.

Table 3 - Parameters considered for the CAPEX and OPEX estimation.

Parameter	Value	Reference
Population (inhabitants)	100,000	This study
Flow rate ($m^3\ h^{-1}$)	790	This study
Water per capita ($L\ inhab^{-1}\ d^{-1}$)	150	(ABNT, 1986)
Return coefficient	0.7	(ABNT, 1986)
Maximum hourly flow coefficient (k1)	1.2	(ABNT, 1986)
Maximum daily flow coefficient (k2)	1.5	(ABNT, 1986)
Biological tank ($US\$\ m^{-3}$)	235	(ABNT, 1986)
Membrane tank ($US\$\ m^{-3}$)	235	(Verrecht et al., 2010)
Mixing energy consumption ($W\ m^3$)	8	(Verrecht et al., 2010)
Investment rate (%)	16.3	This study
Design life plant (years)	15	This study

In addition, the parameters adopted specifically for estimating CAPEX and OPEX of the FO-MD module are shown in Table 4. For DS replenishment costs the reverse salt flux (J_S) and the diffusion flux from the DS to the DT, calculated by Arcanjo et al. (2020), were considered.

Table 4 – Parameters considered for FO-MD CAPEX and OPEX estimation.

Parameter	FO	MD	References
RR FO-MD system (%)	50		This study
Qf FO-MD system ($m^3\ h^{-1}$)	790		This study
Qp FO-MD system ($m^3\ h^{-1}$)	395		This study
Jp FO-MD ($L\ m^{-2}\ h^{-1}$)	0.5		This study
Membrane cost ($US\$\ m^{-2}$)	56	60	(Zarebska-Mølgaard et al., 2022)
$MgCl_2$ requirement ($kg\ m^{-3}\ year^{-1}$)	270	-	This study
$MgCl_2$ price ($US\$\ kg^{-1}$)	0.12		(Zarebska-Mølgaard et al., 2022)
η (%)	85		(Vinardell et al., 2020a)
P_{inlet} (bar)	2		This study
Energy price ($US\$\ kW^{-1}\ h^{-1}$)	0.04		(Z. Zhang et al., 2022a)
Thermal energy price ($US\$\ kW^{-1}\ h^{-1}$)	0.025		(Z. Zhang et al., 2022a)
Energy requirement ($kWh\ d^{-1}$)	1555.2		This study
Thermal energy requirement ($kWh\ d^{-1}$)	256825.7		This study
Density of DS ($kg\ m^{-3}$)	1164		(Arcanjo et al., 2020)
Specific heat DS ($kJ\ kg^{-1}\ K^{-1}$)	4,1788		(Arcanjo et al., 2020)
T_{DS} (ºC)	45		This study
T_{DT} (ºC)	25		This study
Membranes lifespan (year)	5		This study

Specific produced permeate cost (SPC) was calculated according to Equation 5, as proposed by Osipi et al. (2018).

$$SPC = \frac{af . \frac{CAPEX}{f} + OPEX}{Q_p} \quad (5)$$

where f is the utilization factor (equal to 1, considering the maximum system capacity), Q_p is the total annual produced permeate, and af is the amortization factor, calculated according to Equation 6:

$$af = \frac{i_c . (1 + i_c)^{DL}}{(1 + i_c)^{DL} - 1} \quad (6)$$

where i_c is the investment rate and DL is the design lifetime of the plant for the FO-MD system.

Energy requirement for DS and DT circulation pumps and reactor stirring was estimated according to Equation 7, while Equation 8 calculated thermal specific energy consumption (TSEC) for MD heating and cooling:

$$SEC = \frac{W_{pump} . t}{\eta . Q_p} = \frac{P_{inlet} . Q_f . N_c . t}{\eta . Q_p} \quad (7)$$

$$TSEC = \frac{Q_f . \rho_f . C_{pf} . (T_h - T_c)}{Q_p} \quad (8)$$

where W_{pump} is the work done by the pump, t is the daily operating time, Q_f is the feed flow, P_{inlet} is the pump discharge pressure, η is the pump efficiency, N_c is the number of compartments (two for FO and one for MD), ρ_f and C_{pf} is the density and specific heat of the MD feed (draw solution), T_h is the heating temperature, and T_c is the cooling temperature for MD.

5.3 RESULTS AND DISCUSSION

5.3.1 Granular sludge characteristics

The sludge pre-granulation process was evaluated for 145 days. The initial flocculent sludge had an average diameter of 219 µm and a 90th percentile of 624 µm, i.e., 10% of the granules were greater than this value. Until approximately the hundredth day, the increase in granules was moderate, with an average diameter ranging from 214 to 418 µm and a 90th percentile ranging from 589 to 1190 µm. After this period, a more considerable increase in granule diameter was observed, reaching a 90th percentile greater than 2000 µm (considered GS) from

day 133. The process continued until 145 days to evaluate the stability of the anaerobic granule diameter. Figure 2 shows the increase in granule diameter over time and the sludge's optical microscope images (magnified 4x) from day 0 to day 145. On day 0, it is possible to see the sludge with a flocculent appearance, while the granules were apparent on the last day of granulation.

The mechanisms of anaerobic granule formation have yet to be fully elucidated. However, studies show that there are four steps for sludge granulation to occur: (1) transport of a cell to the surface of an uncolonized inert material or another cell; (2) initial reversible adsorption on the substrate by physicochemical forces; (3) irreversible adhesion of cells to the substrate by extracellular polymeric substance (EPS) that fix the cells to the substrate; and (4) cell multiplication and the development of stable granules (Lim & Kim, 2014; Show et al., 2020). Therefore, 133 days for sludge granulation is a reasonable time, given the complexity of the physical, chemical, and biological processes involved. Other studies indicate a granulation time in an upflow reactor seeded with anaerobic flocculent sludge of 4 to 6 months (Y. Liu & Tay, 2004).

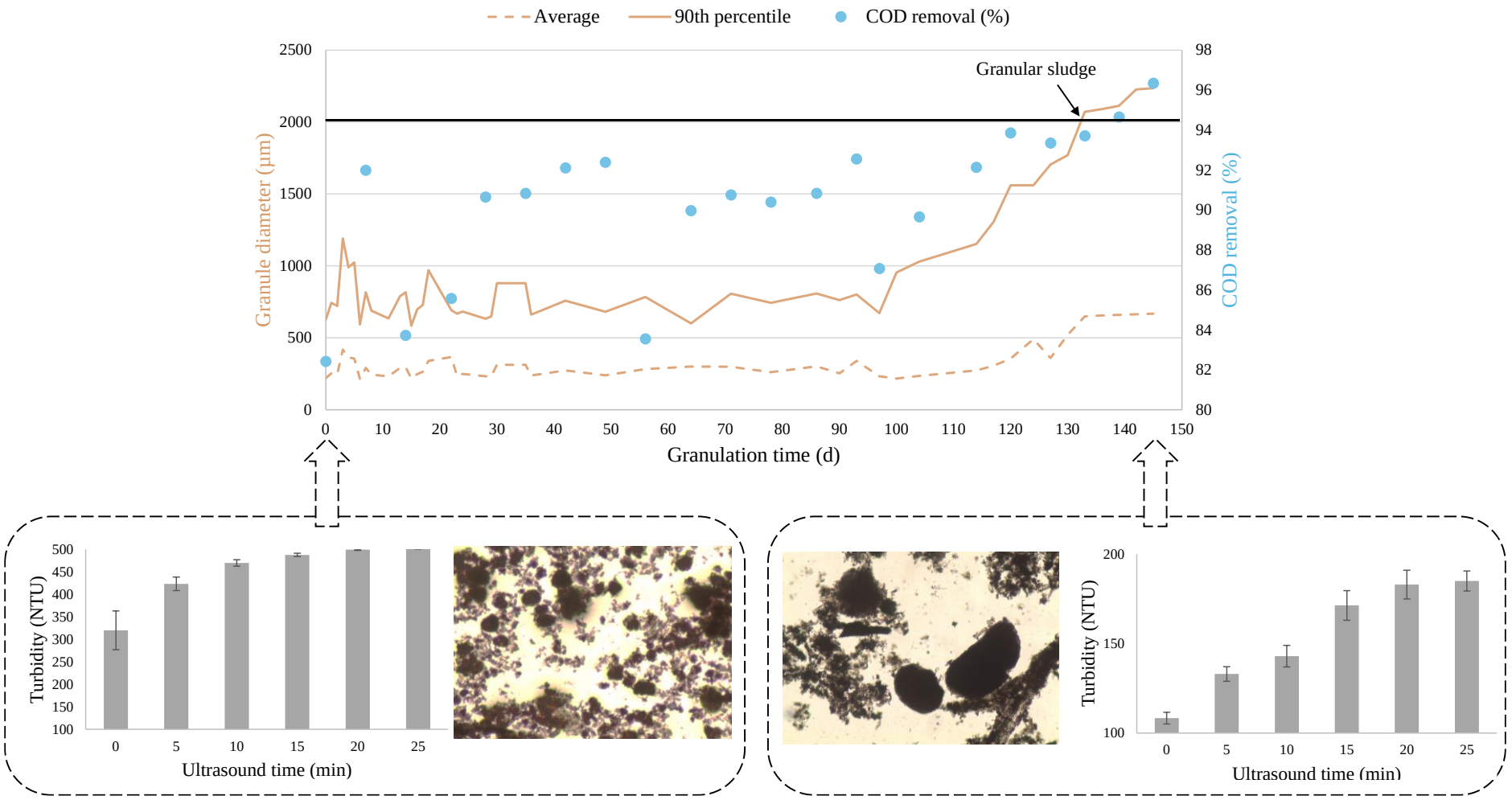
The granule resistance test demonstrated that in a static condition, the turbidity of the flocculent sludge (day 0) was 320 ± 43 NTU. In comparison, the GS had a turbidity of 110 ± 3.3 NTU. After subjecting the sludge samples to 5 minutes of ultrasonic agitation, the turbidity of the flocculent sludge increased considerably, totaling 400 ± 15 NTU, while for the GS, this value was lower (130 ± 4 NTU). After 25 minutes of agitation, the observed turbidity was 500 ± 2.7 NTU and 180 ± 5.6 NTU for the flocculent and GS, respectively (Figure 2). These results show that the flocculent sludge is unstable and can easily dissociate. In contrast, the GS was more stable during the agitation periods. Anaerobic granules tend to weaken as the cell surface's negative charge increases (Y. Liu & Tay, 2004). Therefore, the addition of $CaCl_2$ during the granulation period was essential for the strength of the granules since it helped in the union of negatively charged cells, forming denser microbial nuclei.

On average, organic matter removal was 82.4% for the flocculent sludge (day 0). During the first hundred days of granulation, the average removal increased to 89.5 ± 3%. With the increase in granule diameter, the COD removal tended to increase even more, and at the end of the granulation process, the removal was 96.3% (Figure 2). Several characteristics make GS more efficient in removing organic matter compared to flocculent sludge, such as greater biomass

retention and diversified microbial communities inside the granules, and better sedimentation properties (Show et al., 2020). Therefore, the increased removal of organic matter by GS corroborates the results of other studies (C. V. Faria et al., 2019; Jijai et al., 2015). At the end of the operation, the GS had a VSS concentration equal to 55 g L^{-1}.

A taxonomic evaluation of the microbial groups present in the GS was performed. Figure 3 shows the abundance of bacteria (> 1%) in the sludge after the granulation period. No archaea group was in a proportion greater than 1%. The most abundant bacteria groups were *Rikenellaceae* (11%) and *Rhodocyclaceae* (9%), families of Gram-negative bacteria. Recent studies show that Gram-negative bacteria – through quorum sensing (QS) activity – can secrete EPS, facilitating the granules formation (Hou et al., 2021; Lv et al., 2023). Additionally, Tan et al. (Tan et al., 2014) showed the correlation between granular disintegration and the reduction of N-acyl-homoserine-lactone (AHL) content, a common autoinducer in Gram-negative bacteria during QS activity. Thus, these bacteria are vital in increasing particle aggregation and stability during sludge granulation.

Figure 2 - Sewage sludge particle diameter and COD removal over time, image (magnified 4x) of sludge at day 0 (flocculent) and day 145 (granular) and sludge strength at day 0 (flocculent) and day 145 (granular).



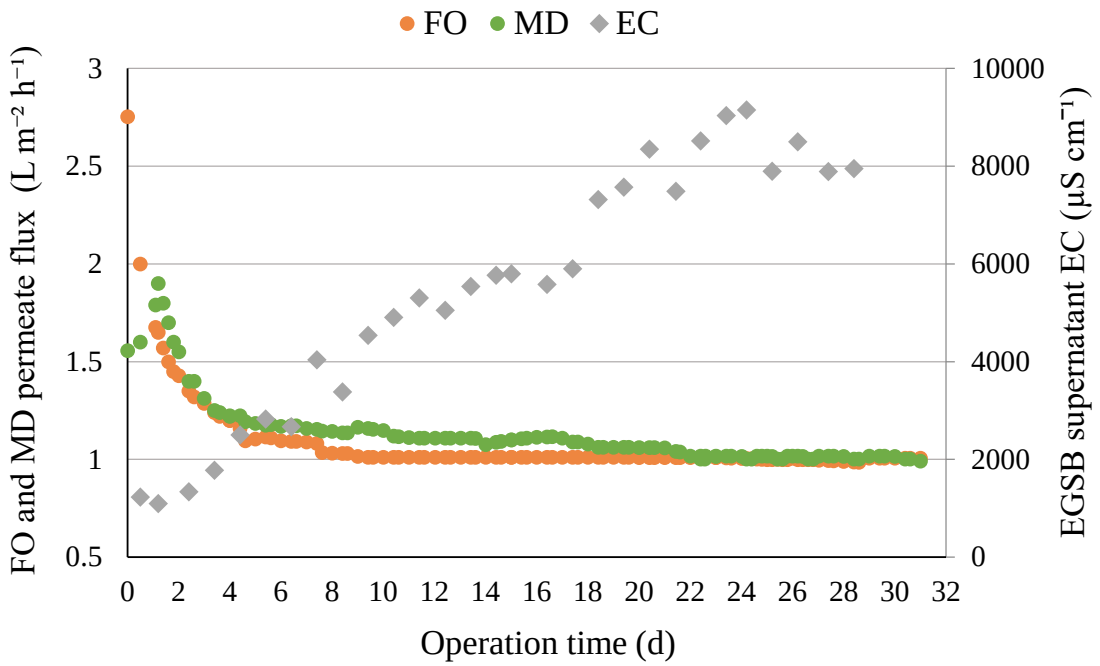
Some groups of filamentous bacteria were also present, such as the genera *Smithella* and *Flexilinea flocculi* (Figure 3). These filamentous bacteria are essential in the initial stages of sludge granulation since their spaghetti-like structure facilitates the aggregation of microbial cells, organic matter, and EPS, trapping them. Thus, this structure evolves and becomes a dense and rounded granule due to hydrodynamic shear (Hulshoff Pol et al., 2004; Show et al., 2020). The role of these microbial groups in contaminant removal during wastewater treatment will be discussed in the following sections.

Figure 3 - Relative abundance (>1%) and taxonomic classification of bacterial sequences present in GS (day 145).

5.3.2 G-AnOMBR/MD permeate flux and removals

FO permeate flux (J_{FO}) was 2.75 L m^2 h^{-1} at the beginning of the operation and decreased more sharply until approximately the fifth day. After this period, it tended to stabilize around 1 L m^2 h^{-1} until the end of the operation. Studies have observed that a common phenomenon in the FO process - internal concentration polarization (ICP) - contributes to J_{FO} reduction. ICP results in DS dilution due to water passage at the interface between the active and support layers of the FO membrane. Thus, a dilution in osmotic pressure occurs, reducing the flux (Achilli et al., 2010). Another reason for the decline in J_{FO} was the accumulation of salinity in the EGSB supernatant, which reduced the driving force of the process. The electrical conductivity in the EGSB supernatant was about 1.8 mS cm^{-1} at the beginning of the operation; at the end, it was about 8,000 µS cm^{-1} (Figure 4). This accumulation of ions is influenced by J_s and by the dissolved compounds retained by the FO membrane.

Figure 4 - FO and MD permeate flux and electrical conductivity (EC) in the EGSB supernatant throughout the G-AnOMBR/MD operation.



For MD, the initial flux was 1.56 L m^2 h^{-1}. A less sharp reduction was observed at the beginning of the operation until stabilization around 1 L m^2 h^{-1} (Figure 4). Although MD performance is relatively independent of feed salinity, concentration and temperature polarization can impact the permeate flux (Ricci et al., 2019). The temperatures in the DS

(45 ºC) and DT (25 ºC) resulted in a MD temperature gradient of 20 °C; however, temperature polarization, which is the reduction of temperature at the membrane interface on the FS side and increment on the DT side, reduced the effective temperature difference across the MD membrane, leading to the flux reduction (Ricci et al., 2019).

In addition, Santos et al. (2023) showed that the flux reduction in FO-MD hybrid module submerged in anaerobic reactor is primarily associated with organic fouling in FO and inorganic fouling in MD, mainly composed of Mg and Cl present in DS. In the previous studies using a FO-MD hybrid module, the permeate flux stabilized around 0.5 L m^2 h^{-1} (Arcanjo et al., 2022; Caroline Ricci et al., 2021; Santos et al., 2023). Thus, the G-AnOMBR/MD configuration increased the permeate flux to twice that found in previous studies. Using GS with high sedimentation capacity in the EGSB reactor and an external membrane tank reduced the VSS in contact with the membranes, reducing the possibility of fouling compared to submerged modules using flocculent sludge.

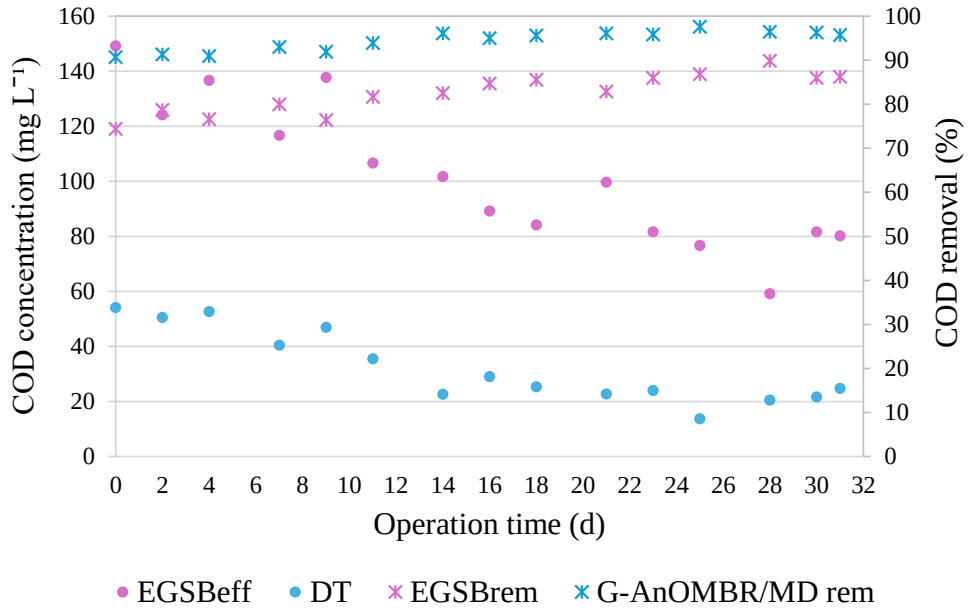
Cleaning procedures are essential to recover permeate flux throughout the operation. Silva et al. (2024) highlight that, for FO-MD modules, chemical cleaning agents can be a strategy. However, using chemicals brings a cost and an ecological footprint associated with their use. Thus, an alternative is physical cleaning, which efficiently removes reversible fouling. In addition, new cleaning options have been developed, such as free nitrous acid, which has biocidal properties and the ability to break the structure of the exopolysaccharide matrix formed by microorganisms, in addition to its relatively low cost and biodegradability (Silva et al., 2024).

The physicochemical characteristics of the FS are presented in Table S1. The average COD concentration in the EGSB effluent was 101.7 ± 26.3 mg L^{-1}, equivalent to an average organic matter removal of 82.6% by the GS (Figure 5). In comparison with the average removal obtained by the sludge during the granulation phase (28.6 mg_{COD} g_{VSS}^{-1}), as reported in Section 2.1, there was a slight reduction in the biodegradation of organic matter by microorganisms in the EGSB reactor (26.4 mg_{COD} g_{VSS}^{-1}). During the operation, the conductivity of the EGSB supernatant increased due to the reverse salt flux through FO membranes (Figure 4). Studies report that increased salinity in anaerobic sludge can inhibit microbial activity and reduce pollutant removals (Arcanjo et al., 2022; Chen et al., 2019). However, generally, GS is more resistant to salinity than flocculent

sludge (Corsino et al., 2018). Furthermore, no reduction in microbial activity was observed due to the presence of BPA. Therefore, the COD removal performance was not significantly affected.

It is essential to highlight that the organic matter biodegradation by the GS in the G-AnOMBR/MD was higher compared to other studies using anaerobic flocculent sludge during the treatment of domestic wastewater (Heffernan et al., 2011; Liu et al., 2020; Mei et al., 2018; Santos et al., 2023). Due to its denser and more compact structure, GS provides better retention of active biomass and lower resistance to substrate transport through the granules. Furthermore, GS retains greater microbial diversity in its granules, with different types of microorganisms organized by layers. This allows more efficient biodegradation due to microbial groups specialized in the degradation of diverse organic matter and nutrients (Lin et al., 2014; Winkler et al., 2018).

Figure 5 - COD concentrations in DT and EGSB effluent and their respective removals throughout the G-AnOMBR/MD operation.



In the present study, the average temperature in the EGSB was 23 °C. It is known that the operational efficiency of AnMBR regarding microbial activity and biogas generation is increased under mesophilic (30–40 °C) and thermophilic (50–60 °C) conditions. However, this is a limiting factor in some locations, especially in non-tropical countries. Thus, room temperature can benefit energy in these cases (Plevri et al., 2021). Therefore, studies have evaluated the efficiency of AnMBR under different temperature and

hydraulic retention time (HRT) conditions, pointing to an efficient removal of organic matter - meeting the limits of the European directive 91/271/EEC - with temperatures ranging from 12 to 26 ºC, for HRT around 12h (Garcia et al., 2013; Plevri et al., 2021; Lettinga et al., 1981). Thus, even at room temperature, EGSB - where the HRT was 15.7h during operation - achieved a satisfactory removal of organic matter.

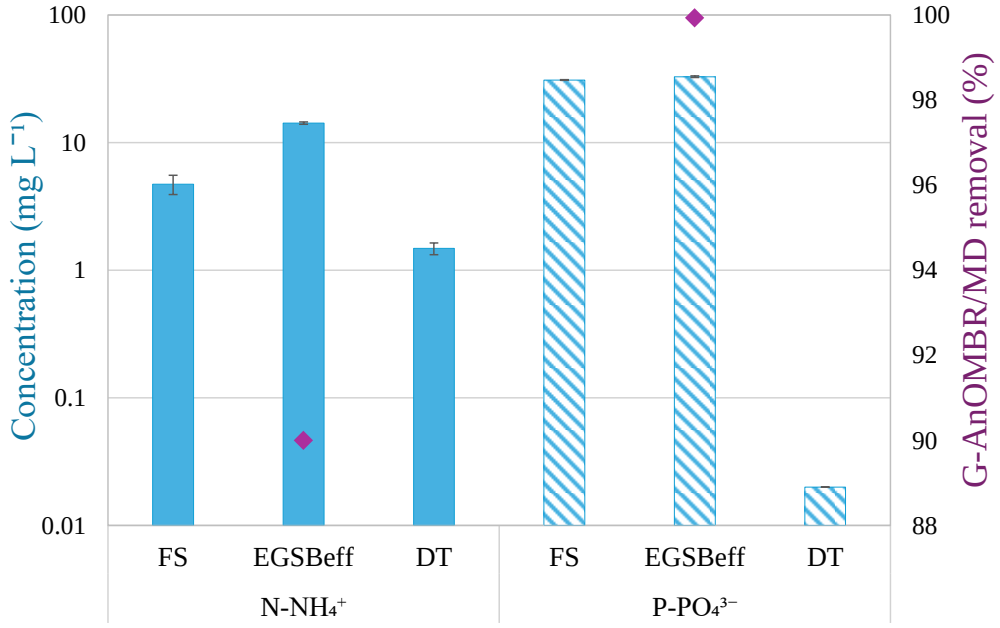
The overall COD removal by the G-AnOMBR/MD was 95.6%, which highlights the role of the FO-MD membranes in achieving a high removal of organic matter by the system, resulting in a permeate with an average COD concentration of 22.8 mg L^{-1} after FO-MD flux stabilization (22nd day). Hybrid FO-MD modules have shown high removal of organic matter, mainly due to the FO exclusion by pore size and rejection by MD, where only water vapor is transported through the membrane pores (Kamel et al., 2023). Despite the high rejection by the FO-MD module, a small portion of organic matter was present in the DT. This may be due to some dissolved organic carbon particles with low molecular weight that cross the FO membranes, such as volatile organic compounds generated during anaerobic processes (Yangali-Quintanilla et al., 2011). When passing through the FO membranes, these compounds can reach the MD permeate more quickly due to their volatility (Arcanjo et al., 2022).

As a comparison with G-AnOMBR/MD, Kwon et al. (2021) used an anaerobic fluidized bed bioreactor integrated with FO-MD and observed an average removal of 90% of COD. In contrast, Morrow et al. (2018) had higher removals of 98.4% of COD and 90.2% of N-NH_4^+ with an osmotic membrane bioreactor-membrane distillation (OMBR-MD). In addition, Nguyen et al. (2021) used a dynamic-osmotic membrane bioreactor/nanofiltration (OsMBR/NF) and achieved removals of 98% of COD, 99% of P-PO_4^{3-}, and 93% of N-NH_4^+. Hybrid AnMBRs using reverse osmosis achieved higher removals. For example, Liu et al. (2020) achieved total organic carbon (TOC) removals of 99.5% using an integrated anaerobic fixed-film membrane bioreactor with reverse osmosis (AnfMBR-RO). Wang et al. (2020) observed 99.9% DOC removals with an aerobic granular sludge membrane bioreactor and reverse osmosis (AGSMBR-RO).

As shown in Figure 6, there was no removal of P-PO_4^{3-} by the anaerobic GS. Instead, there was a slight increase in P-PO_4^{3-} in the EGSB effluent. In other studies using EGSB reactors, P-PO_4^{3-} removal was also null or negative (Ibrar et al., 2022; Nguyen et al.,

2020). However, it is essential to highlight that the removal by the FO-MD membranes was high, resulting in an average global removal of 99.6% by the G-AnOMBR/MD and a P-PO_4^{3-} concentration in the DT < 0.02 mg L^{-1} after system stabilization (flux stabilization).

Figure 6 – G-AnOMBR/MD removals and average concentrations of N-NH_4^+ and P-PO_4^{3-} in FS, EGSB effluent and DT.



Regarding N- NH_4^+, an average concentration of 14.2 ± 0.3 mg L^{-1} was observed in the EGSB reactor effluent (Figure 6). During anaerobic treatment, organic nitrogen is converted to N-NH_4^+. Thus, the presence of this nutrient in the EGSB effluent was expected. The overall removal of N-NH_4^+ by G-AnOMBR/MD was, on average, 91 ± 3.2%, with a mean concentration in the DT of 1.4 ± 0.16 mg L^{-1} after flux stabilization. In previous studies using AnOMBR-MD with flocculent sludge the N-NH_4^+ concentration in the DT was > 5.8 mg L^{-1} (Arcanjo et al., 2021, 2022).

Due to the low molecular weight, some NH_4^+ can pass through the FO membranes. In sequence, since ammonia is a volatile compound, it can permeate MD membranes, reaching the DT. This is more difficult to occur with PO_4^{3-}, which has a relatively larger molecular size than ammonia, leading to higher rejection efficiency by the FO membrane. In addition, phosphate ions are non-volatile, which means they cannot transfer to the vapor phase and permeate the hydrophobic MD membrane. Furthermore, cellulose

triacetate, a polymer component of the FO membrane, generally exhibits a negative charge under neutral pH conditions. Thus, the electrostatic attraction between the FO membrane and NH_4^+, which is positively charged, should be more pronounced than that of the PO_4^{3-} ion, which is negatively charged (Kwon et al., 2021).

5.3.3 G-AnOMBR/MD efficiency for BPA removal

BPA was identified in mass spectra from full scan acquisition mode (m/z 213; 228; 119) at an RT of 9.53 min. The GC-MS chromatogram for the BPA standard sample, $EGSB_{eff}$, and DT were provided in Figure S1. Besides, the obtained linearity, precision (% RSD), mean recovery for DT and $EGSB_{eff}$, limit of detection (LOD), and limit of quantification (LOQ) were shown in Table 5. A satisfactory linearity was obtained ($R^2 = 0.990$) as well as a high precision, especially for the standard concentration of 20 µg L^{-1} (0.25% RSD). Furthermore, a LOD and LOQ of 0.045 µg L^{-1} and 0.150 µg L^{-1} were obtained, respectively. The recovery for DT (101.66%) was better than that for $EGSB_{eff}$ (64.82%). This occurs due to the presence of organic matter and solid particles in the more complex matrices, which can significantly affect the recovery of BPA (Ramos et al., 2021).

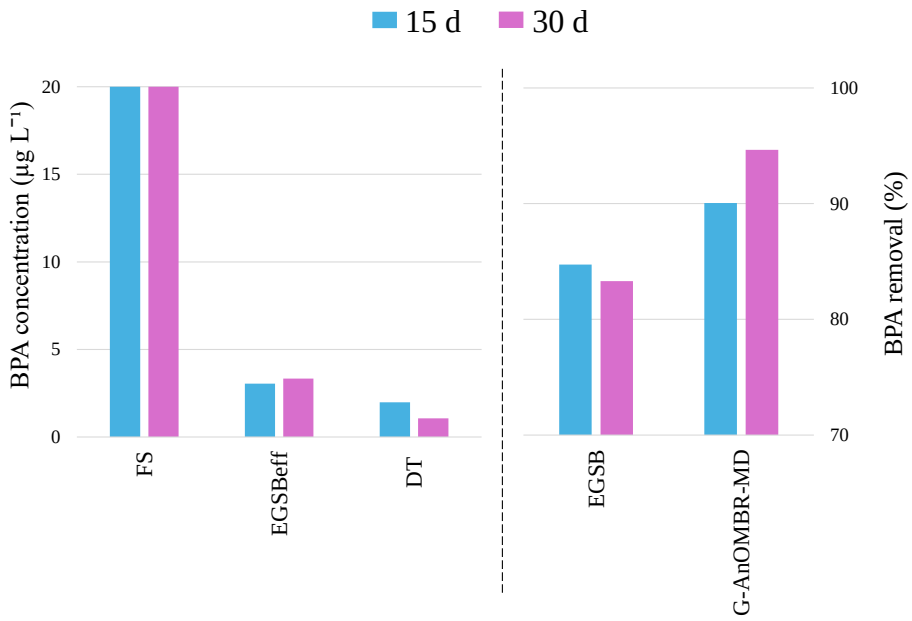
Table 5 - Quality assurance and quality control parameters of BPA.

Characteristic ion (*m/z*)	**RT (min)**	**R^2**	**Precision (%RSD) (n=3)**			**Recovery (%) (n=3)**		**LOD (µg/L) (n=5)**	**LOQ (µg/L) (n=5)**
			0.2 µg/L	**5 µg/L**	**20 µg/L**	**DT**	**$EGSB_{eff}$**		
213; 228; 119	9.53	0.990	7.90	9.78	0.25	101.66	64.82	0.045	0.150

The BPA concentrations in $EGSB_{eff}$ and DT on days 15 and 30 of operation and the respective removals by the EGSB reactor and G-AnOMBR/MD were shown in Figure 7. At 15 days of operation, the BPA concentration in the $EGSB_{eff}$ was 3.05 µg L^{-1}, and at 30 days it increased moderately to 3.34 µg L^{-1}, resulting in a removal of 83.3% (30 d). Generally, the biodegradation of micropollutants is lower under anaerobic conditions. The biodegradation constant for BPA (k_{bio}) was estimated to be 0.23 L gSS^{-1} h^{-1}, while for aerobic, it is 0.30 L gSS^{-1} h^{-1} (H. Wang et al., 2019a; Zhou et al., 2012). However, the EGSB reactor showed a superior removal to conventional anaerobic processes applied to BPA removal (Arias et al., 2018a; Queiroz et al., 2012). For example, Vassalle et al. (Vassalle et al., 2020a) evaluated the removal of several micropollutants by

Upflow Anaerobic Sludge Blanket (UASB) reactor and concluded that BPA was the most recalcitrant to anaerobic treatment, presenting a removal of 1.5%. Similarly, Arias et al. (2018b) observed BPA removals of less than 10% in UASB reactor, while Moya-Llamas et al. (2018a) reported removals of 57 to 59%.

Figure 7 – Concentration (µ L^{-1}) and removal of BPA by EGSB, FO-MD, and G-AnOMBR/MD.



Like other recalcitrant compounds, BPA is more efficiently removed in complex microbial communities where microorganisms cooperate, and the range of metabolic pathways is broad. In this sense, both BPA degraders and non-BPA degraders are important since microorganisms that cannot biodegrade BPA can assist by increasing the activity of BPA degraders or through co-metabolism. For this reason, granular sludge is more efficient in BPA removal. The structure of the granules is densely packed with several microorganisms, which ensures a wide range of metabolic processes simultaneously (Cydzik-Kwiatkowska et al., 2017). In addition, EGSB reactors promote greater biomass-feed contact, which can increase the biodegradation efficiency.

Fan et al. (2022) investigated the influence of several microorganisms on the anaerobic removal of organic compounds and observed that the increased abundance of *Bacteroidetes-vadinHA17* – the third most abundant group in the GS (Figure 3) – was associated with the degradation of phenolic compounds. Furthermore, *Rhodocyclaceae*

and *Pseudomonas*, present in GS among the most abundant, have also been associated with BPA biodegradation (Martínez-Quintela et al., 2023; B. Wang et al., 2021). Thus, these microorganisms present in the EGSB effectively participated in the BPA degradation.

It is essential to consider that in the presence of organic matter - as in EGSB - the degradation of more accessible and readily available carbon sources may be prioritized over BPA, reducing its biological removal rate. On the other hand, the higher solid retention time (SRT) provided by the system allows microorganisms to adapt to metabolize more complex compounds, such as BPA (Hu et al., 2019; Mohapatra et al., 2010). Furthermore, BPA removal can be improved due to its adsorption to particulate organic matter. The hydrophobic nature of BPA (Log K_{ow} = 3.4) facilitates their interaction with the hydrophobic organic matter. Thus, the association of BPA with macromolecules can facilitate its removal by size exclusion by FO membranes (Cheng et al., 2024).

FO-MD hybrid module was essential to reduce BPA concentrations and improve the G-AnOMBR/MD overall removal, which was 90.06% and 94.65% for 15 days and 30 days of operation, respectively. DT's final BPA concentration (30 d) was 1.07 µg L^{-1} (Figure 7). For FO, the rejection of organic compounds is governed mainly by electrostatic interaction and size exclusion (Lutchmiah et al., 2014). Zhu and Li (2013) evaluated an OMBR for removing BPA from synthetic municipal wastewater, and FO had a removal of 68 to 72%. In this system, the FO feed had a concentration of 30.78 µg L^{-1} of BPA (after biological treatment). In another study, Linares et al. (2011) used FO membranes to evaluate the removal of BPA and other organic compounds from secondary wastewater effluent, with a spiked BPA concentration of 8.5 µg L^{-1}. The authors found that BPA was the compound with the lowest removal by FO, namely, 40% for clean FO and 48.7% for fouled FO. The authors attributed the lower removal to the hydrophobicity and neutrality (at pH 7) of BPA. Unlike negatively charged compounds, which can be rejected by electrostatic repulsion and due to hydrophobicity, BPA can interact more easily with the membrane. Furthermore, the molecular weight cutoff (MWCO) of the membrane (≈200 Da) is close to the molecular weight (MW) of BPA (228 g mol^{-1}), which may facilitate its passage through the pores.

Costa et al. (2023) reviewed the removal and mechanisms of MD for several organic compounds. The main mechanisms involving the removal of BPA by MD were related to its non-volatile characteristic (pKH = 10.4) since the mass transfer in MD occurs in the vapor phase; therefore, the higher the volatility, the greater the chance of the compounds permeating the membrane. However, higher removals were found for compounds with pKH > 12. Furthermore, the authors identified that compounds with a pKH/log D ratio < 2.5 tend to have lower removals. For BPA, the pKH/log D ratio is equal to 2.86. In addition, Ramos et al. (2022) highlight that BPA, being a hydrophobic compound, can pass to the permeate side due to its affinity with the membrane surface (adsorption-desorption) or passage through wet pores. However, this passage is reduced with the formation of the fouling layer in MD membranes due to the addition of a physical barrier.

No studies were found evaluating the removal of BPA by hybrid FO-MD or MBRs with a FO-MD module. However, Lee et al. (2019) studied the removal of BPA by a flat-sheet cellulose triacetate (CTA) FO membrane with an asymmetric structure, thickness of 59.3 μm, mean surface roughness of 23.9 nm, and water permeability of 0.821 L m^{-2} h^{-1} bar^{-1}. The authors observed a removal of 85.5% for BPA. Similar BPA removal (90%) was found by Xie et al. (2012) using a CTA FO membrane, with water permeability of 1.1 L m^{-2} h^{-1} bar^{-1}, and mean pore size of 0.74 nm. In addition, Ramos et al. (2022) used a polytetrafluoroethylene MD membrane with an average pore size of 0.2 μm, porosity between 60 and 80%, and contact angle of 125°. The authors achieved a removal of 95% for a temperature of 40 ºC in the feed solution and a ΔT = 15 ºC.

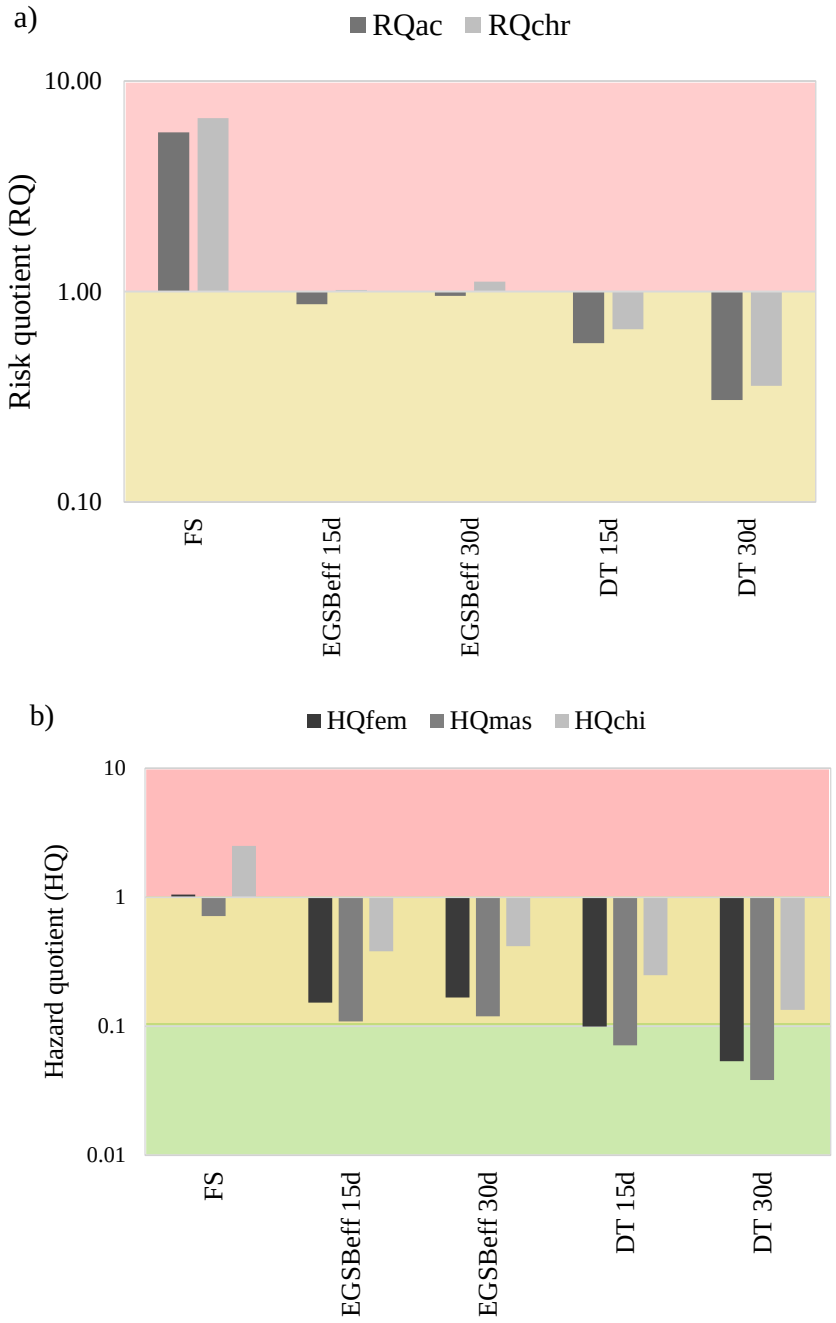
Additionally, other authors have studied the removal of BPA by different MBR configurations. Santos et al. (2024a) reviewed recent studies on removing BPA and its analogues by MBRs and observed an average BPA removal in AnMBR of 43.6%. For example, Song et al. (Song et al., 2018) observed a low BPA removal (17%) by an AnMBR. In contrast, by integrating an MD system into the AnMBR, the removal increased to 90%. Therefore, the G-AnOMBR/MD showed a superior removal efficiency than other AnMBRs due to the GS and the higher selectivity of the FO-MD module compared to conventional MBRs. Furthermore, it is important to highlight that the greater biodegradation of BPA by GS prevents the accumulation of BPA in the reactor due to the high rejection by the membranes.

5.3.4 Environmental and human risk of BPA in GAnOMBR-MD samples

Figure 8 shows the acute and chronic environmental and human health risks for FS, $EGSB_{eff}$, and DT at 15 and 30 days of operation. FS presented high acute and chronic environmental risk (Figure 8a). Therefore, the BPA concentration used in FS (20 μg L^{-1}) – already identified in real raw wastewater (Santos et al., 2024a) – is hazardous to aquatic organisms. This is a concern since, in several developing sites, raw sewage is still discharged into surface waters. Regarding $EGSB_{eff}$, the acute environmental risks were medium, while the chronic ones were high. Despite removing BPA above the expected for anaerobic treatments, as discussed in Section 2.3, the remaining concentration of BPA after the EGSB reactor still promoted environmental risks, even with a considerable reduction in the RQ value compared to FS.

In contrast, the FO-MD module removed high acute and chronic risks for 15 and 30 days of operation, demonstrating the importance of membranes in generating higher-quality effluent with lower environmental impact. Santos et al. (2024a) evaluated the removal of BPA-related environmental risks by various MBR configurations. According to the study, the acute or chronic risk in the final effluent was high in various configurations, especially for sequencing batch reactors - MBRs, aerobic and anaerobic MBRs, enzymatic MBRs, and activated sludge - MBRs. On the other hand, the risks were medium to negligible for configurations using more selective membranes, such as FO, MD, reverse osmosis (RO), and nanofiltration (NF).

Figure 8 – Environmental risk quotient (a) and human hazard quotient (b) related to BPA for FS, $EGSB_{eff}$ and DT.



The human health risk associated with BPA in FS was considered high for adult women and children and medium for adult men (Figure 8b). Importantly, BPA is considered an EDC and can affect the physiology of the human reproductive system by mimicking the activity of androgens and estrogens or blocking the interaction between these hormones and their receptors (Rogers et al., 2013). Thus, BPA has been linked to female fertility

problems such as reduced number of viable oocytes, early puberty, shortened reproductive life span, endometriosis, and fibroids (Vessa et al., 2022). Therefore, although it is not possible to eliminate all sources of exposure to BPA due to the breadth of its use, there is an urgent need to reduce the duration and extent of this exposure (Panagopoulos et al., 2023). Regarding FS, the human health risk related to BPA was medium in $EGSB_{eff}$ for 15 and 30 days of operation, while in DT, it was medium for children and low for men and women.

5.3.5 Acute toxicity assessment

The acute toxicity results (30 min) for the bacteria *A. fischeri* related to the G-AnOMBR/MD samples are presented in Table 6. For FS, the phenomenon called hormesis occurred, described as a positive response of the organism to the medium, which may be related to a manifestation of organisms to overcome a specific imbalance. It is expected that in media where ions such as K^+, Ca^{2+}, and Na^+ are supplied, the luminescence of bacteria is stimulated, causing hormesis (Drzymała & Kalka, 2020a). In contrast, the effluent from the EGSB reactor and the ML in the membrane tank were considered toxic to *A. fischeri*, with TU values of 1.55 and 5.55, respectively. The toxicity in these samples may be related to the concentrations of fatty acids, ammonia, and organic matter. Studies show a positive correlation between ammonia concentration and toxicity to *A. fischeri* (A. M. Costa et al., 2019; Kalčíková et al., 2015). However, these studies observed the correlation considering high ammonia concentrations in landfill leachate (> 700 mg L^{-1}), while in $EGSB_{eff}$ it was 14.2 ± 0.3 mg L^{-1}.

Table 6 - Effect concentration (EC_{50}**)** and the toxic unit (TU) for *A. fischeri* in the GAnOMBR-MD samples.

	EC_{50} (%)	Confidence interval (%)	TU	Classification
FS	Hormesis	-	-	-
$EGSB_{eff}$	64.19	18 - 228.8	1.55	Toxic
Membrane tank	18.02	8.60 - 37.78	5.55	Toxic
DT	>100	-	<1	Non toxic

Few studies have evaluated the toxicity of BPA to *A. fischeri*. Tobajas et al. (2016) found an EC_{50} of 4 mg L^{-1} when evaluating the toxicity of BPA to the bacteria at an exposure time of 15 min, while Arslan-Alaton et al. (2014) observed an EC_{50} of 25.2 mg L^{-1} (15

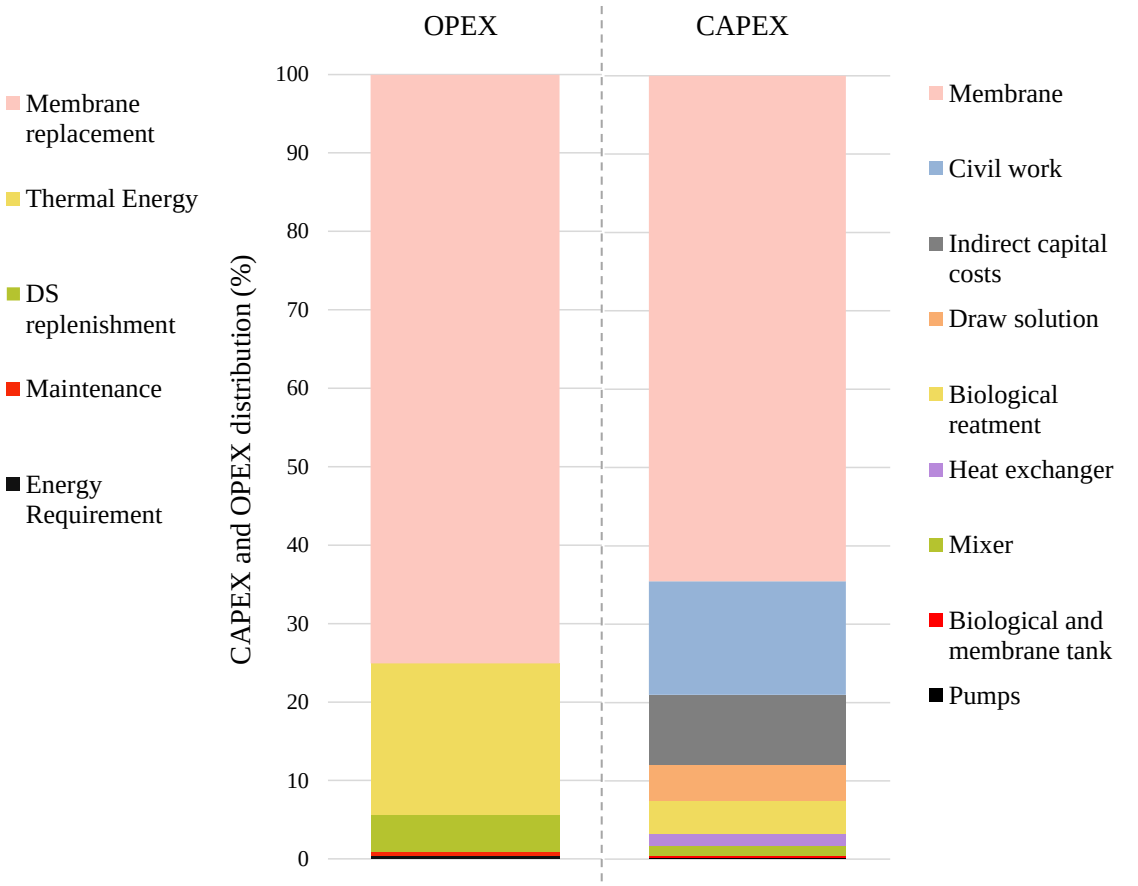
min). These results indicate that the BPA concentration in $EGSB_{eff}$ (Figure 7) was considerably below the toxic concentration for *A. fischeri*. However, it is essential to emphasize that the reported EC_{50} values considered BPA alone; thus, the mixture and interaction of BPA and other pollutants, as in $EGSB_{eff}$, may have promoted a greater toxic effect than the compounds can promote alone.

Regarding DT, the EC_{50} was >100%, i.e., DT was free of toxicity to the *A. fischeri* bacteria, demonstrating the performance of the FO-MD module in achieving high removals of pollutants and their related toxic loads. The findings of these tests are crucial to understanding the environmental impact of treated effluents. Although biological treatment is essential, it was ineffective in terms of toxicity. Therefore, integrated assessment of treated wastewater – considering toxicity to aquatic organisms – is essential for ecosystem safety, especially for discharge into aquatic environments.

5.3.6 Preliminary cost evaluation

The proportion of CAPEX and OPEX values, considering the costs related to the FO-MD hybrid module and anaerobic biological treatment, are shown in Figure 9. The total SPC of G-AnOMBR/MD was US$ 3.91 m^{-3} of treated wastewater, considering the stabilized flux of 1 L m^{-2} h^{-1} for the FO and MD membranes. The costs of G-AnOMBR/MD are comparable to more advanced technologies, aiming at providing a high-quality final effluent. For example, Vinardell et al. (2020) estimated a SPC of 1.38 € m^{-3} for a FO-RO + AnMBR for sewage treatment, considering a recovery of 45% and 90% for RO and FO. The authors considered a J_{FO} = 3.98 L m^{-2} h^{-1}, almost 4x higher than the flux considered in the present study. Furthermore, more than 74% of the total cost was related to the acquisition and replacement of the membranes. Hasanoglu et al. (2024) also concluded that for an AnMF-OMBR, where the SPC was estimated at 1.47 US$ m^{-3} (J_{FO} = 9.61-6.82 L m^{-2} h^{-1}), the cost related to membranes was the most impactful. In contrast, conventional wastewater treatment technologies may have lower costs. For example, Mendoza et al. (2022) measured an SPC equal to 0.14 USD m^{-3} using Gradual Concentric Chambers for sewage treatment. However, the technology promoted a reduction of only 22% in COD and a high release of ammonia from the final effluent.

Figure 9 - Distribution of CAPEX and OPEX values related to the FO-MD module and anaerobic biological treatment.



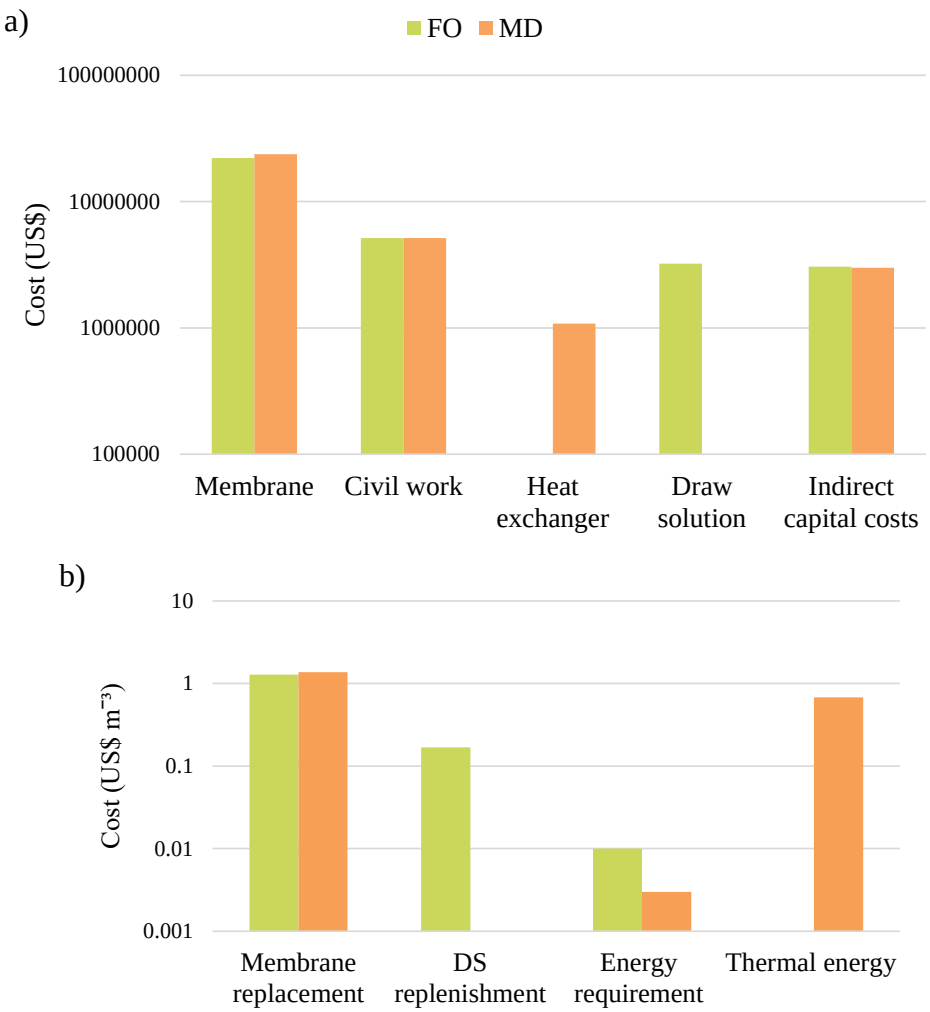
The main CAPEX costs were related to membrane, civil work, draw solution, and indirect costs, totaling US$ 71,009,663.61, equivalent to an amortized value of US$ 0.38 m^{-3} of treated wastewater. For OPEX, the values were considerably higher – about nine times the CAPEX value – mainly due to membrane replacement, thermal energy, and DS replenishment. The total OPEX measured for the system was US$ 3.53 m^{-3}. Compared to the costs of AnOMBR/MD with a module submerged in flocculent sludge investigated by Santos et al. (2023a), a higher initial investment related to the membrane tank was necessary since, in the present study, the FO-MD hybrid module was external to the biological reactor. However, this value was negligible considering the lower costs of the membranes purchase due to the higher permeate flux promoted by the G-AnOMBR/MD configuration. In the study by Santos et al. (2023a) the SPC was US$ 6.84 m^{-3}, mainly due to the membranes purchase.

Since the main costs of the system were related to the membrane filtration stage, the detailed CAPEX and OPEX values of the FO-MD module are presented in detail in Figure 10. The CAPEX for the FO and MD processes were, respectively, US$ 33,547,580.80 and US$ 32,919,363.50 (Figure 10a). Although the cost of the FO membranes was relatively lower, the acquisition of reagents for DS was higher compared to the specifications of the MD process, such as the acquisition of heat exchangers, for example. In contrast, the OPEX costs for the MD process were higher (2.05 US$ m^{-3}) compared to the FO (1.45 US$ m^{-3}), mainly due to the costs with thermal energy (Figure 10b).

The process cost could be considerably reduced by considering waste heat – in the case of high-temperature wastewater treatment – or using renewable energy sources, such as solar energy, for the MD temperature gradient. For example, using 50% waste heat as a heating source, MD OPEX costs would fall to US$ 1.70 m^{-3}. Full use of waste heat would result in an OPEX value for MD of US$ 1.37 m^{-3}, and a total OPEX value for G-AnOMBR/MD of US$ 2.85 m^{-3}. Another factor that impacts the cost of FO-MD is the membrane lifespan. For the present study, a membrane lifespan of 5 years was considered. However, if this value were to be halved (2.5 years), the OPEX costs for FO-MD would increase to US$ 6.18 m^{-3}. Therefore, controlling fouling and cleaning of membranes and the operational conditions of the system is crucial for maximizing the operational lifespan of both FO and MD membranes and making G-AnOMBR/MD costs viable.

Furthermore, developing and using membranes with new materials and membranes modified from applying various nanomaterials, such as carbon nanotubes, graphene, silicon dioxide, and fluorinated compounds, can be promising alternatives to reduce system costs. Studies show that nanomaterials can be used to increase permeability and reduce biological fouling in FO membranes (Ibraheem et al., 2023) and increase hydrophobicity - to reduce wetting - and increase mass transfer rates in the MD process (Hussain et al., 2022). Thus, future studies can strive to evaluate the applicability of modified FO/MD hybrid modules in AnMBR.

Figure 10 - Detailed (a) CAPEX and (b) OPEX costs for FO-MD operation.



Thus, the large-scale application of G-AnOMBR/MD in industrial or municipal wastewater treatment plants is more economically viable when there is the possibility of using renewable energy sources - such as biogas generated in the anaerobic process itself - or residual heat from the effluents and developing techniques that can increase the performance of the FO-MD module regarding permeate flux and scale reduction. Associated with this, it is crucial to consider that a critical point for large-scale application is temperature control in the MD process to maintain the temperature gradient necessary for the driving force of the process. As for FO, although $MgCl_2$ is considered a solute with low reverse salt flux and low diffusion through MD membranes (Arcanjo et al., 2020), other solutes can be evaluated to minimize the need for reconcentration or replacement of the DS over time. Furthermore, to ensure the feasibility of large-scale

application of G-AnOMBR/MD, new operations can be conducted for longer periods and under different operational conditions.

5.4 CONCLUSION AND FUTURE PERSPECTIVES

This study investigated a G-AnOMBR/MD to remove BPA, organic matter, nutrients, toxicity, environmental and human health risks, and costs. With this holistic evaluation of the technology, it was possible to conclude that:

- The G-AnOMBR/MD demonstrated remarkable efficiency in the removal of BPA (94.65%), COD (95.6%), P-PO_4^{3-} (99.6%), and N-NH_4^+ (91%), providing a strong reassurance of its effectiveness.
- The biodegradation of pollutants by GS, including BPA, achieved a removal efficiency above that expected for anaerobic sludges, mainly due to the retention of specific microorganisms and the sludge-contaminant contact area.
- EGSBeff was toxic to the bacteria *A. fischeri*, while DT was classified as not toxic. Thus, the hybrid FO-MD module played a fundamental role in removing pollutants and toxicity.
- FO-MD membranes removed high environmental and human health risks, demonstrating the importance of associating biological treatment with advanced processes.
- The technology was competitive with other advanced treatments, especially AnOMBR/MD with flocculent sludge, due to the higher permeate flux enabled by this configuration.
- The highest cost of the technology was related to the membrane acquisition.
- G-AnOMBR/MD's potential for treating wastewater containing BPA inspires optimism about its future use on a large scale.

This study was a pioneer in the application of G-AnOMBR/MD, and given the findings and challenges encountered, future evaluations may explore the following:

- Membrane fouling and cleaning, aiming to improve permeate flux over time and, consequently, process costs.
- Removal of other EDCs by G-AnOMBR/MD.

- Environmental factors and assessment of the technology's life cycle, considering energy requirements, CO_2 emissions, and waste generation.
- System evaluation using real domestic wastewater.

CHAPTER 6

EVALUATION OF A NOVEL GRANULAR ANAEROBIC MEMBRANE BIOREACTOR WITH RECYCLED UF: ORGANIC MATTER, NUTRIENT AND BISPHENOL A REMOVALS, COST ASSESSMENT, ECOTOXICITY, AND ENVIRONMENTAL AND HUMAN HEALTH RISKS

6.1 INTRODUCTION

The presence of bisphenol A (BPA) in surface waters, as well as in raw and treated wastewater is an irrefutable and alarming issue in many parts of the world due to its high environmental and human health risks (Hu et al., 2019; Loganathan et al., 2023). Therefore, the removal of BPA from wastewater – one of the primary sources of its release into the aquatic environment – has been extensively studied through several technologies seeking to minimize such damage (Loganathan et al., 2023). Among these, membrane bioreactors (MBR) are promising technologies, as they combine biological treatment with membrane separation processes (MSP), providing a dual barrier to prevent the presence of BPA and other endocrine disrupting compounds (EDCs) in treated wastewater.

Dos Santos et al. (2024a) reviewed the removal efficiencies of BPA and its analogues by various MBR configurations. The authors observed that the average BPA removal for conventional aerobic MBRs – using ultrafiltration (UF) or microfiltration (MF) membranes – was 91.5%, while for anaerobic membrane bioreactors (AnMBR), it was only 43.6%. In contrast, in integrated systems combining MBR with more selective membranes, such as reverse osmosis (RO), nanofiltration (NF), forward osmosis (FO), and membrane distillation (MD) – demonstrated average removal rates exceeding 90%, even for AnMBR.

Despite the high removal rates, integrated systems, especially those using more selective membranes driven by hydraulic pressure, require a higher investment for implementation and operation, mainly due to the acquisition and replacement of membranes (Visvanathan et al., 2000). For example, the AnMBR associated with the FO-MD hybrid module for treating wastewater containing trace organic compounds (TrOCs) studied by Santos et al. (2023) (Santos et al., 2023) achieved removals of TrOCs above 96%. The system's total cost was 6.84 USD m^{-3} of treated effluent, with the acquisition and replacement of membranes representing the largest portion. Vinardell et al. (2020a) investigated an AnMBR/FO-RO for municipal wastewater treatment, and the water production cost was estimated at 0.80 to 1.27 € m^{-3} (depending on the FO recovery). In this case, membrane replacement also significantly impacted the operational cost.

In contrast, Pretel et al. (2016a) evaluated the performance of an AnMBR for urban wastewater treatment and measured a cost ranging from 0.03 to 0.12 USD m^{-3} (operating at optimum permeate flux). In addition, Vinardell et al. (2021b) estimated the cost of a wastewater treatment plant (WWTP) using AnMBR to be between 0.35 and 0.42 € m^{-3}. For conventional anaerobic systems, such as the Upflow Anaerobic Sludge Blanket (UASB), the estimated value is 0.15 USD m^{-3} (Medeiros et al., 2023; Vassalle et al., 2020). However, BPA removal is generally low or non-existent, ranging from 10 to 59% (Aguilar et al., 2023; Arias et al., 2018; Medeiros et al., 2023; Moya-Llamas et al., 2018).

Therefore, it is essential to seek technologies that enable the integration of low costs with satisfactory BPA removals and that can be technically and economically viable alternatives to replace conventional anaerobic systems. In this sense, the use of recycled membranes has been gaining ground in several studies aimed at water and wastewater treatment (Aguilar et al., 2023; Coutinho de Paula et al., 2017; de Oliveira et al., 2020; Mota et al., 2024). Membrane recycling consists of reusing end-of-life (EoL) membranes, which would otherwise be discarded due to loss of performance in the filtration processes for which they were initially intended. This can be made possible by converting membranes, usually from RO/NF to UF/MF, using the chemical conversion technique through oxidative attack, which removes the selective dense layer made of aromatic polyamide and produces a porous membrane (Coutinho de Paula and Amaral, 2017; Lawler et al., 2012a).

In addition to the lower costs associated with these membranes, reuse helps develop more sustainable technologies in a circular economy. Generally, discarded membrane modules are classified as inert solid waste, disposed of in landfills or incinerated, with few reuse alternatives (Lawler et al., 2012b). According to Senán-Salinas et al. (2021), 2 million RO membranes will be discarded by 2025. In Brazil, approximately 900 t of RO membranes were generated between 2016 and 2019, and it is estimated that 1800 t will be discarded by 2024 (Grossi et al., 2021). Therefore, recycling can be an alternative to theenvironmental liability related to the increasing disposal of EoL membranes.

Given the above, applying recycled UF membranes (UF_r) in AnMBR may be an economically viable and more sustainable alternative. Despite the limited BPA removal by AnMBR compared to aerobic MBR, changing operating conditions or parameters may

improve the performance of anaerobic microorganisms, such as the application of granular sludge (GS) instead of flocculent sludge (Kang et al., 2023). Studies show that GS can retain specific microorganisms capable of more easily biodegrading recalcitrant compounds (Burzio et al., 2022; Faria et al., 2020a). However, despite several studies evaluating the removal of recalcitrant compounds by aerobic GS, such as EDCs and trace organic compounds (TrOCs), few investigations on the degradation of these compounds by anaerobic GS were found.

Therefore, the present study evaluated the performance of a novel granular anaerobic membrane bioreactor using UF_r (EGSB-MBR) to treat domestic sewage, focusing on BPA removal. The water flux behavior and the removal of organic matter and nutrients were also evaluated during the application of this technology. Furthermore, ecotoxicological tests, environmental and human risk assessment, and cost evaluation were performed. This MBR configuration has not yet been reported in previous studies and represents an advance in investigations on AnMBR using GS and UF_r membranes for BPA removal.

6.2 MATERIALS AND METHODS

6.2.1 Membrane recycling

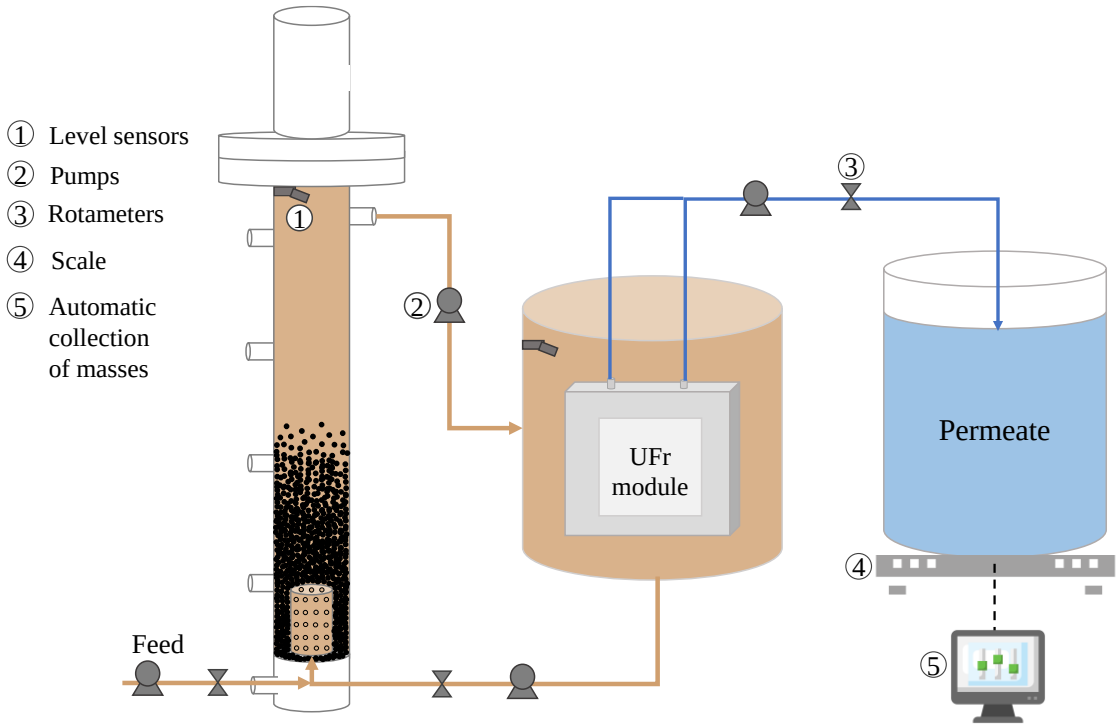
The recycling technique is based on the chemical oxidation of a thin-film-composite RO membrane, proposed by De Paula et al. (2017). The EoF membrane sample used in this study was a spiral module (FilmTec BW30, 0.1 x 1m, filtration area: 7.2 m^2) discarded by a decentralized brackish water desalination plant of the Água Doce Program promoted by the Brazilian Federal Government. For a new BW30 module, the permeate flowrate is 9.1 $m^3\ day^{-1}$ and NaCl (2 g L^{-1}) rejection > 99.5%, according to manufacturer's specification. The module was opened and disassembled. Then, the membrane sheet was cut in samples with an area of 0.0132 m^2. The samples were immersed in deionized water until chemical cleaning. For chemical cleaning, EoL membrane samples were subjected to passive immersion in solutions of NaOH (0.1%) and after HCl (0.2%) for 16 h each. After chemical cleaning, EoL membranes were stored immersed in distilled water until the oxidative treatment was carried out. For oxidative treatment, membranes were immersed in a commercial NaClO bath (contact intensity: ~300,000 parts per million h) at room temperature. Finally, membranes were cleaned

with deionized water to remove free chlorine residual. Before use, recycled membranes were placed in a water-ethanol solution (50% v/v) for 15 min to rewet the polymeric matrix of the membranes.

6.2.2 EGSB-MBR experimental setup and operational conditions

The experimental setup of the granular anaerobic membrane bioreactor (EGSB-MBR) was composed of an Expanded Granular Sludge Bed (EGSB) reactor, an external membrane tank, and a permeate (PT) tank (Figure 1). The EGSB reactor following the same operating conditions suggested by Faria et al. (Faria et al., 2020a). The specific organic loading rate (SOLR) applied was 58.6 mgCOD $gVSS^{-1}$ d^{-1}, and the VSS concentration in EGSB sludge was equal to 18.3 g L^{-1}. The mixed liquor (ML) from the EGSB reactor was pumped into the membrane tank (MT) and occurred the recirculation of ML in the EGSB reactor. The recycled membrane sheet was welded to both side of the membrane module, providing a total membrane surface area of 0.0264 m^2. A pump was coupled to the two upper outlets of the submerged module. The membrane was operated under continuous flux (2.5 L m^{-2} h^{-1}) by regulating the transmembrane pressure. A digital scale linked to a computer was used to record the weight of the PT every 5 min. The conductivity, pH and temperature of samples were monitored daily. In addition, samples from feed solution (FS), $EGSB_{eff}$, MT, and PT were collected weekly for physicochemical characterization. As FS for EGSB-MBR, synthetic sewage simulating real domestic sewage was prepared according to Table S1. FS was fortified with BPA in concentration of 20 μg L^{-1}, determinate based in concentrations of BPA in raw sewage (Santos et al., 2024b). BPA (purity > 97%; product number: 133027) was purchased from Sigma-Aldrich® and the stock solution was prepared in methanol. The physical-chemical characteristics of FS are presented in Table S2.

Figure 1 - Experimental setup of granular membrane bioreactor with UF_r (EGSB-MBR).



6.2.3 Analytical methods

The physicochemical analyses were performed following the methodologies of the Standard Methods for the Examination of Water and Wastewater (2017), as shown in Table 1. The volatile fatty acids (VFA) concentration was determined according to the methodology proposed by Kapp (H. Kapp, 1984).

Table 1 - Analytical methods

Parameter	Method
pH	4500-H^+
Conductivity	2510
Chemical oxygen demand (COD)	5220
Dissolved organic carbon (DOC)	5310 B
Total suspended solids (TSS)	2540 D
Volatile suspended solids (VSS)	2540 E
Total phosphorus ($P-PO_4^{3-}$)	4500-P D
Ammoniacal nitrogen ($N-NH_4^+$)	4500-NH3 B e C
Alkalinity	2320 B

Soluble microbial products (SMP) and extracellular polymeric substances (EPS) from sludge sample were characterized as protein and carbohydrate fractions. For SMP and EPS extraction, 5 mL of sludge were centrifugated at 4450 g for 10 min, the supernatant was collected as SMP and the sludge pellets were resuspended with 50 mL of 0.05% NaCl solution and heated to 80 °C in a water bath for 10 min (He et al., 2017). Following, the solution was centrifugated at 4450 g for 10 min, and the supernatant corresponded to EPS. In addition, three-dimensional excitation–emission matrix (3D-EEM) fluorescence spectroscopy analyses were performed with the FS, $EGSB_{eff}$ and PT samples, using the AQUALOG ® equipment (Horiba). The analysis was performed with a quartz cuvette, integration time of 0.2 seconds and wavelength interval of 3 nm with 4 pixels. Finally, first and second order light beam mask filters were applied.

Extraction and quantification of BPA were carried out according to Kiejza et al. (2022) and Wang et al. (2005). In summary, extraction of BPA from samples was performed using C18-E cartridges and a vacuum manifold (Phenomenex, California, USA). 600 mL of permeate (20th, 40th and 60th day of operation) and 200 mL of EGSBeff (20th, 40th and 60th day of operation) were used for BPA extraction. The analytes were eluted with 4 mL of ethyl acetate, transferred to glass vials and immediately analyzed. BPA determination was performed using gas chromatography-mass spectrometry (GC-MS) with a Shimadzu GCMS-QP2010. The separation was achieved by a DB-5MS column (30 m × 0.25 mm × 0.25 µm film thickness). Helium (99.999%) was used as a carrier gas at a constant flow rate of 1.0 mL min-1. The injector operated in splitless mode at a temperature of 250 °C. The oven temperature program began at 130 °C (held for 3 minutes), followed by an increase of 30 °C min^{-1} until reaching 250 °C (held for 4 minutes), and then a further increase of 20 °C min^{-1} until reaching a final temperature of 310 °C, which was maintained for 5 minutes. The total run time was 19 minutes. The electron impact ionization source temperature was 230 °C, with an electron energy of 70 eV. The quadrupole temperature was maintained at 150 °C, and the GC interface temperature was set at 280 °C.

6.2.4 Permeate flux and removal efficiencies

Permeate flux in UF_r membrane was calculated by Equation 1:

$$J_{UF} = \frac{\Delta m_{PT}\, x\, r}{\Delta t \times A_m} \quad (1)$$

where Δm_{PT} is the increase in PT weight over a period, Δt, ρ is the permeate density and A_m is the module membrane area.

The overall removal efficiency of the AnMBR was calculated by Equation 2:

$$R_{AnMBR} = \frac{C_{FS} - C_{PT}}{C_{FS}} x\ 100 \quad (2)$$

where C_{FS} is the contaminant concentration in the FS, and C_{PT} is the contaminant concentration of the UF_r permeate.

6.2.5 Ecotoxicological tests

Acute toxicity tests were carried out with the bacteria *Aliivibrio fischeri*, using the MICROTOX® model 500 Analyzer (SDI) equipment, and following ABNT NBR 15411-3 (2021). The effect concentration (EC_{50}) was determined from the MICROTOX® 81.9% Basic Test, and the luminescence measurement was carried out for 30 minutes. 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 results obtained were transformed into values of toxic unit (TU), dividing 100 by the EC_{50}, to facilitate discussion of the results. In addition, the toxicity was classified as proposed by Persoone et al. (2003): class I (TU < 1) - non toxic; class II (1 < TU < 10) - toxic; class III (10 < TU <100) - very toxic; class IV (TU > 100) - highly toxic.

6.2.6 Human health and environmental risk assessment for BPA

Acute and chronic environmental risks for BPA were assessed by risk quotient (RQ), as shown in Equation 3:

$$RQ = \frac{MEC}{PNEC} \quad (3)$$

where MEC is the measured concentrations of BPA in FS, $EGSB_{eff}$, and PT on the 20ht, 40ht and 60th days of operation, and PNEC is the predicted no-effect concentration.

For the calculation of the PNEC, acute or chronic toxicities for BPA were considered, 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 toxicity values of BPA, the more critical E(L)C_{50} and NOEC, reported for several trophic levels by Santos et al. (Santos et al., 2024b), were considered. Human health risk, estimated as the hazard quotient (HQ), was calculated through Equation 4:

$$HQ = \frac{MEC}{DWEL} \quad (4)$$

where MEC is the measured concentrations of BPA in FS, $EGSB_{eff}$, and PT on the 20ht, 40ht and 60th days of operation, and DWEL is the drinking water equivalent level.

DWEL was calculated according to established values from Environmental Protection Agency (2011). DWEL considers tolerable daily intake for BPA (4 μg kg bw^{-1} day^{-1}) recommended by the European Food Safety Authority, the body weight for adult (60 kg for > 10 years of age) and children (10 kg for < 10 years of age), the relative contribution of water exposure (0.2), and the daily water intake for adult (2 L d^{-1}) and children (1 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 ≤ R(H)Q ≤ 1, the risk was considered medium; for 0.01 ≤ R(H)Q <0.1 the risk is low; and if R(H)Q <0.01 the risk is negligible (European Commission, 1996).

6.2.7 Preliminary cost evaluation

The preliminary cost evaluation of the EGSB-MBR was conducted, considering both capital expenditures (CAPEX) and operating expenditures (OPEX), based on the experimental results. The direct and indirect CAPEX accounted for cost related to civil works, intake and pretreatment systems, chemical usage, pumps, anaerobic and membrane tank, mixers, and heat exchangers (Osipi et al., 2018). The cost of membrane acquisition was not considered due to the use of recycled UF. Table 2 shows the general parameters used for estimating CAPEX and OPEX for a large-scale system.

Table 2 - Parameters considered for the CAPEX and OPEX estimation.

Parameter	Value	Reference
Population (inhabitants)	100,000	This study
Flow rate ($m^3\ h^{-1}$)	790	This study
Water per capita (L $inhab^{-1}\ d^{-1}$)	150	(ABNT, 1986)
Return coefficient	0.7	(ABNT, 1986)
Maximum hourly flow coefficient (k1)	1.2	(ABNT, 1986)
Maximum daily flow coefficient (k2)	1.5	[35]
Biological tank (US$ m^{-3})	235	(Verrecht et al., 2010)
Membrane tank (US$ m^{-3})	235	(Verrecht et al., 2010)
Mixing energy consumption (W m^3)	8	(Verrecht et al., 2010)
Investment rate (%)	16.3	This study
Design life plant (years)	15	This study

In addition, the parameters adopted for estimating CAPEX and OPEX of the UF_r module are shown in Table 3. Membrane replacement costs considered an average UF_r membrane lifespan of 2 years (Lawler et al., 2015a). However, rather than including the cost of new membranes, the evaluation focused on the expenses associated with the chemicals used in the chemical oxidation recycling process. The required volume of NaClO and cleaning agents were determined based on the recycled membrane area for a system capacity of 790 $m^3\ h^{-1}$, as detailed in Table 2.

Table 3 – Parameters considered for UF_r CAPEX and OPEX estimation.

Parameter	Value	References
HCl requirement (kg m^{-3} $year^{-1}$)		This study
HCl price (US$ kg^{-1})	10	(Carlroth, 2024)
NaOH requirement (kg m^{-3} $year^{-1}$)		This study
NaOH price (US$ kg^{-1})	25.56	(Carlroth, 2024)
NaClO requirement (L m^{-3} $year^{-1}$)		This study
NaClO price (US$ L^{-1})	4.28	(Carlroth, 2024)
Ethanol requirement (L m^{-3} $year^{-1}$)		This study
Ethanol price (US$ L^{-1})	16.75	(Carlroth, 2024)
η (%)	85	(Vinardell et al., 2020b)
P_{inlet} (bar)		This study
Energy price (US$ $kW^{-1}\ h^{-1}$)	0.04	(Zhang et al., 2022)
Energy requirement (kWh d^{-1})		This study
Membranes lifespan (year)	2	(Lawler et al., 2015b)

Specific produced permeate cost (SPC) was calculated according to Equation 5, as proposed by Osipi et al. (2018):

$$SPC = \frac{af \cdot \frac{CAPEX}{f} + OPEX}{Q_p} \quad (5)$$

where f is the utilization factor (equal to 1, considering the maximum system capacity), Q_p is the total annual produced permeate, and af is the amortization factor, calculated according to Equation 6:

$$af = \frac{i_c \cdot (1+i_c)^{DL}}{(1+i_c)^{DL}-1} \quad (6)$$

where i_c is the investment rate and DL is the design lifetime of the plant for the UF_r system.

Specific energy consumption (SEC) for UF hydraulic pressure, and reactor stirring was estimated according to Equation 7:

$$SEC = \frac{W_{pump} \cdot t}{\eta \cdot Q_p} = \frac{P_{inlet} \cdot Q_f \cdot N_c \cdot t}{\eta \cdot Q_p} \quad (7)$$

where W_{pump} is the work done by the pump, t is the daily operating time, Q_f is the feed flow, P_{inlet} is the pump discharge pressure, η is the pump efficiency, and N_c is the number of compartments (one for this module).

6.3 RESULTS AND DISCUSSION

6.3.1 EGSB-MBR removal efficiencies and performance

The pH, conductivity, temperature, volatile fatty acids (VFA), and alkalinity results for the EGSB-MBR samples are shown in Table 4. The pH values remained stable throughout the operation, consistent with the low VFA results. In anaerobic reactors, the degradation of organic matter is carried out by two groups of microorganisms: acidogenic and methanogenic. Acidogenic bacteria are responsible for the degradation of organic matter into VFA, while methanogenic organisms subsequently convert these products into methane and carbon dioxide. When the methanogenic population is sufficient, and conditions are favorable, the products of the acidogenic organisms are rapidly utilized (Amani et al., 2010). This prevents the accumulation of acids in the reactor, maintaining buffering conditions and ensuring that the pH remains neutral, which is favorable to methanogenic activity. Although the molecular sizes of VFA, carbonate and bicarbonate

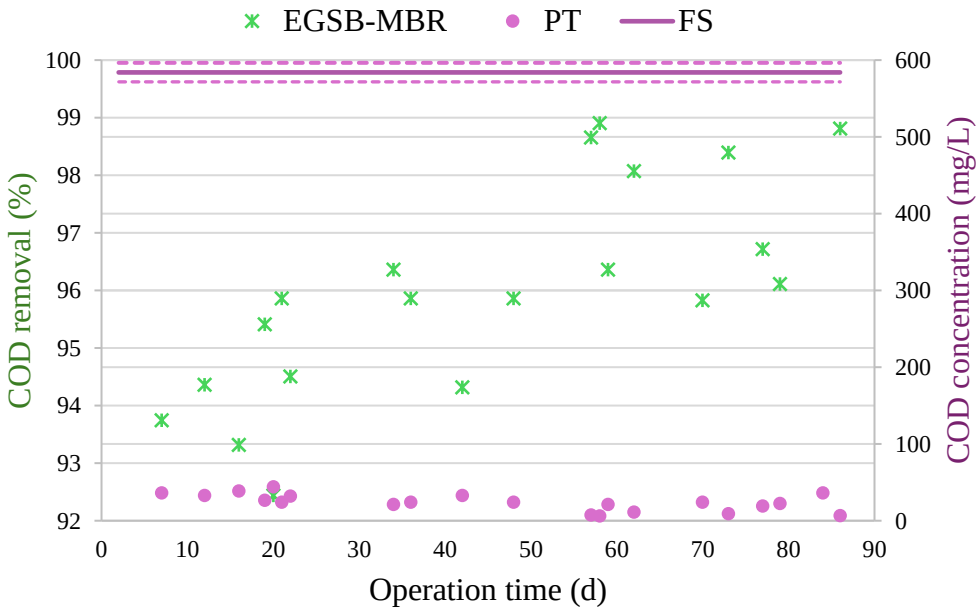
are smaller than the membrane pore size, a retention of 23.01% for VFA and 30.47% for alkalinity by the UF_r was observed (Table 4). These results suggest that the cake layer formed on the membrane surface may have hindered the passage of the VFA, carbonate and bicarbonate through the UF_r membrane.

Table 4 - pH, conductivity, temperature, volatile fatty acids (VFA) and alkalinity for EGSB-MBR samples pH, conductivity, temperature, volatile fatty acids (VFA) and alkalinity for EGSB-MBR samples.

	$EGSB_{eff}$	**Membrane tank**	**PT**
pH	7.1 ± 0.1	7.3 ± 0.2	7.4 ± 0.2
Condutivity (µs cm^{-1})	1124.5 ± 13.7	1114.4 ± 10.0	1082.9 ± 13.7
Temperature (ºC)	23 ± 0.9	22.9 ± 1.1	22.9 ± 0.8
VFA (mgHAc L^{-1})	28.59 ± 2.68	18.53 ± 1.13	14.26 ± 0.97
Alkalinity (mg$CaCO_3$ L^{-1})	187.53 ± 4.57	214.26 ± 5.12	148.97 ± 3.14

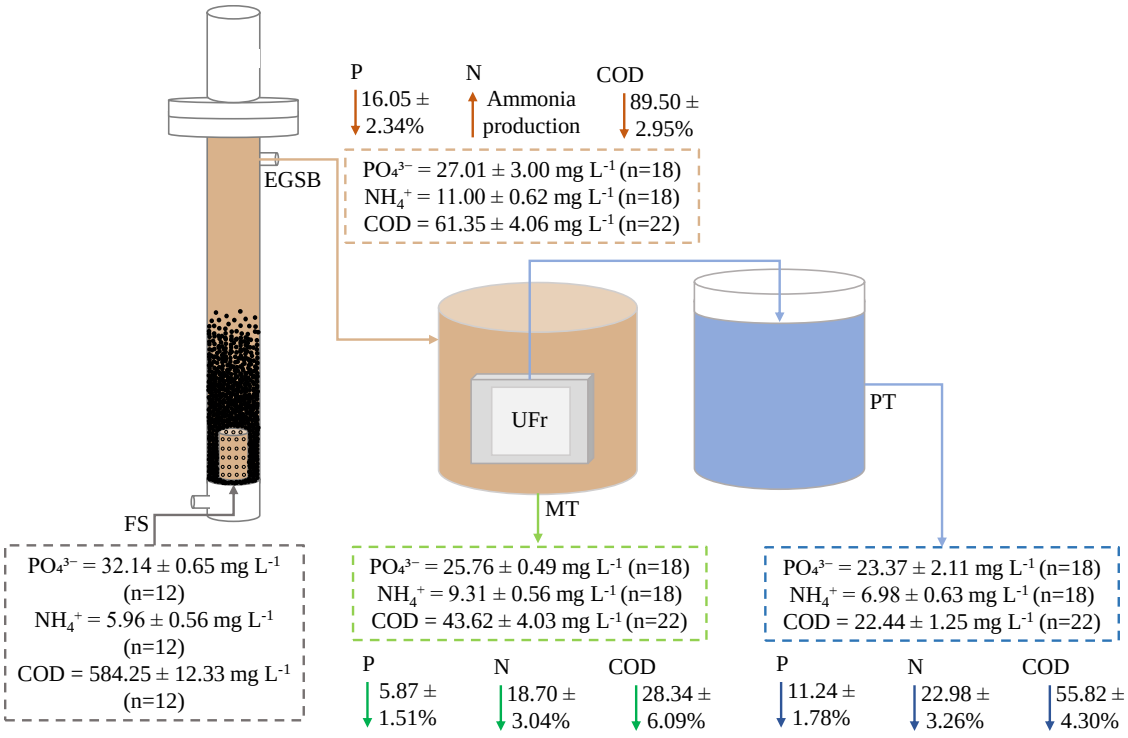
Figure 2 shows the temporal variation in COD concentrations in PT, and removal efficiencies during the EGSB-MBR operation. The overall COD removal by EGSB-MBR system ranged from 92.5 to 99%, with average removal of 95.1%. Thus, the average COD concentration in PT was 22.44 ± 1.25 mg L^{-1}. These results align with the findings of a previous study on EGSB-MBR using commercial UF membranes, which reported COD removal of 98% by EGSB-MBR system (Faria et al., 2020b). As observed in Figure 2, there was a trend of increasing COD removal by the EGSB-MBR throughout the operation. This was mainly due to the increase in COD removal by the EGSB over time, which may have occurred due to the adaptation of the microorganisms. In the first 20 days of operation, the average removal by the EGSB was, on average, 87.5%, while at the end of the operation the average removal was 91.7%. Despite this, no considerable fluctuation in concentrations of UF_r permeate was observed. This stabilization effect promoted by UF membranes has already been observed in other AnMBRs using commercial membranes (Chyoshi et al., 2022; Osman and Hodaifa, 2023).

Figure 2 – COD concentrations in FS (dashed lines represent standard deviation), and PT and EGSB-MBR removal throughout the operation.



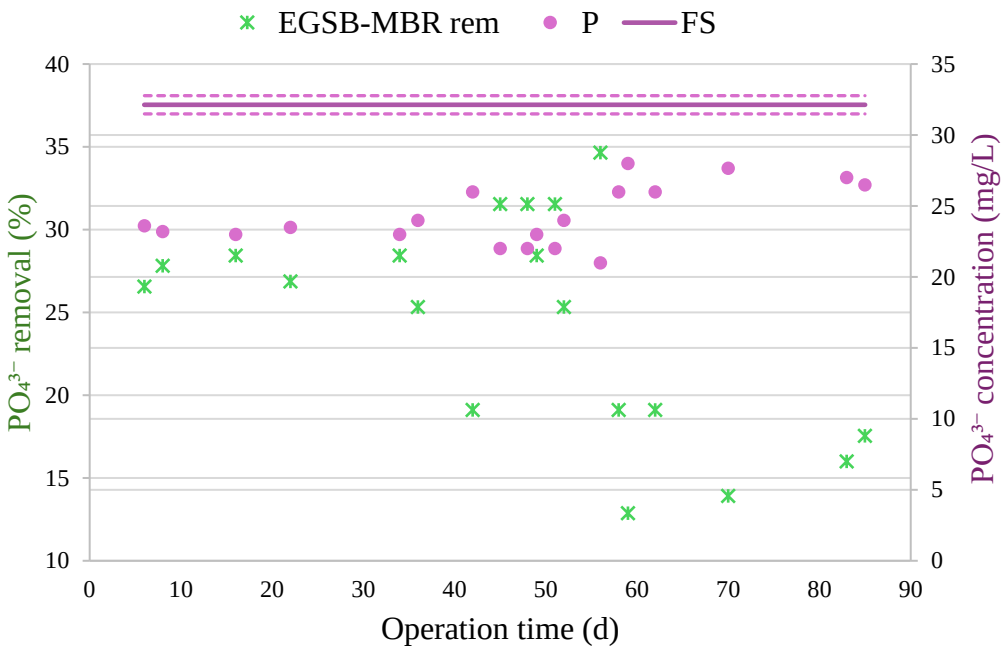
The average COD concentration in $EGSB_{eff}$ was 61.35 ± 4.06 mg L^{-1}, indicating that the GS removed 89.50 ± 2.95% of the organic matter through biodegradation. In addition, the percentage of organic matter removal in the membrane tank (28.34 ± 6.09%) was observed, possibly due to biodegradation by a portion of microorganisms in the tank (Figure 3). Membrane retention contributed to a COD removal of 55.82 ± 4.30% (Figure 3). Size exclusion is the primary mechanism of UF rejection, which includes colloids and macromolecules larger or close to the size of the membrane pore (Peters et al., 2021). Regarding dissolved organic matter, DOC removal of 96 ± 0.88% was observed for EGSB-MBR, resulting in a DOC concentration of 6.3 mg L^{-1} in PT. This high efficiency was mainly due to the high removal by the EGSB (90.74 ± 0.90%). Additionally, DOC biodegradation may have occurred in the membrane tank, in addition to the rejection of macromolecular DOC by the UF_r, such as humic acid, fulvic acid, proteins, and polymeric substances (Liu et al., 2021).

Figure 3 – Concentrations and removals of organic matter and nutrients by compartment of the EGSB-MBR.



Regarding P-PO_4^{3-}, the average removal by EGSB-MBR was 27.00 ± 1.59%, resulting in a concentration of 23.37 ± 2.11 mg L^{-1} in UF_r permeate (Figure 4). Throughout the operation there was a slight increase of P-PO_4^{3-} in the PT, which led to less overall removal from day 60 onwards. A low removal of P-PO_4^{3-} by the EGSB (16.05 ± 2.34%) was observed during the operation, as shown in Figure 3. The concentrations in the $EGSB_{eff}$ in the last 20 days of operation, on average 29 mg L^{-1}, were higher than the average of the previous days (25.20 mg L^{-1}). As observed in Figure 3, some P-PO_4^{3-} removal was achieved by UF_r. Although porous membranes are generally inefficient in removing dissolved ions, P-PO_4^{3-} removal may be associated with its adsorption on larger particles, such as proteins, polysaccharides, or EPS (Shang et al., 2014).

Figure 4 – Concentrations of P-PO_4^{3-} in FS (dashed lines represent standard deviation), and PT and EGSB-MBR removal throughout the operation.



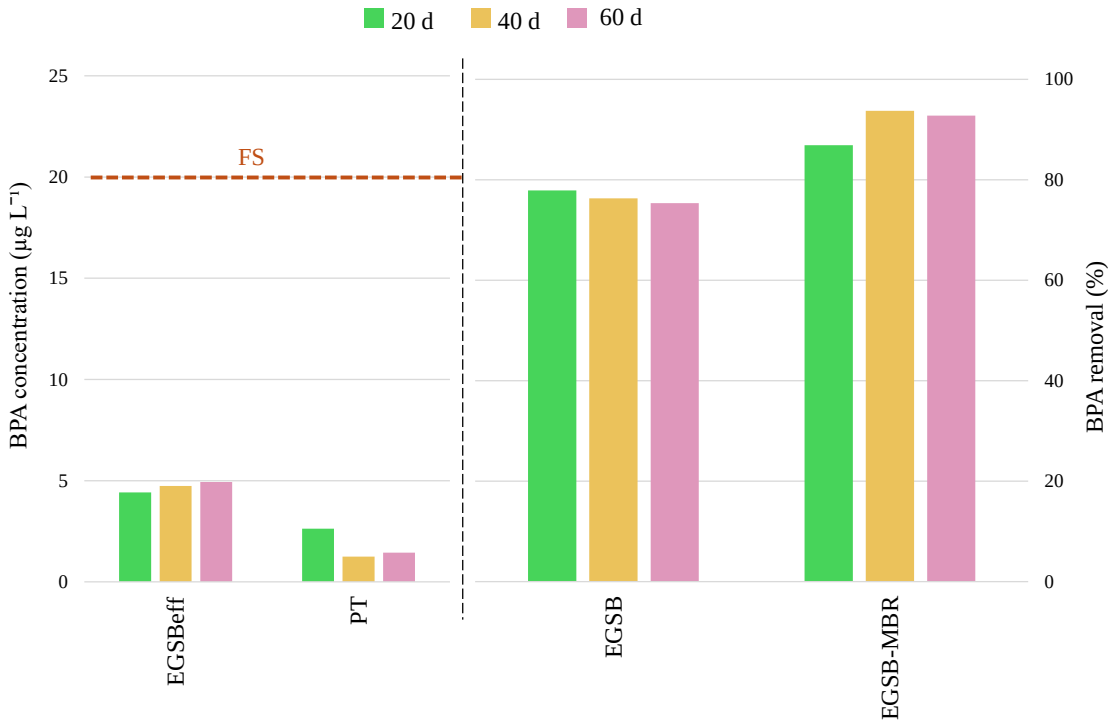
For N-NH_4^+, no overall removal was observed by EGSB-MBR (Figure 3) since the PT concentration was higher than FS. It is possible to note an increase in the concentration of N-NH_4^+ in $EGSB_{eff}$ compared to FS (Figure 3), which is expected since, in anaerobic conditions, organic nitrogen is converted to N-NH_4^+ by microorganisms. In the present study, a removal of 22.98 ± 3.26% by UF_r was observed, which can be attributed, as well as P-PO_4^{3-}, to an indirect removal due to adsorption on macromolecules (Nielsen, 1996).

A barrier to applying AnMBR is the lower direct nutrient removal capacity due to the low yields of typical anaerobic biomass. Therefore, it is essential to highlight the importance of research focusing on a greater removal and controlled capture of nutrients in AnMBR as value-added products, mainly phosphorus (as orthophosphate), for targeted use as fertilizer or raw material for the fertilizer industry (Damodara Kannan et al., 2023; Monballiu et al., 2020; Photiou et al., 2023). Furthermore, improvements in porous membranes for greater nutrient removal, such as the incorporation of adsorptive substances and membranes made with new materials, are essential to achieve better permeate quality (Ayyaru and Ahn, 2022; Liu et al., 2024).

6.3.2 EGSB-MBR efficiency for BPA removal

The GC-MS chromatogram for the BPA standard sample, $EGSB_{eff}$, and PT were provided in Figure S1. The BPA concentrations in FS, $EGSB_{eff}$, and PT on days 20, 40, and 60 of operation and the respective removals by the EGSB reactor and EGSB-MBR were shown in Figure 5. On day 20 of operation, the BPA concentration in the $EGSB_{eff}$ was 4.42 µg L^{-1}, and it remained stable at 4.74 and 4.90 µg L^{-1}, on days 40 and 60 day, respectively. Consequently, the average BPA removal by biodegradation was 76.51 ± 1.29% throughout the operation. Cydzik-Kwiatkowska et al. (2020) showed that the greater BPA biodegradation observed in the GS could be attributed to the retention of specific microorganisms capable of more efficient BPA degradation. In addition, EGSB promoted greater biomass-feed contact in combination with membrane filtration.

Figure 5 - Concentrations (µ L^{-1}) and removal of BPA by EGSB and EGSB-MBR on days 20, 40 and 60 of operation.



At 20 days of operation, the post EGSB removal - associated with some possible biodegradation in MT and removal by UF_r - was 40.67%, and this value increased to 73.62 and 70.73% at 40 and 60 days of operation. Thus, the average global removal of BPA by EGSB-MBR was 91.14 ± 3.72%, equivalent to a BPA concentration of 1.44 µg L^{-1} in the PT at 60 days of operation (Figure 5). Studies have shown that commercial UF

membranes had satisfactory BPA removal. For example, Bing-zhi et al. (Bing-zhi et al., 2008a) showed that UF membranes (MWCO = 10,000 Da), even with membrane pores several orders of magnitude larger than those of BPA, had a removal of 93%. The authors showed that the concentration of BPA in the feed had little impact on the UF removal efficiency. However, increasing the concentration of organic matter in the feed promoted an increase in BPA removal due to its association with macromolecules. In addition, the authors observed that BPA has a stronger adsorption potential on UF membrane.

Wu et al. (2016a) confirmed the contribution of UF (polyvinyl chloride; mean pore size = 33.1 ± 1.1 nm; contact angle = 72.5º; pure water flux = 90.4 ± 6.2 L m^{-2} h^{-1}) to BPA removal, but at lower efficiencies, in the range of 45%, mainly through adsorption. In addition, Acero et al. (2010) (2010) evaluated the removal of micropollutants by several commercial flat sheet UF membranes and identified that adsorption is the primary retention mechanism, mainly for hydrophobic compounds. Thus, the adsorption of BPA by UF_r and organic matter may have contributed to the rejection since the hydrophobic nature of BPA (Log K_{ow} equal to 3.4) facilitates the interaction with the hydrophobic membrane and with organic matter in the cake layer.

Since adsorption is an essential mechanism in BPA removal by UF, the feed pH becomes a determining factor. BPA exists in a neutral form in acidic and neutral environments, such as in $EGSB_{eff}$. At the same time, in alkaline conditions, close to the pKa value of BPA (10.1), the compound loses its proton and becomes negatively charged. As a result, BPA may be repelled from the negatively charged membrane instead of being adsorbed, leading to a lower removal rate since the pore size of the membranes becomes the main retention factor (Bing-zhi et al., 2008b; Muhamad et al., 2016). Therefore, especially for porous membranes, such as UF_r, the feed pH must be controlled and maintained within the appropriate ranges to improve removal by adsorptive action.

During the treatment of domestic sewage by MBR, the pH will hardly reach the value of 10.1. Despite this, it is important to mention that BPA desorption can occur at pH values in the range of or above its pKa value, leading to the release of BPA in the PT (Li et al., 2022; Schäfer et al., 2006). Furthermore, upon reaching an equilibrium state where the adsorption rate equals the desorption rate, the adsorption sites on the membrane surface become saturated, which may lead to reduced BPA removal efficiency (Aldana et al.,

2024; Wu et al., 2016b). The removal of BPA at 40 and 60 days of operation remained stable in the present study; however, it is recommended to carry out investigations that describe the adsorption-desorption behavior by isotherms to quantify the adsorption capacity of BPA by UF_r.

In addition, membrane fouling may have contributed to increased BPA removal. In the first 12 days of operation, a sharp decrease in membrane permeability was observed (Figure 7). As demonstrated by the Hermia models, intermediate pore blocking may have been the main fouling mechanism of the UF_r, causing pore constriction (Section 6.3.5). Thus, partial pore obstruction may have reduced the molecular weight cut-off of the membrane, facilitating BPA removal by size exclusion, especially at 40 and 60 days of operation, when BPA removal was highest. In addition, the cake layer may have acted as an additional layer of filtration and BPA adsorption (Aldana et al., 2024). For example, Wu et al. (2016b) tested three UF membranes for BPA removal and observed removals ranging from 35 to 65%. To evaluate the impact of fouling on BPA removal, the authors filtered a solution containing humic acid (concentration ranging from 2 mg L^{-1} to 10 mg L^{-1}) for 10 min. After membrane fouling, BPA removal ranged from 80% to 92%.

Sanguanpak et al. (2015) evaluated the removal of BPA by a pilot-scale MBR using commercial UF membranes and obtained removal of 89.8% by the MBR with clean UF membranes and 94.3% with fouled membranes. Thus, the evaluation of the UF membranes was performed outside the system. While the virgin membrane removed approximately 15% of BPA, the fouled membrane removed up to 50%. In addition, the authors observed that the higher the log K_{ow} of the evaluated compounds, the greater the removal by the fouled membrane. According to them, the removal of BPA by the fouled UF membrane can be attributed to various factors: (i) the increase in solid particles accumulation on the membrane surface could induce higher adsorption capacities leading to reduction of BPA transport; (ii) increased coverage of pore blocked area could result in an enhanced steric exclusion and less partitioning of BPA transport through the membrane; and (iii) higher hydrophobic characteristic of membrane surface could yield high rejection of hydrophobic compounds. In addition, Zhang et al. (2015) performed BPA filtration tests with commercial hollow fiber UF membranes to directly investigate the effects of various stages of membrane fouling on BPA removal during MBR

operation. The authors observed an apparent increase in BPA removal when membrane fouling was more severe.

Therefore, due to the greater removal of BPA by biodegradation by EGSB, added to the contribution of rejection by UF_r, EGSB-MBR was able to achieve a removal above that expected for anaerobic systems, proving to be a promising technology for replacing conventional anaerobic treatment aiming at BPA removal.

6.3.3 Acute toxicity assessment

The acute toxicity results (30 min) for the bacteria *A. fischeri* related to the EGSB-MBR samples are presented in Table 5. $EGSB_{eff}$ was toxic to the bacteria in all samples evaluated (20, 40, and 60 days of operation). It is possible to notice that the toxicity, in this case, tended to increase throughout the operation, with a TU of 4.71 in 60 days. Toxicity in $EGSB_{eff}$ can be related to the accumulation and mixture of several pollutants such as PO_4^{3-}, NH_4^+, humic acids, VFA, and BPA. Furthermore, during the anaerobic degradation of BPA, intermediate products can be generated, such as p-Cresol, 1,2-bis(4-hydroxyphenyl)-2-propanol, 2,2-bis(4-hydroxyphenyl)-1-propanol, 4-hydroxybenzaldehyde, 4-hydroxyacetophenone, and 4-hydroxybenzoic acid (Amin et al., 2021; He et al., 2024). Although compounds such as nutrients and humic acids (Kalčíková et al., 2015; Tsiridis et al., 2006), BPA (Molkenthin et al., 2013) and BPA degradation products evaluated in the literature (Lee et al., 2018; Renoux et al., 1999) show toxicity to *A. fischeri* at concentrations in the range of mg L^{-1} when tested alone, the effect of the mixture and interaction of these compounds on the bacteria is still unknown.

Although FS did not show toxicity to *A. fischeri*, the phenomenon of hormesis was detected for the three points evaluated, as occurred for PT (Table 5). The mechanisms that drive hormesis in *A. fischeri* are not fully understood but may involve adaptive responses to environmental stressors. Studies propose that, at low doses, toxic pollutants can induce a temporary upregulation of defense genes in bacteria, leading to enhanced luminescence before reaching inhibitory levels (Sebastiano et al., 2022). This adaptive response can be interpreted as a survival strategy, optimizing the organism's ability to cope with adverse environmental conditions.

Therefore, a definitive conclusion on the toxic effects of FS and PT was impossible. In future studies, the diluent used in the toxicity test could be replaced with synthetic

seawater, which, according to Drzymała and Kalka (2020), increased the sensitivity of bacteria to compounds at lower doses, eliminated hormetic effects, and promoted more stable and repeatable responses during toxicity tests with wastewater. In addition, toxicity tests with more aquatic organisms may better represent the impact of these samples on the environment.

Table 5 - Effect concentration (EC_{50}**)** and the toxic unit (TU) for *A. fischeri* in the EGSB-MBR samples.

Sample	Operation day	EC_{50} (%) 30 min	TU	Classification
FS	20	Hormesis	-	
	40	Hormesis	-	
	60	Hormesis	-	
$EGSB_{eff}$	20	82.99	1.20	Toxic
	40	47.50	2.11	Toxic
	60	21.25	4.71	Toxic
PT	20	Hormesis	-	
	40	Hormesis	-	
	60	Hormesis	-	

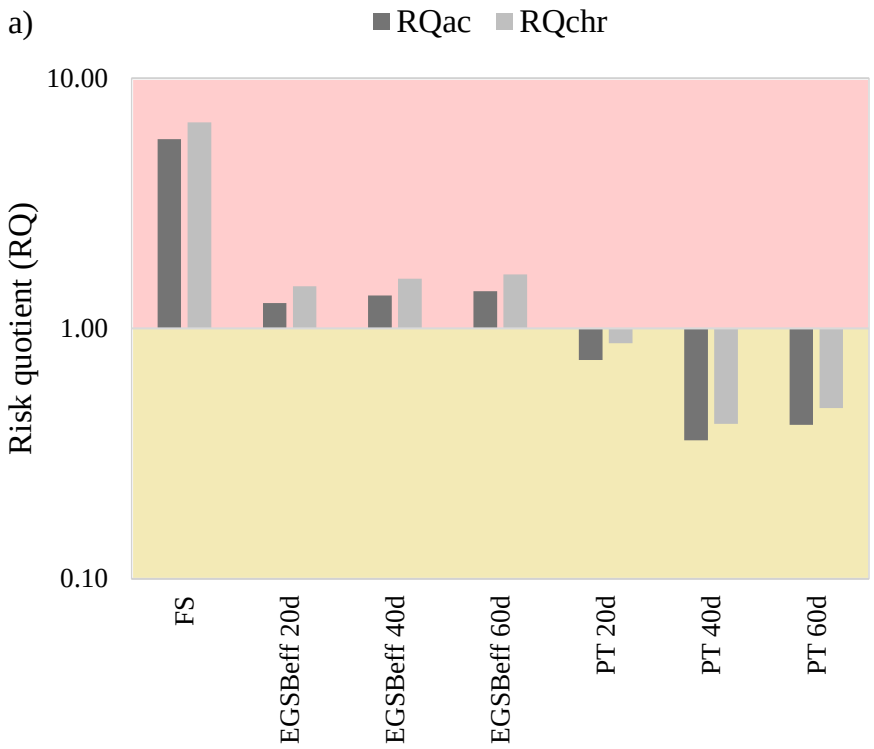
6.3.4 EGSB-MBR efficiency for environmental and human health risk removal

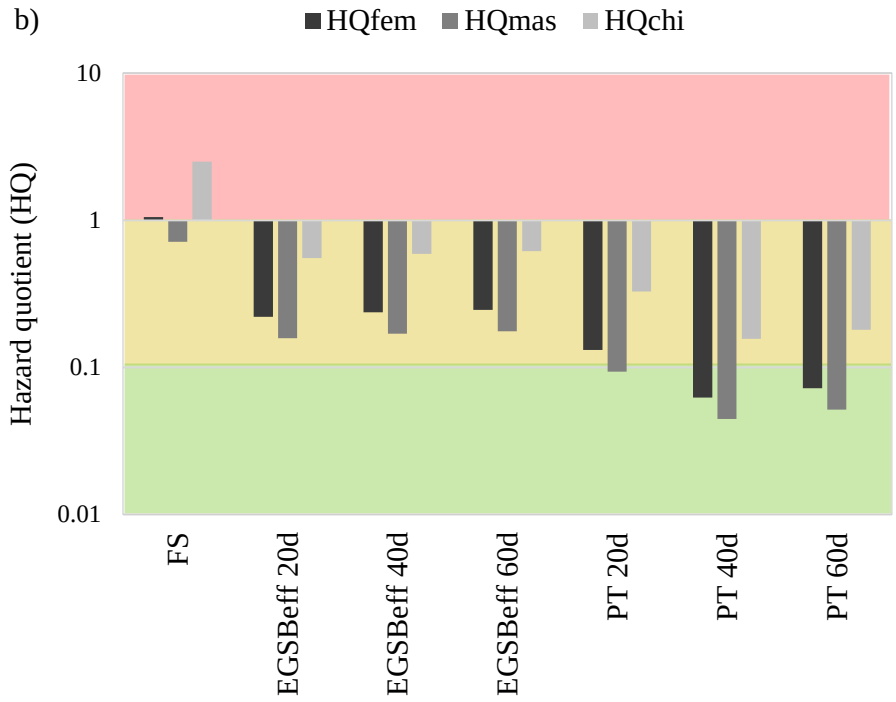
To more fully evaluate the efficiency of EGSB-MBR, an environmental and human health risk assessment was carried out for FS, $EGSB_{eff}$, and PT, according to the BPA concentrations found in these samples at 20, 40, and 60 days of operation. Dos Santos et al. (2022) showed that despite high removals of micropollutants by MBRs, the remaining concentrations in the treated effluent can still promote high risks, which points to the need to integrate these investigations.

The acute and chronic environmental risks and the risk to human health related to BPA are presented in Figure 6. FS and $EGSB_{eff}$ (20, 40, and 60 days) presented high acute and chronic risks (Figure 6a). These results show that the anaerobic reactor could not reduce the BPA concentration sufficiently to reduce the risks posed to aquatic organisms by FS. In contrast, the contribution of UF_r was able to eliminate the high environmental risks for the PT in the three periods evaluated, even with a lower removal of BPA at 20 days of operation. For human health, the anaerobic reactor reduced the risks of BPA concerning FS, where the risks were considered high for women and children (Figure 6b). After

filtration by UF_r, the risks were further reduced and classified as low in the PT, except for children and women at 20 days of operation. Thus, besides satisfactorily removing BPA, EGSB-MBR reduced the high environmental and human health risks posed by FS, which corroborates the technical feasibility of applying the technology.

Figure 6 - Environmental risk quotient (a) and human hazard quotient (b) related to BPA for FS, $EGSB_{eff}$ and PT on days 20, 40 and 60 of operation.

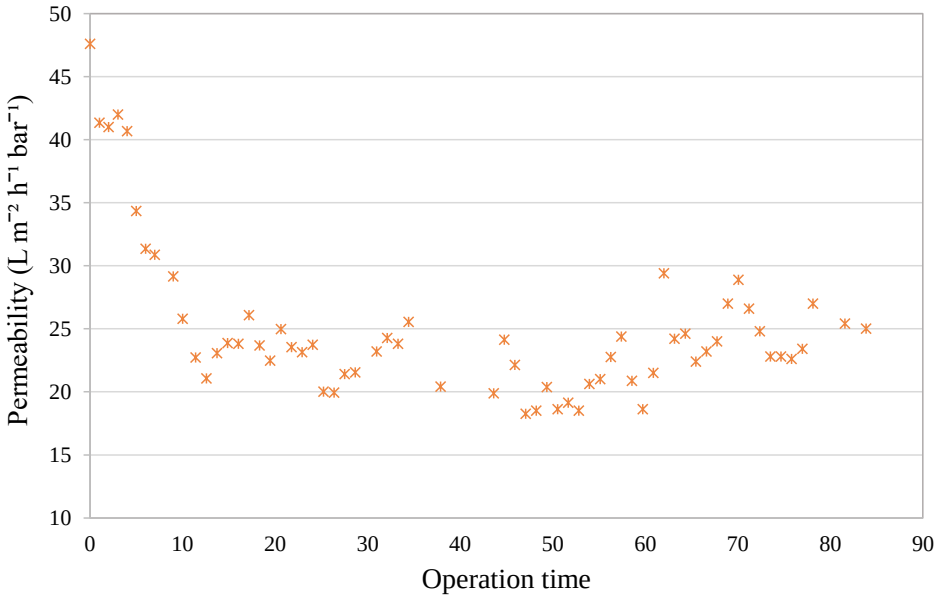




6.3.5 EGSB-MBR permeability and fouling

UF_r presented a hydraulic permeability of 56.2 ± 4.5 L h^{-1} m^{-2} bar^{-1}, salt rejection (NaCl 2 g L^{-1}) of 28.3 ± 2.5%, contact angle of 75.5 ± 1.7° and root mean square roughness of 6.13 ± 0.86 nm. These permeability and salt rejection values are similar to those observed for UF membranes, suggesting that the membrane was effectively recycled (Coutinho de Paula et al., 2017). Figure 7 shows the permeability of the UF_r, maintaining an operating pressure between 0.05 and 0.15 bar. Until the fourth day of operation, membrane permeability was approximately 40.7 L m^{-2} h^{-1} bar^{-1}. From the 5th to approximately the 12th day, there was a more pronounced decrease, and the average permeability was 23 L m^{-2} h^{-1} bar^{-1} until the end of the operation.

Figure 7 – UF_r permeability throughout the EGSB-MBR operation.



A decrease in membrane permeability is expected for UF membranes throughout operation due to the fouling process, especially when using matrices with the presence of suspended particles, organic matter, and other pollutants, as is the case with $EGSB_{eff}$ (Shi et al., 2014). Furthermore, despite GS's larger particle size and greater settleability, a flocculent portion of the sludge is dragged into the membrane tank, contributing to membrane fouling. To interpret the UF_r fouling phenomenon, mainly at the beginning of the operation, the experimental permeate flux data were adapted to the Hermia models, which allows for predicting whether the decline in flux is associated with complete pore blocking, intermediate pore blocking, cake layer, or standard pore blocking (Cancino-Madariaga et al., 2012). The models were applied to the initial stage of operation (until the 12th) in which sharper decrease in permeability were observed (Figure 7). Table 6 shows the fit of the experimental results to the Hermia models through the values of the constant k, which describes the fouling rate for each of the four mechanisms and the correlation coefficient for the models (R^2). The strongest correlation measured was for intermediate pore blocking, with R^2 equal to 1. In this mechanism, particles reach the membrane surface and partially obstruct some pores, causing pore constriction. This occurs mainly due to solute molecules of a size similar to the membrane pore size (Vincent Vela et al., 2009a). Furthermore, in this mechanism, particles depositing on the membrane can attach to other particles on the membrane surface (Zheng et al., 2018a).

Strong correlations (R^2 = 0.97) were also found concerning complete pore blocking. In the early stages of filtration, direct interaction of particles with membrane pores is expected, which can promote ‘‘sealing’’ of some membrane pores, blocking them completely (Shi et al., 2014). Similarly, cake layer formation showed a strong correlation, showing that particles may have contributed to an additional resistance to permeate flux in the first 12 days of operation. The cake layer mainly originates from consolidating a layer of highly concentrated molecules near the membrane surface, which is led by concentration polarization (Zheng et al., 2018b). Generally, complete pore blocking and cake layer occur with molecules larger than the membrane pores (Corbatón-Báguena et al., 2016; Vincent Vela et al., 2009b).

Table 6 - Fitting of experimental permeate flux results to Hermia models.

	Complete Pore Blocking		**Intermediate Pore Blocking**		**Cake Layer**		**Standard Pore Blocking**	
	k (m^{-1})	R^2	k (m^{-1})	R^2	k (m^{-1})	R^2	k (m^{-1})	R^2
P1	0.0108	0.97	0.0653	1.00	0.1611	0.97	0.3980	0.82

For these fouling mechanisms predicted by the models, and considering the configuration of the submerged membrane module used in the EGSB-MBR, the application of backwash may be a first option for flux recovery, capable of removing most of the debris blocking the pores, as well as sludge cake loosely adhered to the membrane (Le-Clech et al., 2006). In addition, acid and alkaline cleanings aimed at removing precipitates of inorganic salts and organic compounds - both present in the membrane tank - may be necessary alternatives. However, the membranes were not cleaned during this operation. Thus, in future applications of EGSB-MBR, the nature of fouling agents and membrane-cleaning techniques can be investigated.

6.3.6 Three-dimensional excitation–emission matrix analyses

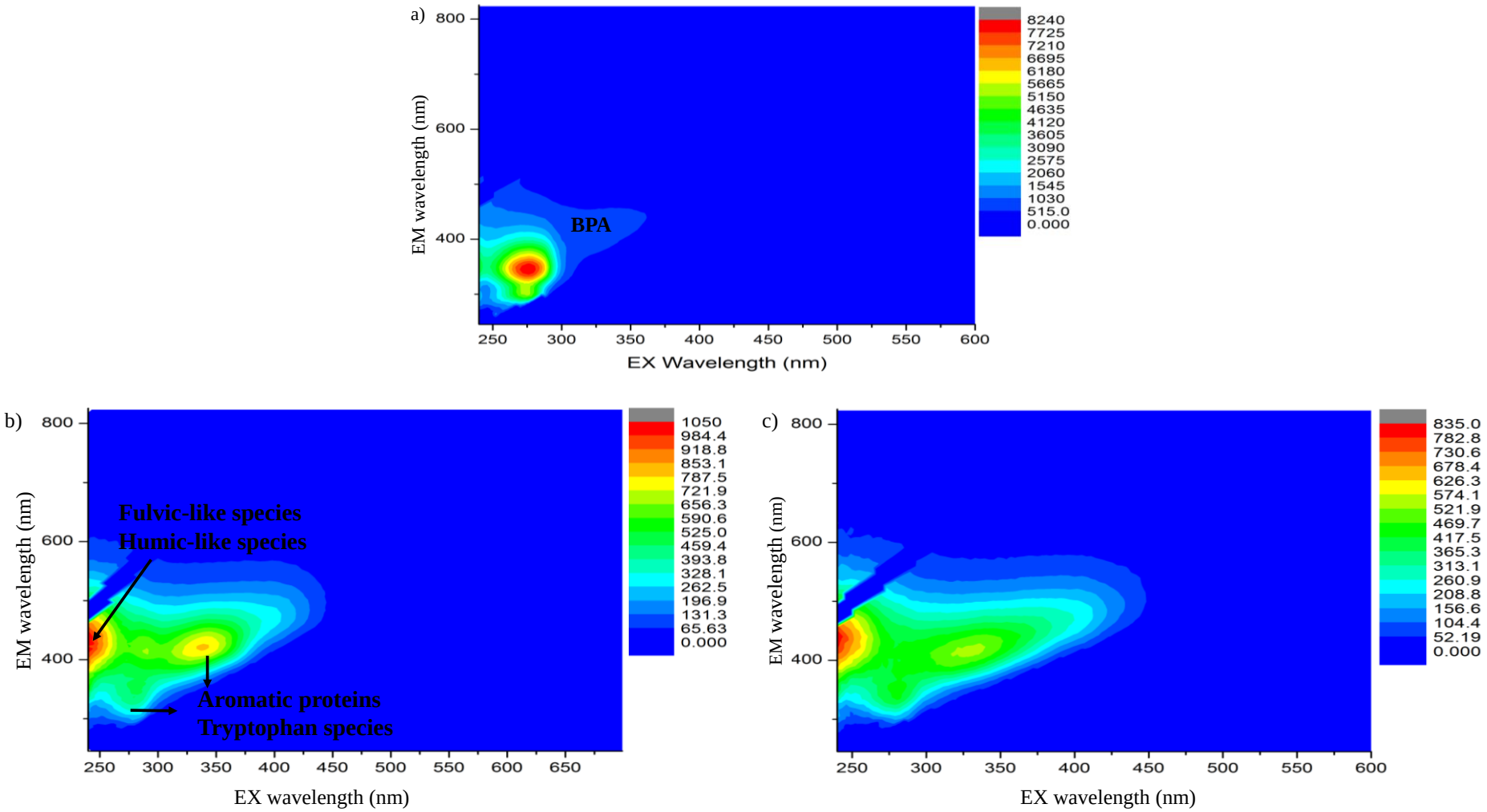
The presence of fouling compounds in $EGSB_{eff}$ can be observed in Figure 8, where the peaks of the 3D-EEM analysis are demonstrated for samples from the beginning, middle, and end of the operation. Previous studies observed that the peaks found in $EGSB_{eff}$ (Figure 8b, Figure 8d and Figure 8f) are related to aromatic proteins linked to the SMP release process due to bacterial activity (Em/Ex = 300/275 nm), tryptophan species (Em /Ex = 350/275 nm), fulvic-like species (Em/Ex = 400/250 nm) and humic-like species

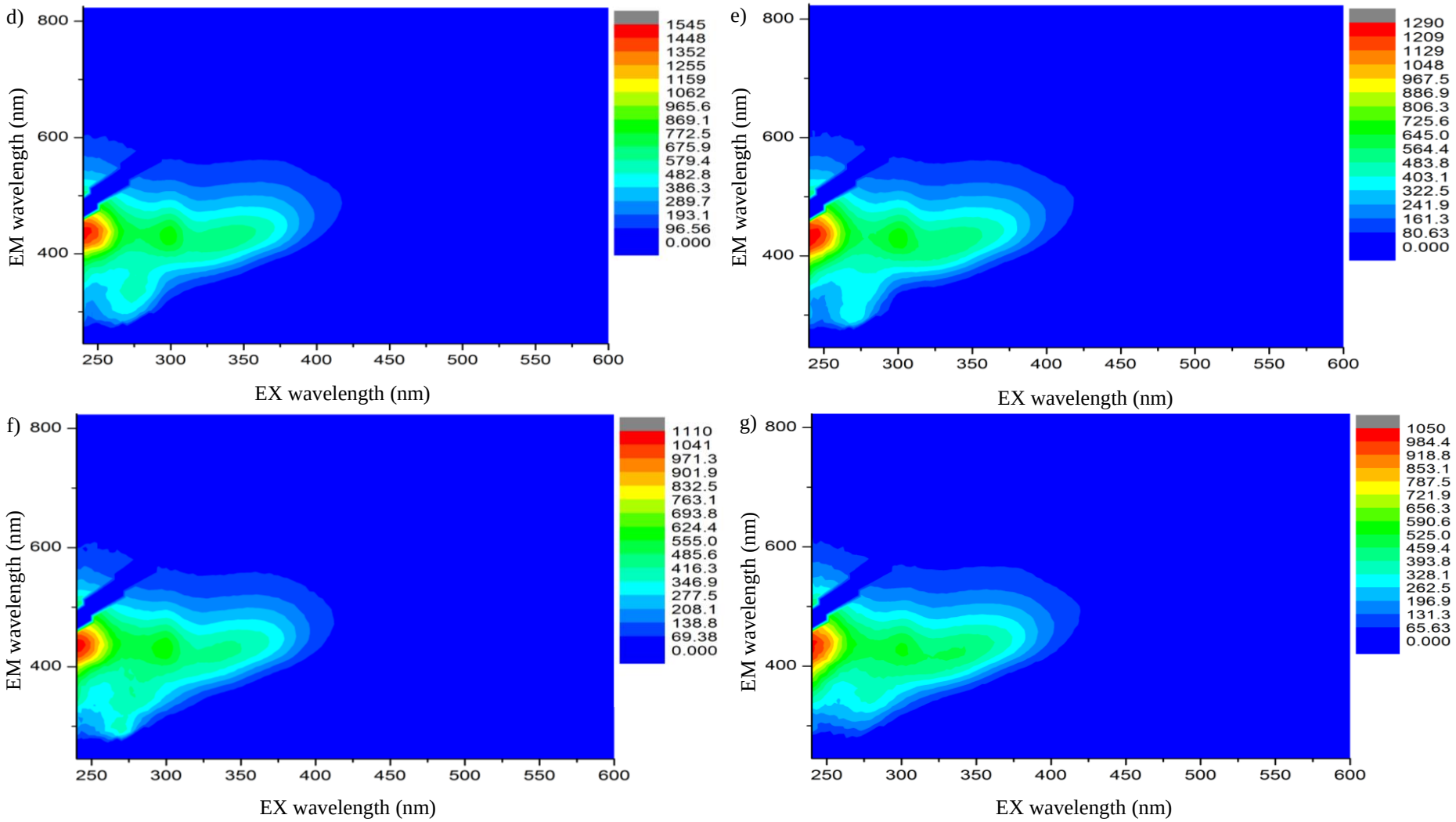
(Em/Ex = 450/250 nm), released during the anaerobic degradation process (Chen et al., 2003; Wang et al., 2009; Xin et al., 2020). Among them, the peaks with the highest intensity in $EGSB_{eff}$ were above 400 nm of emission, mainly related to fulvic and humic acids. These same peaks were observed at lower intensities in the UF_r permeate (Figure 8c, Figure 8e, and Figure 8g). Compared to proteins and polysaccharides, humic substances, mainly fulvic acid, can pass through UF membranes due to their lower molecular weight (Shi et al., 2018).

It is known that SMP, such as polysaccharides, proteins, and humic substances, are generally the components with the greatest fouling potential in MBRs (Shi et al., 2018; Wu et al., 2010). Thus, the presence of these substances contributed to the reduction of UF permeability throughout the operation. During the EGSB-MBR operation, the SMP concentration in the sludge was 2.73 ± 0.09 mg $gSSV^{-1}$, while the EPS concentration was 3.07 ± 0.48 mg $gSSV^{-1}$. In both, the protein portion was slightly higher about carbohydrates, representing 51% of SMP and 58% of EPS. The lower concentration of SMP and EPS concerning other AnMBR (Aslan et al., 2014a, 2014b; Huang et al., 2013) may indicate a stability of the microbial consortium, which is attractive to avoid more significant fouling in the membrane.

In addition, a high-intensity peak at approximately 350/275 (Em/Ex) was observed in the FS. Studies show that Ex/Em wavelengths range from 220 to 290 nm and 290 to 375 nm for BPA (Ingwani et al., 2023; Zhu et al., 2022). Thus, this peak may be related to the BPA present in the FS. The same peak was observed in $EGSB_{eff}$ and PT at lower intensities, as observed mainly for PT with 80 days of operation, confirming the removal of BPA by EGSB-MBR. It is important to emphasize that the substances observed in $EGSB_{eff}$ may have acted as adsorbents for BPA, aiding in its removal, including rejection by UF_r due to its association with macromolecules. Yan et al. (2019) studied the binding of BPA to sludge EPS, and the results indicate that the binding interaction between BPA and EPS is spontaneous. Furthermore, BPA mainly binds to EPS proteins by hydrophobic association.

Figure 8 - 3D-EEM analysis for (a) FS; (b) $EGSB_{eff}$ and (c) PT, at the beginning of the operation; (d) $EGSB_{eff}$ and (f) PT, in the middle of the operation; (e) $EGSB_{eff}$ and (g) PT, at the end of the operation.



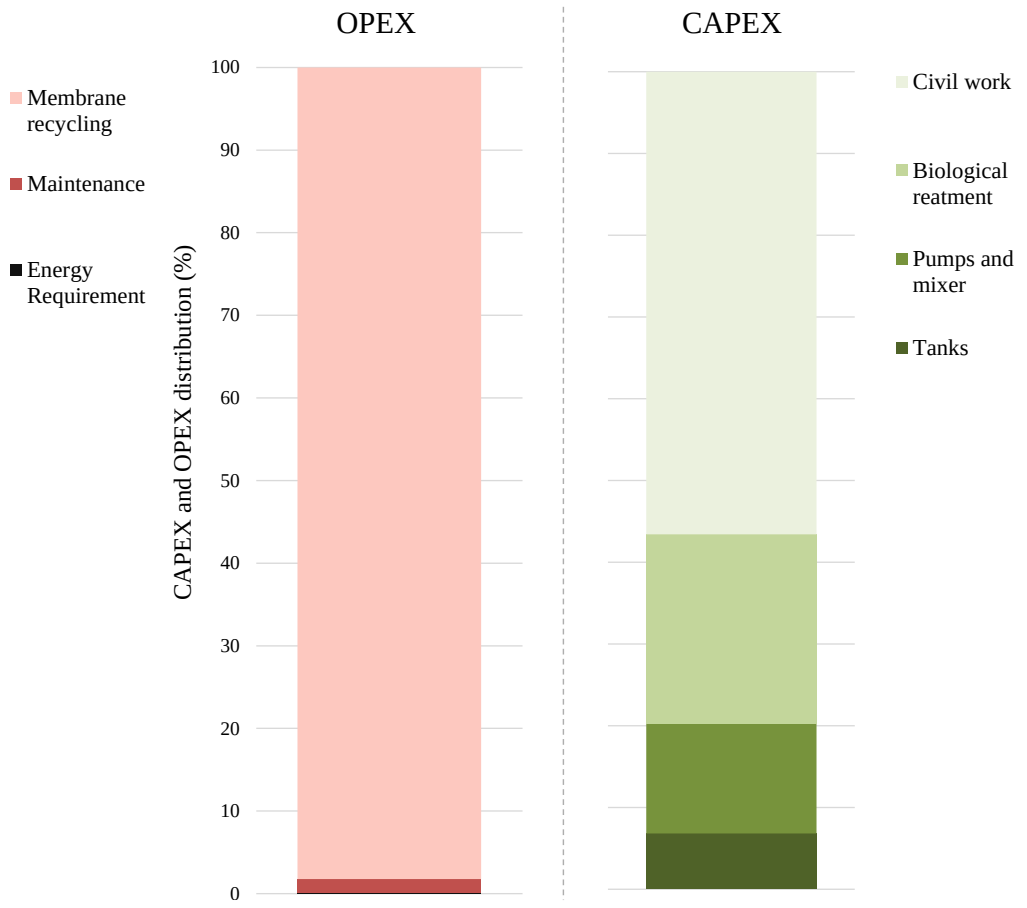

d)
EM wavelength (nm)
EX wavelength (nm)
1545
1448
1352
1255
1159
1062
965.6
869.1
772.5
675.9
579.4
482.8
386.3
289.7
193.1
96.56
0.000
e)
EM wavelength (nm)
EX wavelength (nm)
1290
1209
1129
1048
967.5
886.9
806.3
725.6
645.0
564.4
483.8
403.1
322.5
241.9
161.3
80.63
0.000
f)
EM wavelength (nm)
EX wavelength (nm)
1110
1041
971.3
901.9
832.5
763.1
693.8
624.4
555.0
485.6
416.3
346.9
277.5
208.1
138.8
69.38
0.000
g)
EM wavelength (nm)
EX wavelength (nm)
1050
984.4
918.8
853.1
787.5
721.9
656.3
590.6
525.0
459.4
393.8
328.1
262.5
196.9
131.3
65.63
0.000

6.3.7 Preliminary cost evaluation

The proportion of CAPEX and OPEX, considering the costs related to the EGSB-MBR using UF_r, are shown in Figure 9. The total specific produced permeate cost of the system was US$ 0.21 m^{-3} of permeate, considering the flux of 2.5 L m^{-2} h^{-1}. Noyola et al. (2012) studied the typology of several wastewater treatment technologies applied in Latin America. The authors reported that, for treated wastewater flow rates close to that of the present study (711 m^{-3} h^{-1}), the values for UASB, activated sludge, and stabilization ponds are 0.085, 0.095, and 0.018 USD m^{-3}, respectively. On the other hand, for anaerobic MBR configurations associated with more selective membranes, such as FO, RO and MD, the cost can range from 1.4 to 6.8 USD m^{-3} (Hasanoglu et al., 2024; Santos et al., 2023; Vinardell et al., 2020c). For AnMBR, Pretel et al. (2016b) estimated a cost of 0.136 € m^{-3} for a permeate flux of 22 L m^{-2} h^{-1}. In addition, Vinardell et al. (2021a) evaluated the economic feasibility of AnMBR as a technology for municipal sewage treatment and estimated costs ranging from 0.35 to 0.42 € m^{-3}. Therefore, due to the removals achieved, EGSB-MBR is an economically promising alternative to conventional technologies, especially regarding BPA removal.

The OPEX value of EGSB-MBR was US$ 0.16 m^{-3}, with the highest costs related to membrane recycling (98%) due to the acquisition of reagents necessary for the process, followed by maintenance and energy requirements. Regarding CAPEX, the total costs were US$ 1,008.56 m^{-3} d^{-1}, equivalent to an amortized value of US$ 0.05 m^{-3}. In this case, the highest costs were allocated to civil work, biological treatment, pumps and mixers, and tanks, respectively (Figure 9).

Figure 9 - Distribution of CAPEX and OPEX values related to the EGSB-MBR using UF_r.



The costs of the membrane recycling process were estimated for a membrane lifespan of 2 years. Thus, eight recycling processes were considered during the design plant life (15 years). The costs related to the acquisition of reagents (US$ 0.15 m^{-3}) were allocated, respectively, to ethanol for the wetting step (79.4%), HCl for acid cleaning of the membranes (19.8%), NaClO for oxidation (0.5%) and NaOH for alkaline cleaning of the membranes (0.3%). For comparison purposes, the acquisition cost of new UF membranes during 15 years of operation and considering a membrane lifespan of 5 years was estimated for the same conditions as UF_r. The cost in this case was US$ 0.52 m^{-3}; thus, only the membrane exchange step would exceed the SPC estimated for the EGSB-MBR.

Coutinho de Paula and Santos Amaral (2018) used the material input per unit of service (MIPS) tool to evaluate the recycling process of RO EoL membranes environmentally. They showed that, even with the environmental impact caused by the disposal of

chemicals used in the membrane conversion process and the subsequent disposal of UF_r membranes, the environmental benefits were greater. Thus, besides the economic advantages, it is essential to highlight that applying EGSB-MBR with UF_r brings environmental gains due to reduced waste sent to landfills.

6.7 CONCLUSION AND FUTURE PERSPECTIVES

In this study, EGSB-MBR using UF_r proved to be a promising solution for treating domestic wastewater, especially in removing BPA, reaching an average efficiency of 91.1%. Adsorption of BPA on membrane and macromolecules were essential factors that positively influenced the removal of BPA. The EGSB-MBR system also provided efficient removal of organic matter (95.1%). PO_4^{3-} removal was evaluated at 27%, while for NH_4^+ there was no overall removal, although the UF_r helped to reduce the ammoniacal nitrogen present in $EGSB_{eff}$. In addition, EGSB-MBR has also been demonstrated efficiency to reduce the environmental and human health risks associated with BPA. Finally, the costs indicated that membrane recycling is an economically viable alternative, with the SPC estimated at US$ 0.16 per m^3, significantly lower than the systems using new membranes. Furthermore, membrane recycling reduces solid waste generation, which aligns with sustainability and circular economy principles. Future studies may focus on more extended operations to evaluate BPA removal, besides other EDCs. In addition, further investigations may explore the increased removal and mobilization of nutrients as value-added products, further increasing the economic and environmental potential of the EGSB-MBR system. Furthermore, the efficiency of membrane cleaning and its impact on pollutant removal may be investigated in future studies.

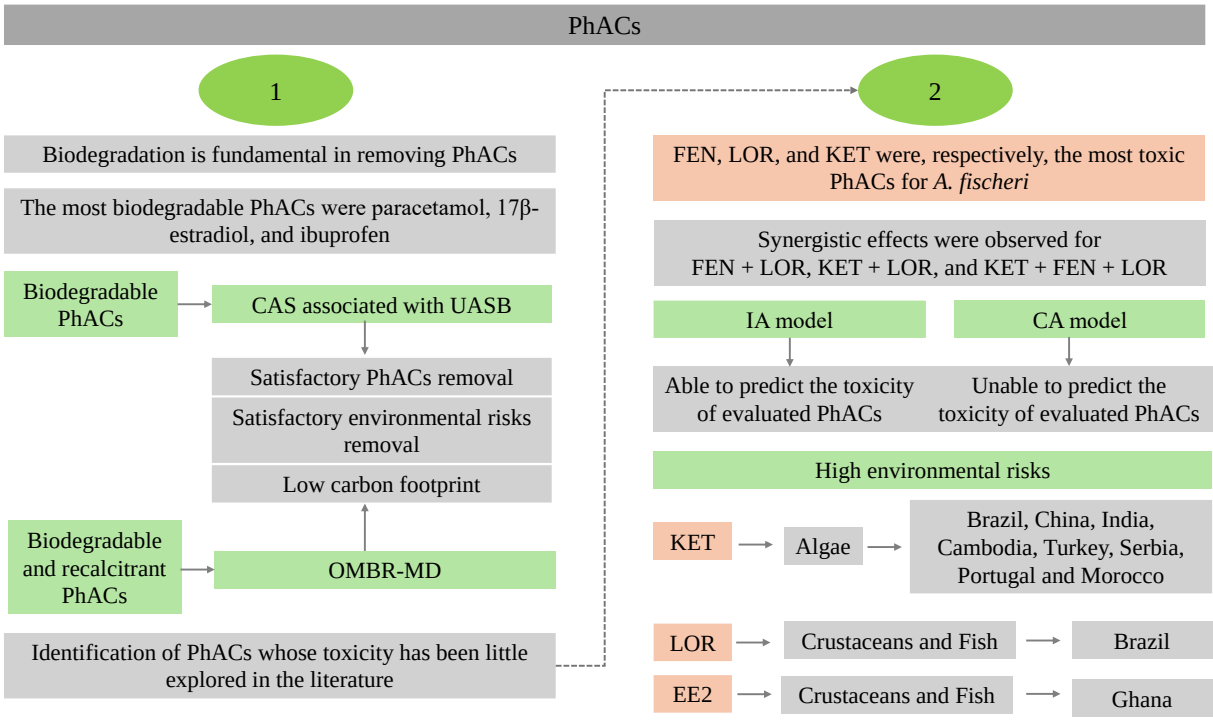
CHAPTER 7

GENERAL CONCLUSIONS

This study uniquely delved into the environmental impacts of TrOCs in the aquatic environment and the technologies applied to their removal, with a special focus on toxicity and environmental risk. The study also honed in on removal by biodegradation, particularly in anaerobic membrane bioreactors with granular sludge.

The study related to PhACs was divided into two lines of research: (1) a review evaluating processes applied to the removal of several PhACs - focusing on biodegradation -, including the removal of environmental risks and carbon footprint; and (2) toxicity and environmental risk tests of PhACs little explored in the literature, alone and in binary and tertiary mixtures. These two lines' main findings and conclusions are represented in the flowchart in Figure 1.

Figure 1 - Research lines related to PhACs



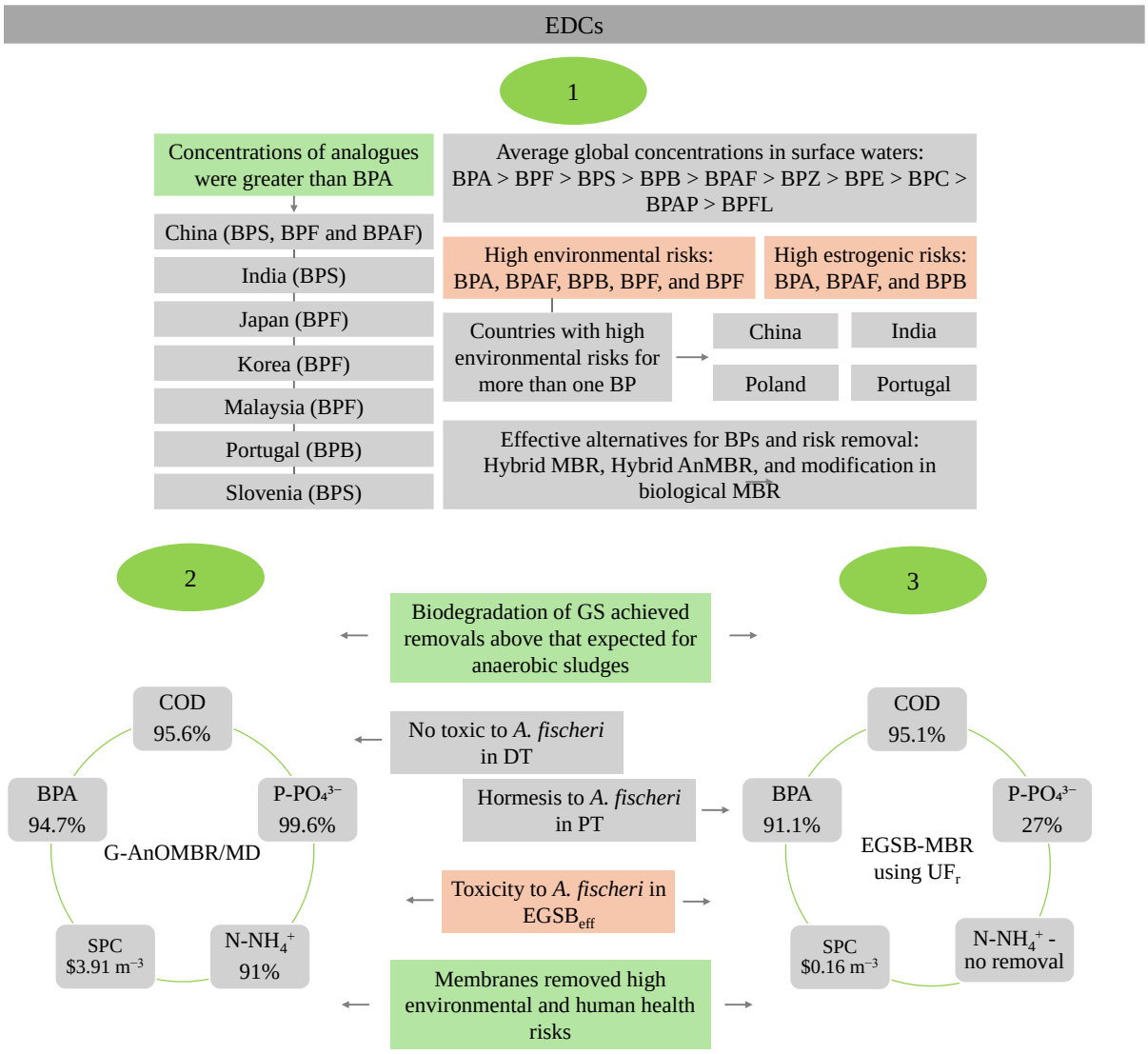
These investigations underscore the practical implications of evaluating PhAC removal technologies, particularly in terms of environmental risks and carbon footprint. Conventional biological treatments, when used in combination (e.g. AS+UASB), can effectively remove more biodegradable PhACs, making them the recommended choice due to their low carbon footprint and due to the consolidation of these technologies. However, for the more recalcitrant PhACs, advanced technologies are necessary to supplement biological treatment, with a focus on those with a lower carbon footprint.

In addition, it was possible to contribute to identifying the aquatic toxicity of PhACs, which is still little explored in the literature, showing their effects alone and mixed. For some mixtures, the toxic effects were greater than those predicted by toxicity prediction models. Thus, the interaction mechanisms of these PhACs in the aquatic environment can amplify their effects on specific organisms. Identifying the model most closely aligned with the experimental results was also possible, which is indicated for application in predicting the toxicity of the evaluated PhACs. Finally, this stage of the study identified, among the PhACs evaluated, those that pose high environmental risks in surface water, specifying the aquatic organisms and locations where this occurs. Therefore, reducing the release of these PhACs should be a priority, as well as adopting technologies capable of removing them and reducing their risks.

In addition, the study contributed to investigations related to EDCs, focusing on BPs. This research was divided into three lines: (1) a review evaluating the occurrence, toxicity, environmental risks, and removal of BPs by MBRs; (2) evaluation of the BPA removal by a G-AnOMBR-MD; and (3) evaluation of the BPA removal by an EGSB-MBR using UF_r. These three lines' main findings and conclusions are represented in the flowchart in Figure 2.

The widespread use of BPA, simultaneously as the pressure for “BPA-free” products, results in high concentrations of it and its analogues in the aquatic environment. Therefore, identifying the occurrence of these compounds was essential to map the concentrations in specific locations. Although BPA leads to concentrations in surface waters globally, it was possible to identify that the concentration of other BPs already exceeds that of BPA in some locations. These results become critical due to the high environmental and estrogenic risks promoted by several BPs. Therefore, the focus on studies evaluating removal technologies capable of efficiently removing them from wastewater is essential.

Figure 2 - Research lines related to EDCs



For the two technologies experimentally tested for the treatment of domestic sewage aiming at removing BPA (G-AnOMBR/MD and EGSB-MBR using UF_r), the biodegradation efficiency of GS was essential in both. The first achieved high removals of organic matter, nutrients, and BPA. However, the costs were high when compared to other conventional technologies. The second achieved high removals of organic matter and BPA; however, the removal of nutrients was low or non-existent. Despite this, the costs were comparable to conventional technologies. In addition, both membrane modules were essential in removing toxicity and environmental and human health risks. Thus, the G-AnOMBR/MD application is viable aiming at a high-quality effluent that can be used for noble purposes, such as potable and non-potable reuse. In this way, the costs are justified by the value added to the final effluent. In addition, using residual heat or

solar energy for MD reduces costs and brings environmental benefits to this system. In contrast, EGSB-MBR and UF_r can replace the conventional technologies currently used in WWTPs due to the comparable costs and high BPA removal. In addition, the possibility of recovering nutrients in the permeate can reduce their concentrations in the final effluent and adds value to the system.

Finally, this study highlights the importance of searching for wastewater treatment technologies to reduce environmental and health concerns associated with TrOCs in aquatic environments. The research contributes valuable insights into the toxicity and environmental risks besides advancing the proposal of new technologies for removing these compounds. It advocates for adopting technologies with lower carbon footprints and high efficacy in mitigating risks. Ultimately, these efforts were crucial for providing a framework for future innovations in wastewater treatment processes.

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ANNEXES

CHAPTER 2

Table S1 - Occurrence of PhACs in surface water worldwide

PhAC	Concentration (ng/L)	Contry	Reference
Betamethasone	0.3	Italy	Speltini et al. 2018
	0.83	China	Gong et al. (201
	7.2	China	Shen et al. 2020
	4,109	Brazil	Reis et al. (201
Fenofibrate	16.21	Portugal	Palma et al. 2020
Fluconazole	6.91	China	Zhang et al. 2019
	32	Spain	Casado et al. 2014
	34.03	China	Ren et al. 2023
	37	Sweden	Malnes et al. 2022
	58.9	China	Yang et al. 2017
	75.7	Thailand	Juksu et al. 2019
	230.2	South Africa	Assress et al. 2020
	573.8	Brazil	Couto et al. 2020
	583	Brazil	Reis et al. 2019
Ketoprofen	9.05	China	Xu et al. 2019
	15	Croatia	Selak et al. 2022
	17	Spain	Moreno-González et al. 2014
	45	Serbia	Petrović et al. 2014
	68.92	Portugal	Palma et al. 2020
	107	India	Sharma et al. 2016
	91.1	China	Xu et al. 2022
	168	Morocco	Chafi et al. 2022
	240	Canboja	Sang et al. 2022
	260	Turkey	Korkmaz et al. 2022a
	298	Brazil	Reis et al. 2019
	370	Turkey	Korkmaz et al. 2022b
	8,070	India	Mishra et al. 2023
	14,215	Brazil	Rico et al. 2021
Loratadine	1.14	Spain	López-Serna et al. 2012
	4	Croatia	Ivankovic et al. 2023
	6.46	England	Burns et al. 2018
	486	Brazil	Reis et al. 2019
Prednisone	0.44	China	Gong et al. 2019
	0.74	China	Xu et al. 2019
	10	China	Wu et al. 2023
	67.1	China	Tang et al. 2021

	2,444	Brazil	Reis et al. 2019
17α-Ethinylestradiol	0.4	China	Deich et al. 2021
	1	Luxembourg	Pailler et al. 2009
	1.4	France	Vulliet et al. 2011
	2.5	Spain	Huerta-Fontela et al. 2011
	2.8	Canada	Goeury et al. 2022
	6	Italy	Merlo et al. 2019
	10	China	Lu et al. 2021
	50	Morocco	Chafi et al. 2022
	310	Brazil	Sodré et al. 2007
	950	Turkey	Korkmaz et al. 2022a
	1,739	Ghana	Adjei et al. 2022

CHAPTER 3

Table S1 - Occurrence of evaluated PhACs in surface water worldwide

PhAC	Concentration (ng/L)	Country	Reference
Betamethasone	0.3	Italy	Speltini et al. 2018
	0.83	China	Gong et al. 2019
	7.2	China	Shen et al. 2020
	4,109	Brazil	Reis et al. 2019
Fenofibrate	16.21	Portugal	Palma et al. 2020
Fluconazole	6.91	China	Zhang et al. 2015
	32	Spain	Casado et al. 2014
	34.03	China	Ren et al. 2023
	37	Sweden	Malnes et al. 2022
	58.9	China	Yang et al. 2017
	75.7	Thailand	Juksu et al. 2019
	230.2	South Africa	Assress et al. 2020
	573.8	Brazil	Couto et al. 2020
	583	Brazil	Reis et al. 2019
Ketoprofen	9.05	China	Xu et al. 2019
	15	Croatia	Selak et al. 2022
	17	Spain	Moreno-González et al. 2014
	45	Serbia	Petrović et al. 2014
	68.92	Portugal	Palma et al. (202
	107	India	Sharma et al. 2016
	91.1	**1.1 China**	Xu et al. 2022
	168	**1.2 Morocco**	Chafi et al. 2022
	240	**1.3 Canboja**	Sang et al. 2022
	260	**1.4 Turkey**	Korkmaz et al. 2022a
	298	Brazil	Reis et al. 2019
	370	Turkey	Korkmaz et al. 2022b
	8,070	India	Mishra et al. 2023
	14,215	Brazil	Rico et al. 2021
Loratadine	1.14	Spain	López-Serna et al. 2012
	4	Croatia	Ivankovic et al. 2023
	6.46	England	Burns et al. 2018
	486	Brazil	Reis et al. 2019
Prednisone	0.44	China	Gong et al. 2019
	0.74	China	Xu et al. 2019
	10	China	Wu et al. 2023

	67.1	China	Tang et al. 2021
	2,444	Brazil	Reis et al. 2019
17α-Ethinylestradiol	0.4	China	Deich et al. 2021
	1	Luxembourg	Pailler et al. 2009
	1.4	France	Vulliet et al. 2011
	2.5	Spain	Huerta-Fontela et al. 2011
	2.8	Canada	Goeury et al. 2022
	6	Italy	Merlo et al. 2019
	10	China	Lu et al. 2021
	50	Morocco	Chafi et al. 2022
	310	Brazil	Sodré et al. 2010
	950	Turkey	Korkmaz et al. 2022a
	1,739	Ghana	Adjei et al. 2022

CHAPTER 4

Table S1 – Concentration of BPs in surface water from several locations.

Compound	Mean concentration (ng L^{-1})	Surface water	Local	Reference
BPA	67.9	Lower stretch of river Ganga	India	Kundu et al., 2024
	161.5	Estuarine zone of river Ganga	India	Kundu et al., 2024
	4460	Middle stretch of river Ganga	India	Chakraborty et al., 2021
	92.57	Taihu Lake	China	Liu et al., 2016
	0.152	Jiulong River	China	Lv et al., 2014
	21	Edogawa River	Japan	Yamazaki et al., 2015
	57	Arakawa River	Japan	Yamazaki et al., 2015
	120	Tamagawa River	Japan	Yamazaki et al., 2015
	431	Sewater of Tokyobay	Japan	Yamazaki et al., 2015
	98	Pearl River	China	Yamazaki et al., 2015
	43	West River	China	Yamazaki et al., 2015
	272	Han River	Korea	Yamazaki et al., 2015
	80	Nakdong River	Korea	Yamazaki et al., 2015
	213	Yeongsan River	Korea	Yamazaki et al., 2015
	628	Cooum River	India	Yamazaki et al., 2015
	512	Adyar River	India	Yamazaki et al., 2015
	33	Korttalaiyar River	India	Yamazaki et al., 2015
	1945	Buckingham Canal	India	Yamazaki et al., 2015
	16.6	St. Lawrence River	Canada	Goeury et al., 2022
	62.3	Mille Iles River	Canada	Goeury et al., 2022
	47.4	Laguna Lake	Philippines	Sta. Ana et al., 2020
	724	Marikina River	Philippines	Sta. Ana et al., 2020
	765	Bagumbayan River	Philippines	Sta. Ana et al., 2020
	554	Buli River	Philippines	Sta. Ana et al., 2020
	665	Tunasan River	Philippines	Sta. Ana et al., 2020
	1355	Biñan River	Philippines	Sta. Ana et al., 2020

4813	Sta. Rosa (Midstream) River	Philippines	Sta. Ana et al., 2020
5344	Sta. Rosa (Downstream) River	Philippines	Sta. Ana et al., 2020
2800	Ala River	Nigeria	Idowu et al., 2022
730	Ose River	Nigeria	Idowu et al., 2022
730	Owena River	Nigeria	Idowu et al., 2022
160	Yangtze River	China	Shi et al., 2013
150	Huaihe River	China	Shi et al., 2013
84	Taihu Lake	China	Shi et al., 2013
803	Hooghly River Riverine region Urban	India	Mukhopadhyay et al., 2021
732	Hooghly River Riverine region Suburban	India	Mukhopadhyay et al., 2021
137.4	Hooghly River Estuarine region Rural	India	Mukhopadhyay et al., 2021
98.11	Hooghly River Estuarine region Port	India	Mukhopadhyay et al., 2021
13.5	Taihu Lake	China	Liu et al., 2020
97	Taihu Lake	China	Yan et al., 2017
8.5	Taihu Lake	China	Jin et al., 2016
64.4	Taihu Lake	China	Wang et al., 2015
119	Yangtze River	China	Liu et al., 2017
21	Ebro River	Spain	Gil-Solsona et al., 2022
13.7	Ebro Delta in the Mediterranean Sea	Spain	Gil-Solsona et al., 2022
58.9	Elbe River	Germany	Huang et al., 2021
1573	Bahe River	China	Wang et al., 2018
32	Yellow River	China	Yin et al., 2022
68	Guangli River	China	Yin et al., 2022
226	Xiaoqing River	China	Yin et al., 2022
11	Bohai Seawater	China	Yin et al., 2022
9.1	St. Lawrence River	Canada	Gewurtz et al., 2021
44	Mimico Creek	Canada	Gewurtz et al., 2021
17	Highland Creek	Canada	Gewurtz et al., 2021
34	Taylor Creek	Canada	Gewurtz et al., 2021
101	Beaverdams Creek	Canada	Gewurtz et al., 2021
13	Upper Beaverdams Creek	Canada	Gewurtz et al., 2021
26	St. Catharines - Dicks Creek	Canada	Gewurtz et al., 2021
14	Grand River	Canada	Gewurtz et al., 2021

13	Thames River	Canada	Gewurtz et al., 2021
75	Wascana Creek	Canada	Gewurtz et al., 2021
10	Serpentine River	Canada	Gewurtz et al., 2021
14.7	Kaveri River	India	Selvaraj et al., 2014
5.6	Vellar River	India	Selvaraj et al., 2014
11.5	Tamiraparani River	India	Selvaraj et al., 2014
52.1	Bnińskie Lake	Poland	Shi et al., 2014
95	Bytyńskie Lake	Poland	Shi et al., 2014
23.2	Lusowskie Lake	Poland	Shi et al., 2014
29	Śremskie Lake	Poland	Shi et al., 2014
31.2	Pamiątkowskie Lake	Poland	Shi et al., 2014
15.8	Wierzbiczańskie Lake	Poland	Shi et al., 2014
78.3	Sama River	Poland	Shi et al., 2014
72.2	Samica Stęszewska River	Poland	Shi et al., 2014
22.4	Mosina River	Poland	Shi et al., 2014
35.7	Główna River	Poland	Shi et al., 2014
27.7	Główna River	Poland	Shi et al., 2014
54	Warta River	Poland	Shi et al., 2014
12.9	Kamionka River	Poland	Shi et al., 2014
56.6	Sai Gon River	Vietnam	Minh et al., 2016
4.6	Dong Nai River	Vietnam	Minh et al., 2016
2510	Velhas River	Brazil	Ramos et al., 2021
49.7	Arkavathi river	India	Gopal et al., 2021
49	Peruque Creek	United States	Kassotis et al., 2015
320	Crooked Creek	United States	Kassotis et al., 2015
100	Flat Creek	United States	Kassotis et al., 2015
50	Perche Creek	United States	Kassotis et al., 2015
35	Missouri River	United States	Kassotis et al., 2015
49	James River	United States	Kassotis et al., 2015
44.85	Yellow River	China	Yu et al., 2023
39.5	Yellow River	China	Wang et al., 2012
41.9	Haihe River	China	Jin et al., 2004
116.5	Taizi River	China	Wang et al., 2011
90	Nagara River	Japan	Funakoshi et al., 2009
1030	Shijing River	China	Zhao et al., 2009

58	Aja River	Japan	Kawahata et al., 2004
100	Guadalquivir River	Spain	Ballesteros-Gómez et al., 2007
320	Rabanales River	Spain	Ballesteros-Gómez et al., 2007
250	Dos Torres River	Spain	Ballesteros-Gómez et al., 2007
157	River	Canada	Kleywegt et al., 2011
295	Llobregat River	Spain	Rodriguez-Mozaz et al., 2004
4.3	Seomjin River	Korea	Duong et al., 2010
473	Jiulong River	China	Sun et al., 2016
118.6	Huai River Basin	China	Fan et al., 2021
21.4	Dourados river	Brazil	Sposito et al., 2018
48.7	Brilhante river	Brazil	Sposito et al., 2018
1540	Jialu River	China	Zhang et al., 2011
9.5	Pearl River Delta	China	Liang et al., 2023
50	Seawater of Jiaozhou Bay	China	Fu et al., 2007
44.9	Chaobai River	China	Li et al., 2013
66	Aquidauana River	Brazil	Finoto Viana et al., 2023
62.78	Pearl River Estuary	China	Diao et al., 2017
817	Besos river	Spain	Bolívar-Subirats et al., 2021
450	Charmoise river	France	Tran et al., 2015
14.53	Taihu Lake	China	Yan et al., 2012
21	Elbe River	Germany	Stachel et al., 2003
38.7	Yeonwoo River	China	Ko et al., 2007
39.4	Songjung River	China	Ko et al., 2007
24.6	Hanam River	China	Ko et al., 2007
29.3	Sandong River	China	Ko et al., 2007
26.2	Danube River	Serbia	Čelić et al., 2020
5	Danube River	Serbia	Loos et al., 2010
159	Hogsmill River, Chertsey Bourne River and Blackwater River	England	Wilkinson et al., 2017
198.66	Velhas River	Brazil	Salgueiro-Weber et al., 2017
4800	Minho River	Portugal	González et al., 2015
881	Pearl River	China	Peng et al., 2008

46	Panlong river	China	Wang et al., 2016
332.75	Dongjiang River	China	Xu et al., 2019
147.63	Wuluo River	Taiwan	Liu et al., 2018
33	Mississippi River	United States	Boyd et al., 2004
19	Pontchartrain Lake	United States	Boyd et al., 2004
56	London canal	United States	Boyd et al., 2004
15.6	Orleans canal	United States	Boyd et al., 2004
530	Velhas River	Brazil	Ramos et al., 2021
48	Turia River	Spain	Carmona et al., 2017
63.3	River	China	Chen et al., 2020
63.6	River Lambro	Italy	Castiglioni et al., 2018
808	Dan-Shui River	Taiwan	Chen et al., 2012
72	Han	China	Bonfoh et al., 2020
229	Ebro River	Spain	Gorga et al., 2015
649	Llobregat River	Spain	Gorga et al., 2015
84	Júcar River	Spain	Gorga et al., 2015
281	Guadalquivir River	Spain	Gorga et al., 2015
50.6	Atibaia River	Brazil	Sodré et al., 2010
9.4	Glatt River	Switzerland	Jonkers et al., 2009
330	Seawater of Bocht van Wattum	Netherlands	Belfroid et al., 2002
190	Seawater of Dantziggat	Netherlands	Belfroid et al., 2002
14	Seawater of Den Oever	Netherlands	Belfroid et al., 2002
130	Dommel River	Netherlands	Belfroid et al., 2002
170	Meuse River	Netherlands	Belfroid et al., 2002
92	Ebro River	Spain	Herrero-Hernández et al., 2013
97.3	River	Saudi Arabia	Picó et al., 2021
76.3	Tama River	Japan	Furuichi et al., 2004
7	River	Mexico	Félix–Cañedo et al., 2013
2.12	River	China	Chen et al., 2016
12.7	River	United States	Padhye et al., 2014
8.5	Taihu Lake	China	Jin et al., 2016
47	Liaohe river	China	Jin et al., 2016
40	Hunhe river	China	Jin et al., 2016

26	Seawater of Hangzhou bay	China	Yang et al., 2014
207.5	Rivers, lakes and channels	Germany	Fromme et al., 2002
78	Jinze reservoir	China	Li et al., 2021
38	River	China	Li et al., 2021
196045	Erren River	Taiwan	Chen et al., 2016
233	Geylang River	Singapore	Xu et al., 2011
105	Kallang River	Singapore	Xu et al., 2011
330	Rocher Canal	Singapore	Xu et al., 2011
300	Stamford Canal	Singapore	Xu et al., 2011
213	Stamford Canal	Singapore	Xu et al., 2011
20	Bremer River	Australia	Ying et al., 2009
31.7	Svratka River	Czech Republic	Matějíček et al., 2012
54	Guanabara Bay	Brazil	Coutinho et al., 2022
25	Seawater of Thermaikos Gulf	Greece	Arditsoglou et al., 2012
27	Lamone River	Italy	Pignotti et al., 2018
35	Fiumi Uniti River	Italy	Pignotti et al., 2018
62	Bevano River	Italy	Pignotti et al., 2018
73	Savio River	Italy	Pignotti et al., 2018
158	Marecchia River	Italy	Pignotti et al., 2018
53	Channels	Italy	Pignotti et al., 2018
12	Pialassa Baiona	Italy	Pignotti et al., 2018
15	Seawater	Spain	Sánchez-Avila et al., 2011
44	River	Spain	Sánchez-Avila et al., 2011
18	Coastal seawater of Mediterranean Sea	Spain	Sánchez-Avila et al., 2012
57	Port seawater	Spain	Sánchez-Avila et al., 2012
22	River mouth seawater	Spain	Sánchez-Avila et al., 2012
20	River	Spain	Sánchez-Avila et al., 2012
122.83	Tunuyán River	Argentina	Iturburu et al., 2024
15.15	San Carlos River	Argentina	Iturburu et al., 2024
8.84	Negro River	Argentina	Iturburu et al., 2024
18.37	Claro River	Argentina	Iturburu et al., 2024
6.42	Zampal River	Argentina	Iturburu et al., 2024
185	Douro River	Portugal	Cunha et al., 2022

2820	Tagus River	Portugal	Cunha et al., 2022
1186	Ashaiman Lake	Ghana	Adjei et al., 2022
6363	Chemu Lagoon	Ghana	Adjei et al., 2022
1007	Fosu Lagoon	Ghana	Adjei et al., 2022
509	Kakum River	Ghana	Adjei et al., 2022
1993	Densu River	Ghana	Adjei et al., 2022
448	Korle Lagoon	Ghana	Adjei et al., 2022
200	Luoma Lake	China	Wang et al., 2022
215	River	China	Wang et al., 2022
22.19	Yangtze River Basin	China	Qin et al., 2024
223	Anhumas River	Brazil	Madeira et al., 2023
13.1	Pinheiros River	Brazil	Madeira et al., 2023
205	Atibaia River	Brazil	Madeira et al., 2023
589.5	Atibainha River	Brazil	Madeira et al., 2023
15	Cachoeira River	Brazil	Madeira et al., 2023
94.9	Camanducaia River	Brazil	Madeira et al., 2023
91.2	Capivari River	Brazil	Madeira et al., 2023
248	Corumbataí River	Brazil	Madeira et al., 2023
46.3	Jaguari River	Brazil	Madeira et al., 2023
41.7	Jundiaí River	Brazil	Madeira et al., 2023
27.5	Mogi Guaçu River	Brazil	Madeira et al., 2023
118	Mogi Mirim River	Brazil	Madeira et al., 2023
895	Piracicaba River	Brazil	Madeira et al., 2023
42.7	Pirapitingui River	Brazil	Madeira et al., 2023
26	Taihu Lake	China	Liu et al., 2017
2.7	San Francisco Bay	United States	Shimabuku et al., 2022
119	Lake Mjøsa	Czech Republic	Šauer et al., 2021
59.3	River	Slovenia	Grobin et al., 2024
165	Seawater of Black Sea	Italy	Chiriac et al., 2021
435.6	Drwina River	Poland	Styszko et al., 2021

24.2	Wisla River	Poland	Styszko et al., 2021
119	Pearl River	China	Gong et al., 2023
89	Rivers and Lakes of Albufera Natural Park	Spain	Sadutto et al., 2021
200.7	Al-Asfar and Al-Hubail Lakes	Saudi Arabia	Picó et al., 2020
55.97	Pearl River Delta	China	Chen et al., 2022
20.68	Jinsha River Basin	China	Liu et al., 2021
23	Seawater of East China Sea	China	Xie et al., 2022
12.8	Rivers, lakes and reservoirs	China	Zhang et al., 2019
32	Taff River	United Kingdom	Kasprzyk-Hordern et al., 2009
34	Ely River	United Kingdom	Hordern et al., 2009
193.2	Seawater of Gdansk Gulf	Poland	Staniszewska et al., 2015
363	Tangxun Lake	China	Yi et al., 2023
19.1	Zijiang River	China	Li et al., 2023
59.01	Seawater of Port Dickson coastline	Malaysia	Zainuddin et al., 2023
54.65	Lahore canal	Pakistan	Ashfaq et al., 2023
8.38	Seawater of Beibu Gulf	China	Gao et al., 2023
253	Yangtze River	China	Zheng et al., 2019
170	Oruński Stream	Poland	Caban et al., 2020
3113	Kozacki Stream	Poland	Caban et al., 2020
200	Luoma Lake	China	Wang et al., 2022
145	Yi River	China	Wang et al., 2022
215	Laoyi River	China	Wang et al., 2022
240	Zhongyun River	China	Wang et al., 2022
270	Fangting River	China	Wang et al., 2022
265	Bulao River	China	Wang et al., 2022
36.9	Pearl River	China	Wang et al., 2022
371.5	River, Port, Lake and Chanel of Jiangyan District	China	Cai et al., 2021
29	Danube River and Jiu River	Romania	Chiriac et al., 2021
979.76	Gomti River, Sarayu River, Ganga River, Yamuna River	India	Karsauliya et al., 2022
42.6	Yellow River	China	Zhao et al., 2020
86	Taihu Lake	China	Chen et al., 2017
315.8	Yangtze River	China	Liu et al., 2022

	97	Taihu Lake	China	Yan et al., 2017
	86	Luoma Lake	China	Yan et al., 2017
	196	Taihu Lake, Gehu Lake and Rivers	China	Si et al., 2019
	24.6	Pearl River Estuary	China	Zhao et al., 2019
	471	Zhujiang River	China	Huang et al., 2020
	406	Dongjiang	China	Huang et al., 2020
	922	Liuxi River	China	Huang et al., 2018
	362505	Danshuei River, Beigang River, Puzih River, Jishuei River, Jiangjyun River and Erren River	Taiwan	Chou et al., 2015
	22330	14 Rivers	Taiwan	Lee et al., 2013
BPS	4.7	Edogawa River	Japan	Yamazaki et al., 2015
	7.6	Arakawa River	Japan	Yamazaki et al., 2015
	8.7	Tamagawa River	Japan	Yamazaki et al., 2015
	15	Sewater of Tokyobay	Japan	Yamazaki et al., 2015
	135	Pearl River	China	Yamazaki et al., 2015
	42	Han River	Korea	Yamazaki et al., 2015
	3644	Cooum River	India	Yamazaki et al., 2015
	7204	Adyar River	India	Yamazaki et al., 2015
	2099	Buckingham Canal	India	Yamazaki et al., 2015
	8.7	Korttalaiyar River	India	Yamazaki et al., 2015
	16.1	Ebro River	Spain	Gil-Solsona et al., 2022
	5.1	Ebro Delta in the Mediterranean Sea	Spain	Gil-Solsona et al., 2022
	0.54	Pearl River Delta	China	Liang et al., 2023
	14.7	Hogsmill River, Chertsey Bourne River and Blackwater River	England	Wilkinson et al., 2017
	6	Taihu Lake	China	Jin et al., 2016
	14	Liaohe river	China	Jin et al., 2016
	11	Hunhe river	China	Jin et al., 2016
	4.6	Seawater of Hangzhou bay	China	Yang et al., 2014
	739	Tagus River	Portugal	Cunha et al., 2022
	5.5	Luoma Lake	China	Wang et al., 2022
	5.7	River	China	Wang et al., 2022
	6.42	Yangtze River Basin	China	Qin et al., 2024
	16	Taihu Lake	China	Liu et al., 2017

	23.9	San Francisco Bay	United States	Shimabuku et al., 2022
	6.2	Lake Mjøsa	Czech Republic	Šauer et al., 2021
	105	River	Slovenia	Grobin et al., 2024
	10	Rhône River	France	Schmidt et al., 2020
	2.2	Seawater of East China Sea	China	Xie et al., 2022
	1.1	Rivers, lakes and reservoirs	China	Zhang et al., 2019
	0.94	Yangtze River	China	Wan et al., 2018
	10.96	Seawater of Port Dickson coastline	Malaysia	Zainuddin et al., 2023
	0.34	Seawater of Beibu Gulf	China	Gao et al., 2023
	39.2	Yangtze River	China	Zheng et al., 2019
	122	Oruński Stream	Poland	Caban et al., 2020
	5.45	Luoma Lake	China	Wang et al., 2022
	5.25	Yi River	China	Wang et al., 2022
	4.45	Laoyi River	China	Wang et al., 2022
	5.1	Zhongyun River	China	Wang et al., 2022
	4.85	Fangting River	China	Wang et al., 2022
	6.65	Bulao River	China	Wang et al., 2022
	38.7	Pearl River	China	Wang et al., 2022
	37.1	River, Port, Lake and Chanel of Jiangyan District	China	Cai et al., 2021
	914	Taihu Lake	China	Han et al., 2023
	744.71	Gomti River, Sarayu River, Ganga River, Yamuna River	India	Karsauliya et al., 2022
	5.6	Yellow River	China	Zhao et al., 2020
	101	Taihu Lake	China	Chen et al., 2017
	51.6	Yangtze River	China	Liu et al., 2022
	120	Taihu Lake	China	Yan et al., 2017
	21	Luoma Lake	China	Yan et al., 2017
	56.1	Taihu Lake, Gehu Lake and Rivers	China	Si et al., 2019
	10.3	Pearl River Estuary	China	Zhao et al., 2019
	44.5	Zhujiang River	China	Huang et al., 2020
	12.7	Dongjiang	China	Huang et al., 2020
	3720	Liuxi River	China	Huang et al., 2018
BPF	445	Edogawa River	Japan	Yamazaki et al., 2015
	81.6	Arakawa River	Japan	Yamazaki et al., 2015

2846	Tamagawa River	Japan	Yamazaki et al., 2015
1474	Sewater of Tokyobay	Japan	Yamazaki et al., 2015
1113	Pearl River	China	Yamazaki et al., 2015
105	West River	China	Yamazaki et al., 2015
1301	Han River	Korea	Yamazaki et al., 2015
27	Adyar River	India	Yamazaki et al., 2015
289	Buckingham Canal	India	Yamazaki et al., 2015
0.016	Pearl River Delta	China	Liang et al., 2023
66	Ebro River	Spain	Herrero-Hernández et al., 2013
0.83	Taihu Lake	China	Jin et al., 2016
3.2	Seawater of Hangzhou bay	China	Yang et al., 2014
48	Guanabara Bay	Brazil	Coutinho et al., 2022
159	Douro River	Portugal	Cunha et al., 2022
159	Luoma Lake	China	Wang et al., 2022
161	River	China	Wang et al., 2022
5830	Dianchi Laoyu River	China	Wan et al., 2018
1.04	Yangtze River Basin	China	Qin et al., 2024
78	Taihu Lake	China	Liu et al., 2017
33.2	San Francisco Bay	United States	Shimabuku et al., 2022
21	Lake Mjøsa	Czech Republic	Šauer et al., 2021
11.2	Seawater of Black Sea	Italy	Chiriac et al., 2021
2.18	Rivers, lakes and reservoirs	China	Zhang et al., 1019
1143.88	Seawater of Port Dickson coastline	Malaysia	Zainuddin et al., 2023
2.2	Yangtze River	China	Zheng et al., 2019
159	Luoma Lake	China	Wang et al., 2022
165	Yi River	China	Wang et al., 2022
111	Laoyi River	China	Wang et al., 2022
170	Zhongyun River	China	Wang et al., 2022
210	Fangting River	China	Wang et al., 2022
175	Bulao River	China	Wang et al., 2022

	42.9	River, Port, Lake and Chanel of Jiangyan District	China	Cai et al., 2021
	295	Taihu Lake	China	Han et al., 2023
	114	Taihu Lake	China	Chen et al., 2017
	12.2	Yangtze River	China	Liu et al., 2022
	140	Taihu Lake	China	Yan et al., 2017
	6.8	Luoma Lake	China	Yan et al., 2017
	5.82	Taihu Lake, Gehu Lake and Rivers	China	Si et al., 2019
	35	Pearl River Estuary	China	Zhao et al., 2019
	12.2	Zhujiang River	China	Huang et al., 2020
	25.2	Dongjiang	China	Huang et al., 2020
	82.8	Liuxi River	China	Huang et al., 2018
BPB	4	Ebro Delta in the Mediterranean Sea	Spain	Gil-Solsona et al., 2022
	115	Douro River	Portugal	Cunha et al., 2022
	3143	Tagus River	Portugal	Cunha et al., 2022
	5	Luoma Lake	China	Wang et al., 2022
	5.7	River	China	Wang et al., 2022
	20	Taihu Lake	China	Liu et al., 2017
	1	Rivers, lakes and reservoirs	China	Zhang et al., 2019
	0.03	Seawater of Beibu Gulf	China	Gao et al., 2023
	5	Luoma Lake	China	Wang et al., 2022
	5.7	Bulao River	China	Wang et al., 2022
	4.6	Pearl River	China	Wang et al., 2022
	6.6	Taihu Lake	China	Chen et al., 2017
	5.8	Taihu Lake	China	Yan et al., 2017
	8.8	Luoma Lake	China	Yan et al., 2017
	1.51	Pearl River Estuary	China	Liu et al., 2022
BPAF	0.28	Taihu Lake	China	Jin et al., 2016
	1.9	Liaohe river	China	Jin et al., 2016
	2.4	Hunhe river	China	Jin et al., 2016
	74.8	Seawater of Hangzhou bay	China	Yang et al., 2014
	3080	Xitang river	China	Song et al., 2012
	27	Guanabara Bay	Brazil	Coutinho et al., 2022
	238	Douro River	Portugal	Cunha et al., 2022
	0.03	Yangtze River Basin	China	Qin et al., 2024
	110	Taihu Lake	China	Madeira et al., 2023
	91	Lake Mjøsa	Czech Republic	Šauer et al., 2021

	0.34	Seawater of East China Sea	China	Xie et al., 2022
	3	Rivers, lakes and reservoirs	China	Zhang et al., 2019
	0.53	Seawater of Beibu Gulf	China	Gao et al., 2023
	5.1	Yangtze River	China	Zheng et al., 2019
	8.3	Pearl River	China	Wang et al., 2022
	18.3	Pearl River	China	Wang et al., 2022
	13.2	River, Port, Lake and Chanel of Jiangyan District	China	Cai et al., 2021
	39.8	Yellow River	China	Zhao et al., 2020
	7.8	Taihu Lake	China	Chen et al., 2017
	10.9	Yangtze River	China	Liu et al., 2022
	8.2	Taihu Lake	China	Liu et al., 2022
	17	Luoma Lake	China	Yan et al., 2017
	1.43	Taihu Lake, Gehu Lake and Rivers	China	Si et al., 2019
	0.7	Pearl River Estuary	China	Zhao et al., 2019
	0.35	Zhujiang River	China	Huang et al., 2020
	4.2	Dongjiang	China	Huang et al., 2020
BPAP	0.033	Taihu Lake	China	Jin et al., 2016
	0.0035	Liaohe river	China	Jin et al., 2016
	1.9	Taihu Lake	China	Liu et al., 2017
	0.65	Pearl River	China	Wang et al., 2022
	4.8	Taihu Lake	China	Chen et al., 2017
	4.8	Taihu Lake	China	Yan et al., 2017
	11	Luoma Lake	China	Yan et al., 2017
BPFL	0.0095	Liaohe river	China	Jin et al., 2016
	0.0069	Hunhe river	China	Jin et al., 2016
BPZ	0.054	Liaohe River	China	Jin et al., 2016
	2.8	Luoma Lake	China	Wang et al., 2022
	0.53	Yangtze River Basin	China	Qin et al., 2022
	17	Taihu Lake	China	Liu et al., 2017
	2.8	Luoma Lake	China	Wang et al., 2022
	0.5	Pearl River	China	Wang et al., 2022
	0.4	River, Port, Lake and Chanel of Jiangyan District	China	Cai et al., 2021
	3.4	Taihu Lake	China	Wan et al., 2018
	840	Gomti River, Sarayu River, Ganga River, Yamuna River	India	Karsauliya et al., 2022
	4	Taihu Lake	China	Chen et al., 2017
	1.3	Yangtze River	China	Liu et al., 2022
	3.9	Taihu Lake	China	Yan et al., 2017
	7.7	Luoma Lake	China	Yan et al., 2017

BPE	223	Douro River	Portugal	Cunha et al., 2022
	0.12	River	Slovenia	Grobin et al., 2024
	16.5	Seawater of Black Sea	Italy	Chiriac et al., 2021
	0.98	Rivers, lakes and reservoirs	China	Zhang et al., 2019
	0.83	Yangtze River	China	Zheng et al., 2019
	1.9	Yangtze River	China	Liu et al., 2022
BPC	4.6	Pearl River	China	Wang et al., 2022
	14	Taihu Lake	China	Han et al., 2023

Table S2 – Acute and chronic toxicities for each BP.

Compound	Organism	Endpoint	Exposure time	Specie	Evaluated effect	Effect concentration (ng L^{-1})	Reference
BPA	Algae	Growth rate	72 h	Desmodesmus subspicatus	E(L)C50	19.6	Tišler et al., 2016
	Algae	Growth rate	96 h	Chlorella pyrenoidosa	E(L)C50	44.9	Li et al., 2017
	Algae	Growth rate	96 h	Scenedesmus obliquus	E(L)C50	33.9	Li et al., 2017
	Algae	Growth rate	14 d	Desmodesmus armatus	E(L)C50	42.06	Czarny-Krzymińska et al., 2022
	Algae	Growth rate	14 d	Chlorella vulgaris	E(L)C50	42.4	Czarny-Krzymińska et al., 2022
	Algae	Growth rate	2 d	Chlorella vulgaris	E(L)C50	41.43	Ding et al., 2020
	Algae	Growth rate	144 h	Chlorella pyrenoidosa	E(L)C50	17.7	Li et al., 2022
	Crustacean	Mortality	96 h	Artemia salina	E(L)C50	107.2	Naveira et al., 2021
	Crustacean	Immobility	48 h	Daphnia similis	E(L)C50	12.05	Spadoto et al., 2018
	Crustacean	Immobility	48 h	Ceriodaphnia silvestri	E(L)C50	14.44	Spadoto et al., 2018
	Crustacean	Mortality	24 h	Daphnia magna	E(L)C50	8.9	Tišler et al., 2016
	Crustacean	Mortality	48 h	Daphnia magna	E(L)C50	7.3	Tišler et al., 2016
	Crustacean	Mortality	24 h	Daphnia magna	E(L)C50	24	Chen et al., 2002
	Crustacean	Mortality	48 h	Daphnia magna	E(L)C50	10	Chen et al., 2002
	Crustacean	Mortality	96 h	Daphnia magna	E(L)C50	11.7	Li et al., 2017
	Fish	Mortality	48 h	Zebrafish embryo	E(L)C50	13.4	Tišler et al., 2016
	Fish	Mortality	96 h	Zebrafish embryo	E(L)C50	10.43	Mu et al., 2018
	Fish	Mortality	96 h	Zebrafish larvae	E(L)C50	12	Moreman et al., 2017
	Fish	Hatching rate	72 h	Zebrafish larvae	E(L)C50	5.7	Moreman et al., 2017
	Fish	Mortality	24 h	Adult zebrafish	E(L)C50	9.51	Ren et al., 2017
	Fish	Mortality	48 h	Adult zebrafish	E(L)C50	9.31	Ren et al., 2017
	Fish	Mortality	72 h	Adult zebrafish	E(L)C50	8.09	Ren et al., 2017

	Fish	Mortality	96 h	Adult zebrafish	E(L)C50	8.09	Ren et al., 2017
	Fish	Mortality	96 h	Channa punctatus	E(L)C50	7.6	Sharma et al., 2021
	Fish	Mortality	96 h	Poecilia vivipara	E(L)C50	3.5	Naveira et al., 2021
	Fish	Mortality	96 h	Oryzias latipes	E(L)C50	9.4	Li et al., 2017
	Crustacean	Reproduction	21 d	Daphnia magna	NOEC	5	Tišler et al., 2016
	Crustacean	Mortality	21 d	Daphnia magna	NOEC	5	Tišler et al., 2016
	Crustacean	Body length	21 d	Daphnia magna	NOEC	5	Tišler et al., 2016
	Crustacean	Reproduction	42 d	Hyalella azteca	NOEC	0.49	Mihaich et al., 2009
	Crustacean	Induction of aromatase	3 d	Moina macrocopa	NOEC	0.56	Jung et al., 2020
	Crustacean	Brood size	8 d	Ceriodaphnia silvestri	NOEC	1.38	Spadoto et al., 2018
	Fish	Body length	7 d	Zebrafish larvae	NOEC	2	Wenjuan et al., 2017
	Fish	Biochemistry	21 d	Cyprinus carpio	NOEC	24	Jung et al., 2020
	Fish	Induces vtg production	-	Pimephales promelas	NOEC	0.016	Staples et al., 2011
	Fish	-	96 h	Chironomus tentans	NOEC	1.4	Mihaich et al., 2009
	Algae	Growth rate	3 d	Pseudokirchneriella subcapitata	NOEC	1189	Jung et al., 2020
	Algae	Growth rate	14 d	Chlorella vulgaris	NOEC	25	Czarny-Krzymińska et al., 2022
	Algae	Growth rate	14 d	Desmodesmus armatus	NOEC	50	Czarny-Krzymińska et al., 2022
	Algae	Growth rate	3 d	Chlorella vulgaris	NOEC	10	Ding et al., 2020
	Aquatic plant	Growth rate	7 d	Lemna gibba	NOEC	7.8	Mihaich et al., 2009
	Rotifer	Reproduction	2 d	Brachionus calyciflorus	NOEC	1.8	Mihaich et al., 2009
BPS	Crustacean	Mortality	24 h	Daphnia magna	E(L)C50	76	Chen et al., 2002
	Crustacean	Mortality	48 h	Daphnia magna	E(L)C50	55	Chen et al., 2002
	Fish	Mortality	24 h	Zebrafish embryo	E(L)C50	361	Ren et al., 2017
	Fish	Mortality	48 h	Zebrafish embryo	E(L)C50	346	Ren et al., 2017
	Fish	Mortality	72 h	Zebrafish embryo	E(L)C50	331	Ren et al., 2017

	Fish	Mortality	96 h	Zebrafish embryo	E(L)C50	323	Ren et al., 2017
	Fish	Heart rate	78 h	Zebrafish embryo	E(L)C50	318	Ren et al., 2017
	Fish	Hatching rate	120 h	Zebrafish embryo	E(L)C50	200	Ren et al., 2017
	Fish	Mortality	96 h	Zebrafish larvae	E(L)C50	199	Moreman et al., 2017
	Fish	Hatching rate	72 h	Zebrafish larvae	E(L)C50	155	Moreman et al., 2017
	Fish	Mortality	24 h	Adult zebrafish	E(L)C50	343	Ren et al., 2017
	Fish	Mortality	48 h	Adult zebrafish	E(L)C50	343	Ren et al., 2017
	Fish	Mortality	72 h	Adult zebrafish	E(L)C50	343	Ren et al., 2017
	Fish	Mortality	96 h	Adult zebrafish	E(L)C50	343	Ren et al., 2017
	Algae	Growth rate	2 d	Chlorella vulgaris	E(L)C50	3.16	Ding et al., 2020
	Algae	Growth rate	120 h	Chlorella vulgaris	E(L)C50	25.19	Li et al., 2021
	Algae	Growth rate	120 h	Navicula sp.	E(L)C50	3.89	Li et al., 2021
	Algae	Growth rate	96 h	Chlamydomonas mexicana	E(L)C50	85.48	Yadav et al., 2023
	Algae	Growth rate	144 h	Chlorella pyrenoidosa	E(L)C50	66.07	Wang et al., 2022
	Bacteria	Reduction of luminescence	30 min	Aliivibrio fischeri	E(L)C50	15.42	Owczarek et al., 2018
	Fish	Body length	7 d	Zebrafish larvae	NOEC	300	Wenjuan et al., 2017
	Fish	Reproduction	7 d	Zebrafish	NOEC	0.001	Naderi et al., 2014
	Algae	Growth rate	120 h	Chlorella vulgaris	NOEC	10	Li et al., 2021
	Algae	Navicula sp.	120 h	Growth rate	NOEC	5	Li et al., 2021
	Crustacean	Reproduction	21 d	Daphnia magna	NOEC	2.5	Park et al., 2019
	Crustacean	Reproduction	7 d	Moina macrocopa	NOEC	0.03	Park et al., 2019
BPF	Algae	Growth rate	48 h	Desmodesmus subspicatus	E(L)C50	22.1	Tišler et al., 2016
	Algae	Growth rate	96 h	Chlamydomonas mexicana	E(L)C50	30.53	Yadav et al., 2023
	Algae	Growth rate	72 h	Pseudokirchneriella subcapitata	E(L)C50	9.2	Elersek et al., 2021
	Crustacean	Mortality	48 h	Daphnia magna	E(L)C50	8.7	Tišler et al., 2016
	Crustacean	Mortality	24 h	Daphnia magna	E(L)C50	80	Chen et al., 2022

	Crustacean	Mortality	48 h	Daphnia magna	E(L)C50	56	Chen et al., 2022
	Fish	Mortality	48 h	Zebrafish embryo	E(L)C50	1.1	Tišler et al., 2016
	Fish	Missing body pigmentation	96 h	Zebrafish embryo	E(L)C50	19.59	Mu et al., 2018
	Fish	Mortality	48 h	Zebrafish embryo	E(L)C50	6.8	Tišler et al., 2016
	Fish	Hatching rate	24 h	Zebrafish embryo	E(L)C50	9.13	Ren et al., 2017
	Fish	Mortality	48 h	Zebrafish embryo	E(L)C50	8.93	Ren et al., 2017
	Fish	Mortality	72 h	Zebrafish embryo	E(L)C50	8.56	Ren et al., 2017
	Fish	Mortality	96 h	Zebrafish embryo	E(L)C50	7.4	Ren et al., 2017
	Fish	Mortality	96 h	Zebrafish larvae	E(L)C50	32	Moreman et al., 2017
	Fish	Hatching rate	72 h	Zebrafish larvae	E(L)C50	14	Moreman et al., 2017
	Fish	Mortality	24 h	Adult zebrafish	E(L)C50	10.1	Ren et al., 2017
	Fish	Mortality	48 h	Adult zebrafish	E(L)C50	9.86	Ren et al., 2017
	Fish	Mortality	72 h	Adult zebrafish	E(L)C50	9.51	Ren et al., 2017
	Fish	Mortality	96 h	Adult zebrafish	E(L)C50	9.51	Ren et al., 2017
	Bacteria	Reduction of luminescence	30 min	Aliivibrio fischeri	E(L)C50	5.67	Owczarek et al., 2018
	Crustacean	Reproduction	21 d	Daphnia magna	NOEC	0.84	Tišler et al., 2016
	Crustacean	Mortality	21 d	Daphnia magna	NOEC	6.7	Tišler et al., 2016
	Crustacean	Body length	21 d	Daphnia magna	NOEC	1.68	Tišler et al., 2016
	Fish	Body length	7 d	Zebrafish larvae	NOEC	6	Wenjuan et al., 2017
	Fish	Malonic dialdehyde content	7 d	Zebrafish	NOEC	0.08	Han et al., 2022
	Fish	Hatching rate	72 h	Zebrafish larvae		1.25	Gao et al., 2022
	Algae	Growth rate	7 d	Chlorella vulgaris	NOEC	0.1	Zhang et al., 2021
	Algae	Growth rate	72 h	Pseudokirchneriella subcapitata	NOEC	2.9	Elersek et al., 2021
BPAF	Algae	Growth rate	72 h	Desmodesmus subspicatus	E(L)C50	3	Tišler et al., 2016
	Algae	Growth rate	14 d	Desmodesmus armatus	E(L)C50	34.8	Czarny-Krzymińska et al., 2022

	Algae	Growth rate	14 d	Chlorella vulgaris	E(L)C50	29	Czarny-Krzymińska et al., 2022
	Algae	Growth rate	96 h	Chlamydomonas mexicana	E(L)C50	1.78	Yadav et al., 2023
	Crustacean	Mortality	24 h	Daphnia magna	E(L)C50	3.4	Tišler et al., 2016
	Crustacean	Mortality	48 h	Daphnia magna	E(L)C50	2.7	Tišler et al., 2016
	Fish	Mortality	96 h	Zebrafish embryo	E(L)C50	1.95	Mu et al., 2018
	Fish	Mortality	48 h	Zebrafish embryo	E(L)C50	4.2	Tišler et al., 2016
	Fish	Hatching rate	48 h	Zebrafish embryo	E(L)C50	2.2	Tišler et al., 2016
	Fish	Mortality	48 h	Zebrafish embryo	E(L)C50	3.89	Ren et al., 2017
	Fish	Mortality	72 h	Zebrafish embryo	E(L)C50	3.49	Ren et al., 2017
	Fish	Mortality	96 h	Zebrafish embryo	E(L)C50	2.04	Ren et al., 2017
	Fish	Mortality	96 h	Zebrafish larvae	E(L)C50	1.6	Moreman et al., 2017
	Fish	Hatching rate	72 h	Zebrafish larvae	E(L)C50	0.92	Moreman et al., 2017
	Fish	Mortality	24 h	Adult zebrafish	E(L)C50	3.15	Ren et al., 2017
	Fish	Mortality	48 h	Adult zebrafish	E(L)C50	2.64	Ren et al., 2017
	Fish	Mortality	72 h	Adult zebrafish	E(L)C50	2.47	Ren et al., 2017
	Fish	Mortality	96 h	Adult zebrafish	E(L)C50	2.47	Ren et al., 2017
	Fish	Induces vtg production	4 d	Cyprinus carpio	E(L)C50	0.57	Letcher et al., 2005
	Crustacean	Reproduction	21 d	Daphnia magna	NOEC	0.23	Tišler et al., 2016
	Crustacean	Mortality	21 d	Daphnia magna	NOEC	0.9	Tišler et al., 2016
	Crustacean	Body length	21 d	Daphnia magna	NOEC	0.23	Tišler et al., 2016
	Fish	Body length	7 d	Zebrafish larvae	NOEC	0.5	Wenjuan et al., 2017
	Algae	Growth rate	14 d	Chlorella vulgaris	NOEC	10	Czarny-Krzymińska et al., 2022
	Algae	Growth rate	14 d	Desmodesmus armatus	NOEC	50	Czarny-Krzymińska et al., 2022
	Algae	Reactive oxygen species	72 h	Phaeodactylum tricornutum	NOEC	5	Sendra et al., 2023
BPAP	Fish	Mortality	24 h	Zebrafish embryo	E(L)C50	2.84	Ren et al., 2017

	Fish	Mortality	48 h	Zebrafish embryo	E(L)C50	2.61	Ren et al., 2017
	Fish	Mortality	72 h	Zebrafish embryo	E(L)C50	2.57	Ren et al., 2017
	Fish	Mortality	96 h	Zebrafish embryo	E(L)C50	2.29	Ren et al., 2017
	Fish	Mortality	24 h	Adult zebrafish	E(L)C50	3.04	Ren et al., 2017
	Fish	Mortality	48 h	Adult zebrafish	E(L)C50	2.7	Ren et al., 2017
	Fish	Mortality	72 h	Adult zebrafish	E(L)C50	2.42	Ren et al., 2017
	Fish	Mortality	96 h	Adult zebrafish	E(L)C50	2.28	Ren et al., 2017
	Algae	Growth rate	-	Desmodesmus armatus	E(L)C50	26.8	Czarny et al., 2021
	Fish	Body length	7 d	Zebrafish larvae	NOEC	0.25	Wenjuan et al., 2017
	Algae	Reactive oxygen species	72 h	Nannochloropsis gaditana	NOEC	1.4	Sendra et al., 2023
BPB	Crustacean	Mortality	24 h	Daphnia magna	E(L)C50	9	Chen et al., 2002
	Crustacean	Mortality	48 h	Daphnia magna	E(L)C50	5.5	Chen et al., 2002
	Crustacean	Mortality	48 h	Daphnia magna	E(L)C50	3.93	Wang et al., 2021
	Fish	Mortality	24 h	Zebrafish embryo	E(L)C50	7.18	Ren et al., 2017
	Fish	Mortality	48 h	Zebrafish embryo	E(L)C50	6.54	Ren et al., 2017
	Fish	Mortality	72 h	Zebrafish embryo	E(L)C50	4.53	Ren et al., 2017
	Fish	Mortality	96 h	Zebrafish embryo	E(L)C50	3.88	Ren et al., 2017
	Fish	Mortality	24 h	Adult zebrafish	E(L)C50	5.07	Ren et al., 2017
	Fish	Mortality	48 h	Adult zebrafish	E(L)C50	4.64	Ren et al., 2017
	Fish	Mortality	72 h	Adult zebrafish	E(L)C50	4.15	Ren et al., 2017
	Fish	Mortality	96 h	Adult zebrafish	E(L)C50	4.15	Ren et al., 2017
	Fish	Mortality	96 h	Danio rerio	E(L)C50	4.13	Wang et al., 2021
	Algae	Growth rate	96 h	Chlamydomonas mexicana	E(L)C50	12.09	Yadav et al., 2023
	Algae	Growth rate	96 h	Tetradesmus obliquus	E(L)C50	12.3	Wang et al., 2021
	Fish	Body length	7 d	Zebrafish larvae	NOEC	1	Wenjuan et al., 2017
	Fish	Body length	120 h	Zebrafish larvae	NOEC	0.001	Qiu et al., 2021

	Fish	Malformation rates	144 h	Zebrafish larvae	NOEC	0.01	Yang et al., 2021
	Algae	Growth rate	72 h	Chlamydomonas mexicana	NOEC	10	Yadav et al., 2023
BPP	Crustacean	Mortality	24 h	Daphnia magna	E(L)C50	4	Chen et al., 2002
	Crustacean	Mortality	48 h	Daphnia magna	E(L)C50	1.6	Chen et al., 2002
	Fish	Mortality	24 h	Zebrafish embryo	E(L)C50	0.81	Ren et al., 2017
	Fish	Mortality	48 h	Zebrafish embryo	E(L)C50	0.66	Ren et al., 2017
	Fish	Mortality	72 h	Zebrafish embryo	E(L)C50	0.4	Ren et al., 2017
	Fish	Mortality	96 h	Zebrafish embryo	E(L)C50	0.37	Ren et al., 2017
	Fish	Mortality	48 h	Adult zebrafish	E(L)C50	0.7	Ren et al., 2017
	Fish	Mortality	72 h	Adult zebrafish	E(L)C50	0.46	Ren et al., 2017
	Fish	Mortality	96 h	Adult zebrafish	E(L)C50	0.4	Ren et al., 2017
	Fish	Body length	7 d	Zebrafish larvae	NOEC	0.2	Wenjuan et al., 2017
	Fish	Hatching rate	72 h	Zebrafish larvae	NOEC	0.1	Wang et al., 2019
BPZ	Fish	Mortality	48 h	Zebrafish embryo	E(L)C50	3.39	Ren et al., 2017
	Fish	Mortality	72 h	Zebrafish embryo	E(L)C50	3.25	Ren et al., 2017
	Fish	Mortality	96 h	Zebrafish embryo	E(L)C50	2.98	Ren et al., 2017
	Fish	Mortality	24 h	Adult zebrafish	E(L)C50	3.43	Ren et al., 2017
	Fish	Mortality	48 h	Adult zebrafish	E(L)C50	2.72	Ren et al., 2017
	Fish	Mortality	72 h	Adult zebrafish	E(L)C50	2.63	Ren et al., 2017
	Fish	Mortality	96 h	Adult zebrafish	E(L)C50	2.63	Ren et al., 2017
	Algae	Growth rate	96 h	Chlamydomonas mexicana	E(L)C50	9.54	Yadav et al., 2023
	Algae	Growth rate	14 d	Chlorella vulgaris	E(L)C50	48.76	Czarny et al., 2021
	Algae	Growth rate	-	Desmodesmus armatus	E(L)C50	82.65	Czarny et al., 2021
	Fish	Body length	7 d	Zebrafish larvae	NOEC	0.5	Wenjuan et al., 2017
	Algae	Growth rate	72 h	Chlamydomonas mexicana	NOEC	5	Yadav et al., 2023
BPC	Fish	Induces vtg production	4 d	Cyprinus carpio	E(L)C50	16.61	Letcher et al., 2005

	Algae	Growth rate	14	Anabaena variabilis	E(L)C50	31.51	Czarny et al., 2021
	Algae	Growth rate	-	Microcystis aeruginosa	E(L)C50	54.87	Czarny et al., 2021
	Bacteria	Reduction of luminescence	30 min	Aliivibrio fischeri	E(L)C50	7.92	Owczarek et al., 2018
	Fish	Malonic dialdehyde content	7 d	Zebrafish	NOEC	0.02	Han et al., 2022
	Fish	Hatching rate	72 h	Zebrafish larvae	NOEC	0.5	Gao et al., 2022
	Algae	Growth rate	72 h	Phaeodactylum tricornutum	NOEC	1.4	Sendra et al., 2023
BPE	Bacteria	Reduction of luminescence	30 min	Aliivibrio fischeri	E(L)C50	12.41	Owczarek et al., 2018
	Fish	Hatching rate	72 h	Zebrafish larvae	NOEC	3.5	Gao et al., 2022

Table S3 – Acute and chronic RQ values of BPs by aquatic organisms.

Compound	Organism	Acute RQ	Chronic RQ
BPA	Algae	20.48	0.36
	Crustacean	49.66	7.40
	Fish	103.57	226.57
	Rotifer	-	2.01
BPS	Algae	2.28	0.01
	Crustacean	0.13	2.40
	Fish	0.05	72.04
	Bacteria	0.47	-
BPF	Algae	0.63	0.58
	Crustacean	0.67	0.07
	Fish	5.30	0.73
	Bacteria	1.03	-
BPAF	Algae	1.73	0.01
	Crustacean	1.14	0.13
	Fish	5.40	0.06
BPAP	Algae	0.0004	0.0004
	Fish	0.0048	0.0022
BPB	Algae	0.26	0.02
	Crustacean	0.80	-
	Fish	0.81	157.15
BPZ	Algae	0.088	0.008
	Fish	0.32	0.084
BPC	Algae	0.0004	0.001
	Fish	0.001	0.035
	Bacteria	0.002	-
BPE	Fish	-	0.006
	Bacteria	0.02	-

Table S4 – Relative potency (RP) and 17β-estradiol equivalents (EEQ) for BPs.

Compound	Relative Potency	Bioassay / Analytical Method	Reference	MEC (ng L^{-1})	EEQ (ng L^{-1})	MECmax (ng L^{-1})	EEQmax (ng L^{-1})
BPA	1.01E-04	BLYES	Ruan et al., 2015	2540.74	0.26	362505	36.61
BPAF	7.23E-04	BLYES	Ruan et al., 2015	144.79	0.10	3080	2.23
BPAP	8.03E-04	NI	Wang et al., 2019	3.31	0.0027	11	0.01
BPB	8.60E-04	Estrogen receptor (ER) competitive-biding assay	Blair et al., 2000	222.12	0.19	3143	2.70
BPC	1.29E-03	NI	Wang et al., 2019	9.30	0.01	14	0.02
BPE	5.92E-05	BLYES	Ruan et al., 2015	40.56	0.00	223	0.01
BPF	1.08E-04	BLYES	Ruan et al., 2015	399.15	0.04	5830	0.63
BPS	1.06E-04	BLYES	Ruan et al., 2015	374.89	0.04	7204	0.76
BPZ	2.12E-03	NI	Wang et al., 2019	68.03	0.14	840	1.78

NI = Not informed.

Table S5 – BPs' concentration in raw wastewater and treated wastewater, removal efficiency by MBRs and treatment characteristics.

Compound	Conc. RWW (µg/L)	Conc. TWW (µg/L)	Removal efficiency (%)	Treatment description	Acronym	Scale	Biological degradation	HRT (h)	SRT (d)	MLVSS (g/L)	Type of WW	Location	Reference
Bisphenol A	1.7	0.17	90	Aerobic membrane bioreactor	MBR	Lab-scale	Aerobic	24	70	8.3	Synthetic wastewater	Australia	Alturki et al., 2010
Bisphenol A	5	2.5	50	Membrane bioreactor	MBR	Lab-scale	Aerobic	6	-	7.08	Synthetic wastewater	Australia	Luo et al., 2015
Bisphenol A	2.75	0.14	95	Aerobic membrane bioreactor	MBR	Lab-scale	Aerobic	24	-	2.65	Synthetic wastewater	Australia	Luo et al., 2015
Bisphenol A	5	0.5	90	Membrane bioreactor	MBR	Lab-scale	Aerobic	24	50	4.8	Synthetic wastewater	Australia	Luo et al., 2015
Bisphenol A	5	0.5	90	Membrane bioreactor with salinity build-up (16 g NaCl)	MBR	Lab-scale	Aerobic	24	50	4.8	Synthetic wastewater	Australia	Luo et al., 2015
Bisphenol A	5	0.25	95	Aerobic membrane bioreactor	MBR	Lab-scale	Aerobic	24	NI	5	Synthetic wastewater	Australia	Nguyen et al., 2013
Bisphenol A	0.75	0.015	98	Membrane bioreactor with salinity build-up (16.5 g NaCl)	MBR	Lab-scale	Aerobic	27	-	NI	Synthetic wastewater	Australia	Phan et al., 2016
Bisphenol A	2.38	0.016	99	Aerobic membrane bioreactor	MBR	Pilot-scale	Aerobic	28.8	27	3.195	Municipal wastewater	Austria	Clara et al., 2005
Bisphenol A	0.14	0.01	92	Aerobic membrane bioreactor	MBR	Full-scale	Aerobic	8	7	5.6	Municipal wastewater	Canada	Guerra et al., 2015
Bisphenol A	1000	4.2	99	Aerobic membrane bioreactor	MBR	Lab-scale	Aerobic	5.5	140	12	Synthetic wastewater	Canada	Seyhi et al., 2013
Bisphenol A	5	0.3	94	Aerobic membrane bioreactor with external membrane	MBR	Lab-scale	Aerobic	24	50	4.87	Synthetic wastewater	China	Liu et al., 2020

Bisphenol A	200	4	98	Aerobic membrane bioreactors operated at 25 °C	MBR	Lab-scale	Aerobic	19	-	11	Synthetic wastewater	China	Wang et al., 2023
Bisphenol A	200	12.2	93.9	Aerobic membrane bioreactor	MBR	Lab-scale	Aerobic	12	-	7.5	Synthetic wastewater	China	Zhu et al., 2013
Bisphenol A	0.95	<0.05	94.7	Aerobic membrane bioreactor with submerged membrane	MBR	Pilot-scale	Aerobic	35	27.5	7.6	Municipal wastewater	Finland	Gurung et al., 2017
Bisphenol A	3.7	7.1	92	Conventional activated sludge with submerged membrane	MBR	Pilot-scale	Aerobic	NI	2.5	3	Municipal wastewater	Israel	Sahar et al., 2011
Bisphenol A	1	0.07	93.5	Aerobic membrane bioreactor with submerged membrane	MBR	Pilot-scale	Aerobic	50	30	8	Municipal wastewater	Spain	Cartagena et al., 2013
Bisphenol A	1	0.07	92.1	Aerobic membrane bioreactor with submerged membrane	MBR	Pilot-scale	Aerobic	50	30	8	Municipal wastewater	Spain	Cartagena et al., 2013
Bisphenol A	7.2	5.9	18	Enzymatic membrane bioreactor	EMBR	Lab-scale	Aerobic	16	NI	NI	Synthetic wastewater	Australia	Asif et al., 2020
Bisphenol A	5	2.9	42	Enzymatic membrane reactor	EMBR	Lab-scale	Aerobic	8	NI	NI	Synthetic wastewater	Australia	Nguyen et al., 2016
Bisphenol A	5	0.3	94	Enzymatic membrane reactor with redox-mediators syringaldehyde for improve laccase-catalyzed degradation	EMBR	Lab-scale	Aerobic	8	NI	NI	Synthetic wastewater	Australia	Nguyen et al., 2016
Bisphenol A	20	0.2	99	Enzymatic membrane distillation bioreactor	EMBR-MD	Lab-scale	Aerobic	30	NI		Synthetic wastewater	Australia	Asif et al., 2018
Bisphenol A	7.2	0.14	98	Enzymatic membrane bioreactor	EMBR-NF	Lab-scale	Aerobic	16	NI	NI	Synthetic wastewater	Australia	Asif et al., 2020

Bisphenol A	50	1.55	96.9	Membrane Aerated Biofilm Reactor (MABR)	MABR	Lab-scale	Aerobic	20	NI	NI	Municipal wastewater	Saudi Arabia	Sanchez-Huerta et al., 2022
Bisphenol A	5	0.5	90	Hybrid moving bed biofilm reactor–membrane bioreactor with sponge cubes	MBBR-MBR	Lab-scale	Aerobic	24+6	-	0.89	Synthetic wastewater	Australia	Luo et al., 2015
Bisphenol A	1.7	0.051	97	Aerobic membrane bioreactor associated with NF	MBR-NF	Lab-scale	Aerobic	24	70	8.3	Synthetic wastewater	Australia	Alturki et al., 2010
Bisphenol A	1.7	0.017	99	Aerobic membrane bioreactor associated with NF	MBR-NF	Lab-scale	Aerobic	24	70	8.3	Synthetic wastewater	Australia	Alturki et al., 2010
Bisphenol A	0.09	0.004	95.6	Aerobic membrane bioreactor with NF	MBR-NF	Pilot-scale	Aerobic	7.8	20	5.6	Municipal wastewater	Korea	[191]
Bisphenol A	1.7	0.017	99	Aerobic membrane bioreactor associated with NF RO	MBR-RO	Lab-scale	Aerobic	24	70	8.3	Synthetic wastewater	Australia	Alturki et al., 2010
Bisphenol A	1.7	0.034	98	Aerobic membrane bioreactor associated with NF RO	MBR-RO	Lab-scale	Aerobic	24	70	8.3	Synthetic wastewater	Australia	Alturki et al., 2010
Bisphenol A	3.7	0.1	97	Conventional activated sludge with submerged membrane associated with RO	MBR-RO	Pilot-scale	Aerobic	NI	2.5	3	Municipal wastewater	Israel	Sahar et al., 2011
Bisphenol A	0.09	0.003	96.7	Aerobic membrane bioreactor with RO	MBR-RO	Pilot-scale	Aerobic	7.8	20	5.6	Municipal wastewater	Korea	Lee et al., 2008
Bisphenol A	2.75	0.4	85	Aerobic osmotic membrane bioreactor	OMBR	Lab-scale	Aerobic	24	-	2.65	Synthetic wastewater	Australia	Luo et al., 2015
Bisphenol A	200	4	98	Aerobic osmotic membrane bioreactor	OMBR	Lab-scale	Aerobic	NI	-	7.5	Synthetic wastewater	China	Zhu et al., 2013

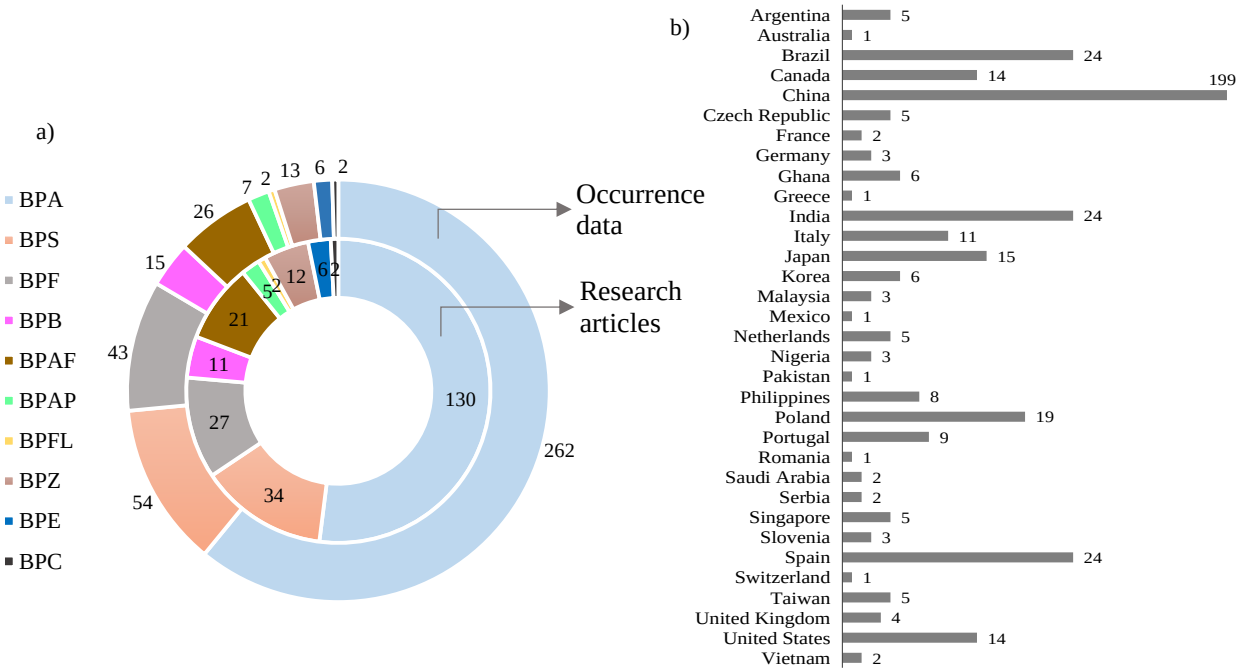
Bisphenol A	5	0	100	Aerobic osmotic membrane bioreactor	OMBR	Lab-scale	Aerobic		20	5	Synthetic wastewater	China	Luo et al., 2018
Bisphenol A	5	0.4	92	Aerobic osmotic membrane bioreactor with membrane distillation	OMBR-MD	Lab-scale	Aerobic	35	20	6	Synthetic wastewater	Australia	Luo et al., 2017
Bisphenol A	5	0	100	Aerobic osmotic membrane bioreactor integrated with reverse osmosis	OMBR-RO	Lab-scale	Aerobic	NI	20	5	Synthetic wastewater	China	Zhang et al., 2017
Bisphenol A	5	0	100	Aerobic osmotic membrane bioreactor integrated with reverse osmosis	OMBR-RO	Lab-scale	Aerobic	NI	20	5	Synthetic wastewater	China	Zhang et al., 2017
Bisphenol A	3000	120	96	Sequencing batch reactor (SBR) linked to an external filtration system	SBR-MBR	Lab-scale	Aerobic	8	NI	2.2	Synthetic wastewater	Kazakhstan	Kanafin et al., 2023
Bisphenol A	20	0.2	99	Sequential batch reactor (SBR) with submerged NF	SBR-MBR-NF	Lab-scale	Aerobic	12	NI	1	Synthetic wastewater	Saudi Arabia	Wei et al., 2018
Bisphenol A	2	1.2	40	Anaerobic membrane bioreactor	AnMBR	Lab-scale	Anaerobic	120	140	11	Synthetic wastewater	Australia	Song et al., 2016
Bisphenol A	2	1.64	18	Anaerobic membrane bioreactor with salinity build-up (15 g/L of NaCl)	AnMBR	Lab-scale	Anaerobic	120	140	6	Synthetic wastewater	Australia	Song et al., 2016
Bisphenol A	5	3.5	30	Anaerobic membrane bioreactor	AnMBR	Lab-scale	Anaerobic	24	50	15.42	Synthetic wastewater	China	Liu et al., 2020
Bisphenol A	2	0.2	90	Anaerobic membrane distillation bioreactor	AnMBR-MD	Lab-scale	Anaerobic	96	NI	4.9	Synthetic wastewater	Australia	Song et al., 2018

Bisphenol A	5	0.05	99	Anaerobic membrane bioreactor	AnOMBR	Lab-scale	Anaerobic	96	180	10	Synthetic wastewater	Australia	Wijekoon et al., 2015
Bisphenol A	1000	0	100	Anaerobic granular activated carbon fluidized bed membrane bioreactor	GAC-AnFMBR	Lab-scale	Anaerobic	8	NI	0.4	Synthetic wastewater	Korea	Lee et al., 2021
Bisphenol A	1000	0	100	Gas-sparged Anaerobic membrane bioreactor	G-AnMBR	Lab-scale	Anaerobic	8	NI	1.2	Synthetic wastewater	Korea	Lee et al., 2021
Bisphenol A	2.03	1.39	31.5	Membrane upflow anaerobic sludge blanket reactor	UASB-MBR	Lab-scale	Anaerobic	6	30	NI	Synthetic wastewater	Australia	Monsalvo et al., 2014
Bisphenol A	0.63	0.14	78	Anaerobic-Anoxic-Oxic membrane bioreactor	AAO-MBR	Full-scale	Three-stage	NI	NI	NI	Municipal wastewater	China	Huang et al., 2021
Bisphenol A	0.27	0.005	98	Anaerobic-Anoxic-Oxic membrane bioreactor	AAO-MBR	Full-scale	Three-stage	14 + 0.5 (MBR)	20	11.5	Municipal wastewater	China	Xue et al., 2010
Bisphenol A	0.4	0.007	98.25	Anaerobic-Anoxic-Oxic membrane bioreactor	AAO-MBR	Full-scale	Three-stage	NI	NI	11.5	Municipal wastewater	China	Wu et al., 2011
Bisphenol A	3.7	1.1	70	Anaerobic-Anoxic-Oxic membrane bioreactor	AAO-MBR	Lab-scale	Three-stage	NI	40	10	Municipal wastewater	Israel	Sahar et al., 2011
Bisphenol A	20	3	85	Anaerobic-Anoxic-Oxic membrane bioreactor	AAO-MBR	Pilot-scale	Three-stage	9		7.9	Synthetic wastewater	Spain	Alvarino et al., 2019
Bisphenol A	3.7	<0.04	>99	Anaerobic-Anoxic-Oxic membrane bioreactor with RO	AAO-MBR-RO	Lab-scale	Three-stage	NI	40	10	Municipal wastewater	Israel	Sahar et al., 2011
Bisphenol A	5	0.1	98	Anoxic-aerobic membrane bioreactor	AA-MBR	Lab-scale	Two-stage	24	infinite	2.1	Synthetic wastewater	Australia	Phan et al., 2016
Bisphenol A	0.318	0.0795	75	Anoxic-Aerobic membrane bioreactor	AA-MBR	Pilot-scale	Two-stage	NI	65	2.6	Municipal wastewater	United States of America	Holloway et al., 2014

Bisphenol A	0.318	0.067	78.93	Anoxic-Aerobic osmotic membrane bioreactor	AA-MBR	Pilot-scale	Two-stage	30	65	2.6	Municipal wastewater	United States of America	Holloway et al., 2014
Bisphenol A	0.318	0.02385	92.5	Anoxic-Aerobic osmotic membrane bioreactor with reverse osmosis	AA-MBR		Two-stage	30	65	2.6	Municipal wastewater	United States of America	Holloway et al., 2014
Bisphenol AF	0.067	0.106	-58	Aerobic membrane bioreactor	MBR	Full-scale	Aerobic	10	NI	NI	Municipal wastewater	China	Qian et al., 2021
Bisphenol AP	0.21	0.13	38	Aerobic membrane bioreactor	MBR	Full-scale	Aerobic	10	NI	NI	Municipal wastewater	China	Qian et al., 2021
Bisphenol B	0.3	0.159	47	Aerobic membrane bioreactor	MBR	Full-scale	Aerobic	10	NI	NI	Municipal wastewater	China	Qian et al., 2021
Bisphenol C	0.0118	<0.00035	>97	Aerobic membrane bioreactor	MBR	Full-scale	Aerobic	NI	NI	NI	Industrial, hospital, municipal wastewater	Slovenia	Česen et al., 2018
Bisphenol C	0.0088	0.0014	84	Anaerobic-Anoxic-Oxic membrane bioreactor	AAO-MBR	Full-scale	Three-stage	NI	NI	NI	Municipal wastewater	China	Huang et al., 2021
Bisphenol E	0.22	0.14	36	Aerobic membrane bioreactor	MBR	Full-scale	Aerobic	10	NI	NI	Municipal wastewater	China	Qian et al., 2021
Bisphenol F	0.26	0.21	19	Aerobic membrane bioreactor	MBR	Full-scale	Aerobic	10	NI	NI	Municipal wastewater	China	Qian et al., 2021
Bisphenol F	0.0062	<0.00047	>92.4	Aerobic membrane bioreactor	MBR	Full-scale	Aerobic	NI	NI	NI	Industrial, hospital, municipal wastewater	Slovenia	Česen et al., 2018
Bisphenol F	0.02	0.00085	95.8	Anaerobic-Anoxic-Oxic membrane bioreactor	AAO-MBR	Full-scale	Three-stage	NI	NI	NI	Municipal wastewater	China	Huang et al., 2021
Bisphenol S	0.062	<0.0033	>94	Aerobic membrane bioreactor	MBR	Full-scale	Aerobic	10	NI	NI	Municipal wastewater	China	Qian et al., 2021

Bisphenol S	0.032	0.00015	99.5	Anaerobic-Anoxic-Oxic membrane bioreactor	AAO-MBR	Full-scale	Three-stage	NI	NI	NI	Municipal wastewater	China	Huang et al., 2021
Bisphenol Z	0.2499	0.2925	-17.05	Aerobic membrane bioreactor	MBR	Full-scale	Aerobic	10	NI	NI	Municipal wastewater	China	Qian et al., 2021
Bisphenol Z	0.0047	<0.0012	>74	Aerobic membrane bioreactor	MBR	Full-scale	Aerobic	NI	NI	NI	Industrial, hospital, municipal wastewater	Slovenia	Česen et al., 2018
Bisphenol Z	0.001	<0.00013	>87	Anaerobic-Anoxic-Oxic membrane bioreactor	AAO-MBR	Full-scale	Three-stage	NI	NI	NI	Municipal wastewater	China	Huang et al., 2021

Figure S1 – Number of studies and occurrence data about a) BPA and its analogues in surface waters, and b) number of studies by country from 2013 to 2024.

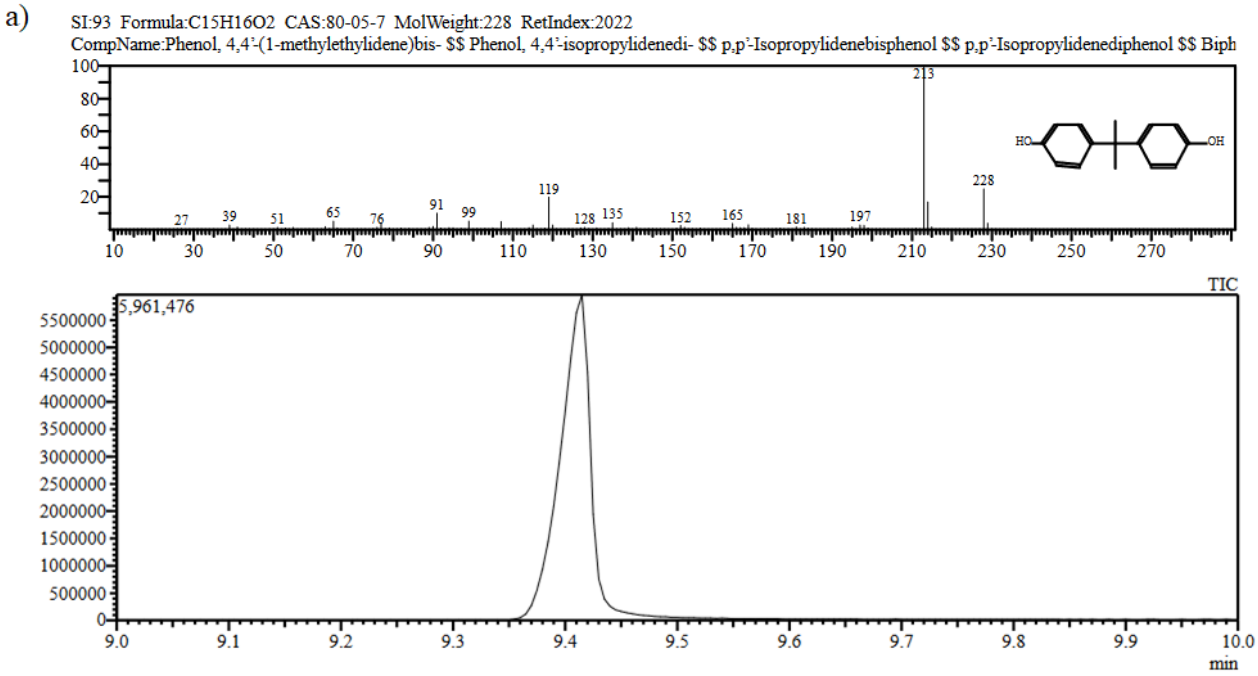


CHAPTER 5

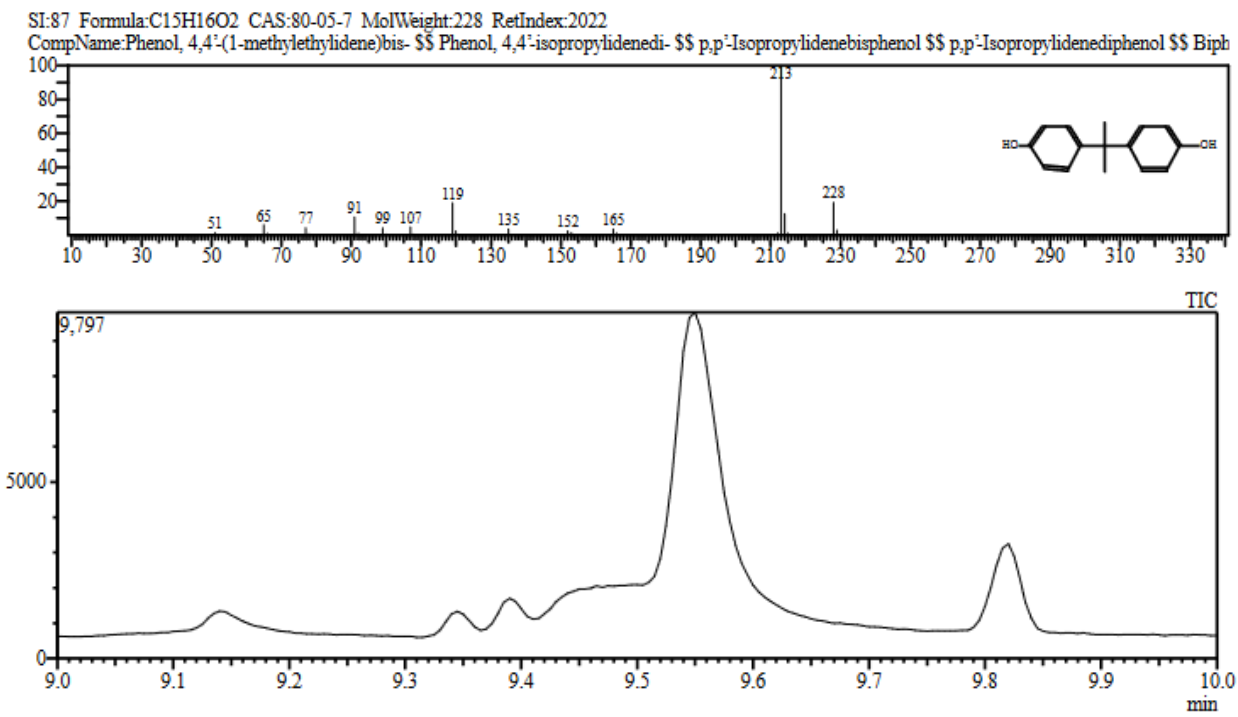
Table S1 - Physicochemical characterization of the synthetic sewage used as feed solution (FS) in the G-AnOMBR/MD

Parameter	Value
pH	7.7 ± 0.1
Electrical conductivity (µS cm^{-1})	1,055.1 ± 126.7
COD (mg L^{-1})	584.3 ± 21.4
P-PO_4^{3-} (mg L^{-1})	31 ± 0.25
N-NH_4^+ (mg L^{-1})	4.7 ± 0.82

Figure S1 – Examples of GC-MS chromatogram for the (a) BPA standard sample (100 mg L^{-1}), (b) $EGSB_{eff}$ (30 d), and (c) DT (30 d).



b)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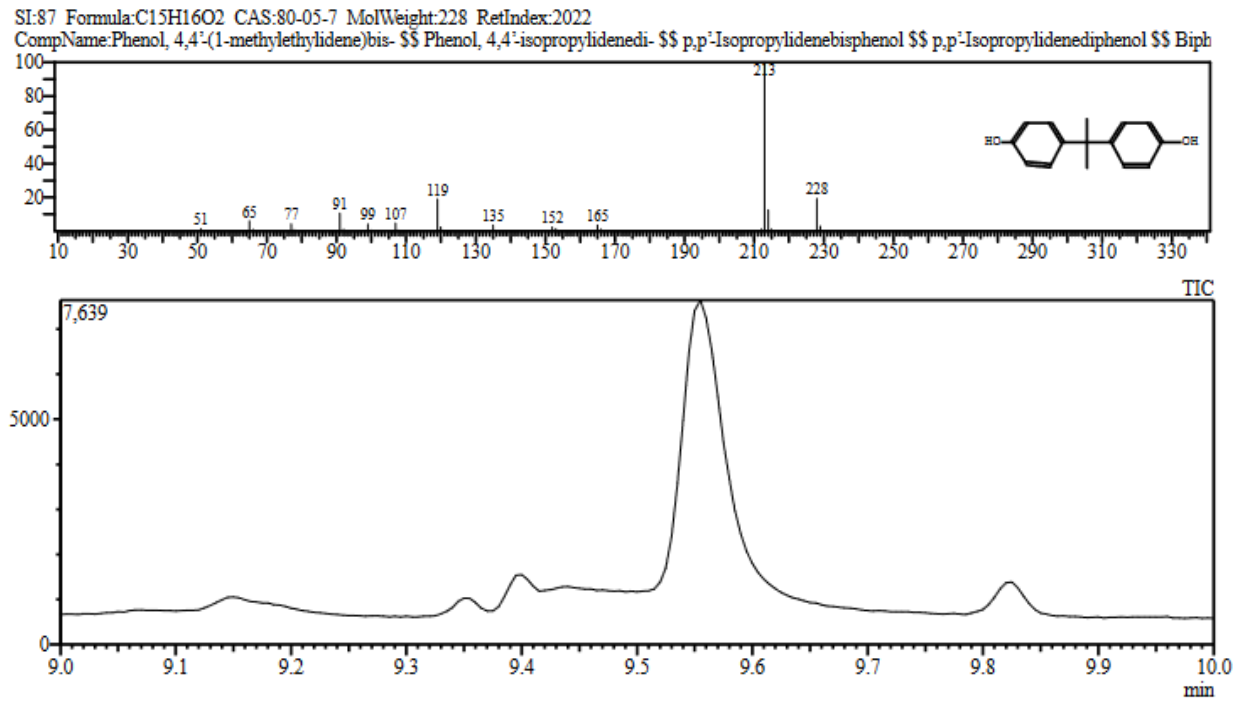
CompName:Phenol, 4,4'-(1-methylethylidene)bis- $$ Phenol, 4,4'-isopropylidenedi- $$ p,p'-Isopropylidenebisphenol $$ p,p'-Isopropylidenediphenol $$ Biph
213
228
119
TIC
9,797
min

c)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213
228
119
TIC
7,639
min

CHAPTER 6

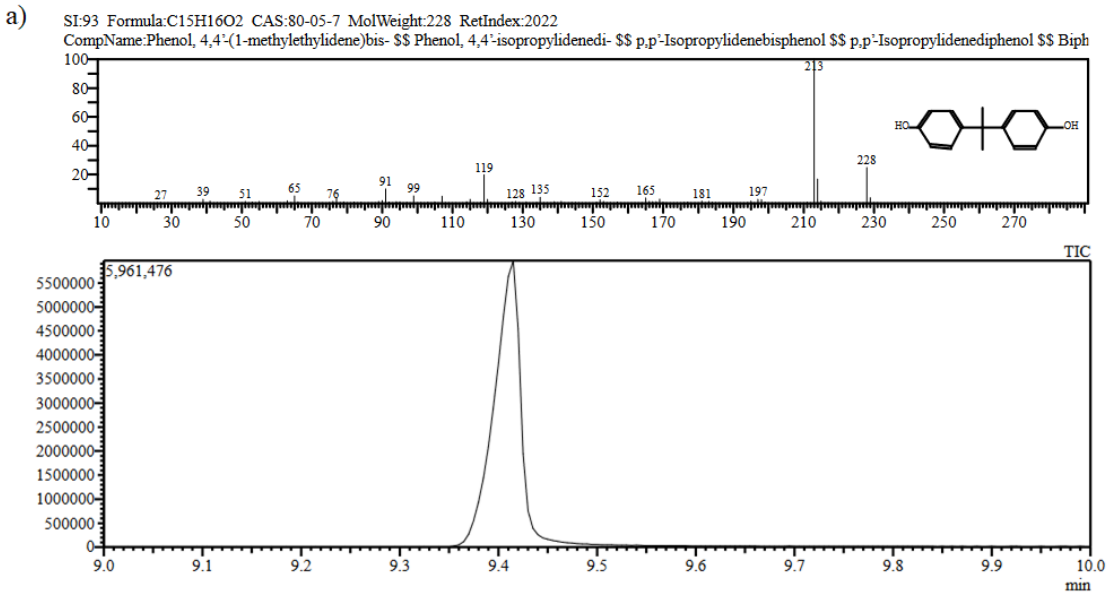
Table S1 - Composition of synthetic sewage.

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

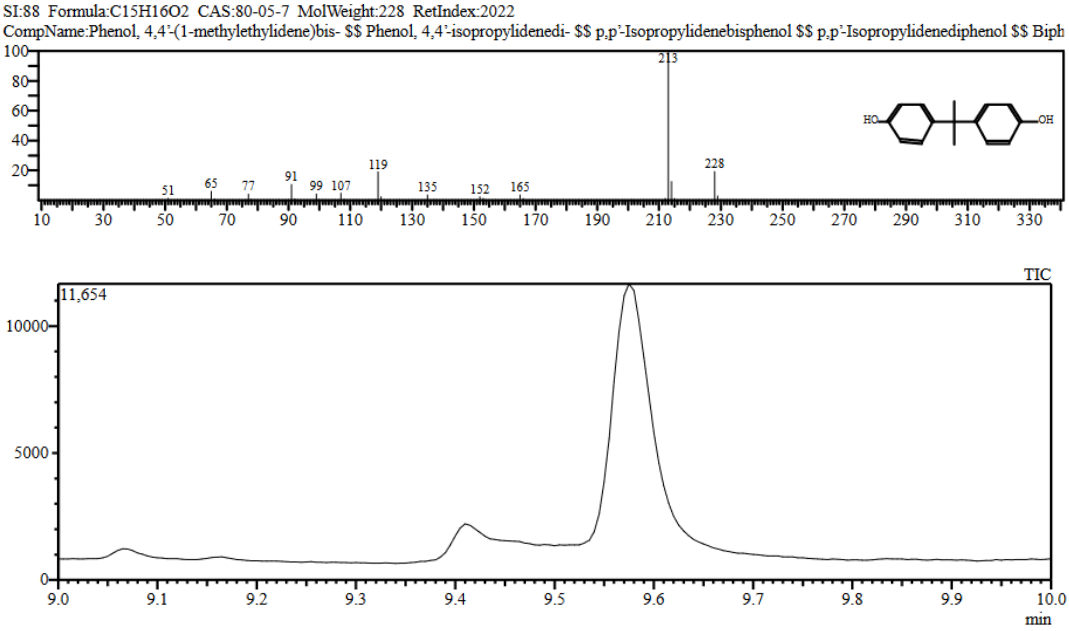
Table S2 - Physicochemical characterization of the synthetic sewage used as feed solution (FS) in the G-AnOMBR/MD

Parameter	Value
pH	7.3 ± 0.3
Electrical conductivity (µS cm^{-1})	1,051.8 ± 232.7
COD (mg L^{-1})	584.3 ± 21.4
DOC (mg L^{-1})	156.4 ± 31.1
P-PO_4^{3-} (mg L^{-1})	34.1 ± 2.8
N-NH_4^+ (mg L^{-1})	5.8 ± 2.2

Figure S1 – Examples of GC-MS chromatogram for the (a) BPA standard sample (100 mg L^{-1}), (b) $EGSB_{eff}$ (20 d), and (c) PT (20 d).



b)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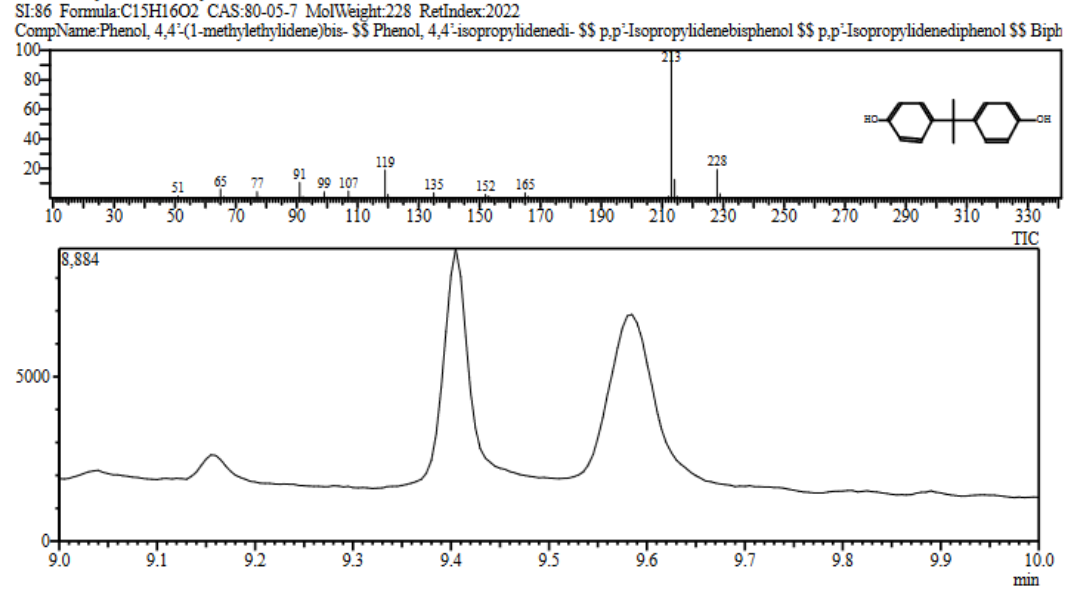
213
228
119
91
65
77
51
99
107
135
152
165
HO
OH
TIC
11,654
min

c)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213
228
119
91
65
77
51
99
107
135
152
165
HO
OH
TIC
8,884
min

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