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MANAGEMENT OF PHARMACEUTICAL MICROPOLLUTANTS IN URBAN WATERS: REDUCTION AND CONTROL STRATEGIES FOR THE REGION OF CURITIBA/PR

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"MANAGEMENT OF PHARMACEUTICAL MICROPOLLUTANTS IN URBAN WATERS: REDUCTION AND CONTROL STRATEGIES FOR THE REGION OF CURITIBA/PR"

Por

DEMIAN DA SILVEIRA BARCELLOS

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ABSTRACT

Pharmaceutical micropollutants are a latent problem in urban waters in large cities, which has received worldwide attention in the last decade. The lack of financial resources and the distant prospect of universal sanitation are two of the main arguments that have stalled advances in the field of pharmaceutical micropollutants management in emerging countries such as Brazil. In this study, the aim is to propose viable paths with technical, political, and economic feasibility for the management of pharmaceutical micropollutants in the urban waters of Curitiba. This investigation consists of different methodological approaches and is divided into four parts: 1) systematic review of 3,027 scientific documents to characterize the different management approaches worldwide and identify opportunities for developing countries; 2) prioritization through a workshop with 37 stakeholders from the pharmaceutical chain to identify the priority pharmaceutical micropollutants and the most crucial sectoral management initiatives; 3) literature review on the Blue-Green Infrastructure as a systemic solution for cities, discussing its potential to remove pharmaceutical micropollutants, its feasibility and possible scenarios for implementation; and 4) economic analysis of a complementary water treatment system to reduce concentrations of pharmaceutical micropollutants in the sanitation cycle. The main results of this investigation indicate that the management of micropollutants in the developing world is more dependent on social technologies, initiatives, and convergence of interests in networks formed by multiple actors involved in the chain of these pollutants. This approach debunks the myth of the inherent need for heavy investment or universal sanitation. Although there are engineering solutions with the technical feasibility to reduce pollution by pharmaceutical micropollutants in urban waters, these depend on a paradigm shift in urban planning and sanitation financing. In addition to public policies that bring these new precepts to the reality of cities, it is necessary to expand the role and responsibilities of corporations and countries that produce and disseminate pharmaceutical products.

Keywords: Environmental management. Urban waters. Pollution control. Emerging contaminants. Environmental governance.

RESUMO

Os micropoluentes farmacêuticos são um problema latente nas águas urbanas das grandes metrópoles, que tem recebido destaque mundial na última década. A falta de recursos financeiros e a distante perspectiva da universalização do saneamento são dois dos principais argumentos que tem imobilizado avanços no campo da gestão de micropoluentes farmacêuticos em países emergentes, como o Brasil. Neste estudo o objetivo é propor caminhos viáveis, com viabilidade técnica, política e econômica para a gestão de micropoluentes farmacêuticos nas águas urbanas de Curitiba. Essa investigação é constituída por diferentes abordagens metodológicas e dividida em quatro partes: 1) revisão sistemática em 3.027 documentos científicos para caracterizar mundialmente as diferentes abordagens de gestão e identificar oportunidades para os países em desenvolvimento; 2) priorização por meio de um workshop com 37 stakeholders integrantes da cadeia farmacêutica para identificar os micropoluentes farmacêuticos prioritários e as iniciativas de gestão setoriais mais importantes; 3) revisão de literatura sobre a Infraestrutura Azul-Verde como solução sistêmica para as cidades, discutindo seu potencial para remover micropoluentes farmacêuticos, sua viabilidade e possíveis cenários para implementação; e 4) análise econômica de um sistema complementar de tratamento de água para reduzir as concentrações de micropoluentes farmacêuticos no ciclo do saneamento. Os principais resultados desta investigação apontam que a gestão de micropoluentes no mundo em desenvolvimento é mais dependente de tecnologias sociais, iniciativas e convergência de interesses em redes formadas por múltiplos atores envolvidos na cadeia desses poluentes. Essa abordagem derruba o mito da necessidade inerente de investimentos pesados ou saneamento universal. Embora, existam soluções de engenharia com viabilidade técnica para reduzir a poluição por micropoluentes farmacêuticos nas águas urbanas essas dependem de uma mudança de paradigma no planejamento urbano e financiamento do saneamento. Além de políticas públicas que tragam esses novos preceitos para a realidade das cidades é preciso ampliar o papel e as responsabilidades das corporações e países que produzem e difundem os produtos farmacêuticos.

Palavras-chave: Gestão ambiental. Águas urbanas. Controle da poluição. Contaminantes emergentes. Governança ambiental.

LIST OF FIGURES

Chapter 1

Chapter 2

Chapter 3

Chapter 4

LIST OF TABLES

Chapter 5

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION

In a world that is already predominantly urban, the interactions between the urban phenomenon and the natural environment have caused profound changes in all environmental compartments. Cities resemble systems that receive the matter, energy, and information they need for their endogenous functioning in a concentrated way, returning their residues, noise, and heat diffusely. This process has impaired its vital functions progressively, delaying its regeneration and accelerating the ecosystem's overall degradation. The quality of water in urban rivers is no exception. In general, it goes through this process of continued degradation, serving as a recipient of many conservative or difficult-to-degrade substances, including chemical residues, whose ability to affect environmental processes has occupied the center of studies and discussions in the country's so-called developed.

The society that succeeded the “industrial city”, described by Lefebvre (2010, p 67-68), started to count on the comforts of the technological revolution that covered practically all areas of applied sciences, among them, the so-called “chemical revolution” (Colborn et al., 2002, p. 208). The "chemical revolution" was a period that began in the second half of the 20th century with the second world war. The expansion of the chemical industry characterized it by the transformation of modern living conditions, maximizing agricultural production, eliminating endemic pests, preventing and controlling diseases, and increasing human longevity, among other achievements. On the other hand, its conservative residues pollute the environmental matrices and mainly the river waters. In the long run, part of these residues can be incorporated into natural and recycled biogeochemical cycles, but in general, they have the effect of accumulating in the environment and negatively affect its functioning, causing dysfunctions and imbalances with consequences not yet entirely known. Among the synthetic chemicals, those produced by the pharmaceutical industry have an apparent ambiguity: they are necessary for human health, but their residues have a high potential impact in urban river waters, leading an increasing number of researchers to consider them as important markers in urban waters.

Since a great part of the water supply systems collects raw water in the rivers, traces of pharmaceutical substances in drinking water are already pointed out as possible drivers of the progressive drop in human reproductive health and in rivers and sewers related to the development of resistant pathogenic bacteria (Skakkebaek, 2010; Owen & Jobling, 2013; Kümmerer, 2009). The most common environmental effects of chronic exposure to drug residuals are chronic toxicity, genotoxicity, and endocrine interference (Kim & Aga, 2007; Halling-Sørensen et al., 1998; Kümmerer, 2009). Due to these risks to public health, as well as their environmental effects, the so-called developed countries where urban sanitation is already in the management model described by Tucci (2008) as a “sustainable phase”, have dedicated more attention to studies and, more recently, the control of these pollutants.

The alternatives for drug-pollution management and control in Brazilian urban waters are major challenges since this topic has not been addressed in countries with emerging economies (Bollmann et al., 2019, p. 661-664; Barcellos et al., 2019a, p. 151). Especially in Brazil, the incipient discussions that have started still have a sectorial character. The drug take-back program needs a sectoral agreement and intersectoral collaboration (Rebehy et al., 2019, Aquino et al., 2018). The disarticulation among the pharmaceutical sector, industrial sector, policymakers, academics, and sanitation sector (Barcellos & Bollmann, 2020). The environmental monitoring campaigns in Brazil are isolated, and Active Pharmaceuticals Ingredients (API) has not yet been identified (Barcellos et al., 2019b; Reichert et al., 2019). The research on the efficiency of drug removal in waters is generally carried out by academics working without cooperation and not considering what is feasible for Brazilian reality at the local level (Barcellos et al., 2019a, p. 143). These efforts are valid, but they are not systematic and linked, contrary to international experiences, which show the need for an integrated vision and a collective approach.

In the context of the sectorized management discussions and proposals that recently emerged in Brazil, this research intends to propose ways to manage pharmaceuticals in waters with a systemic view of the problem. Look ways to manage pharmaceuticals in water considering the entire drug production chain, the actors/processes involved, and the political and technical solutions to the problem is something that has not yet been done in Brazil and other developing countries. There is still little information regarding the actual situation of environmental contamination by pharmaceutical residuals and the solutions to this problem in the Brazilian case. Developed countries in Europe and North America have holistically managed and discussed this problem, but they have environmental, social, and economic conditions different from Brazil's. As a result, this is a new and unpredictable field to be explored in the national territory.

a. Research Questions

In Brazil, the management of pharmaceutical micropollutants is a controversial issue. Because the country is still far from an ideal scenario of universal sanitation, micropollutants are seen as future demands for sanitation management. The central defense for this argument is that the developed world only started to worry about this problem when it became economically and technically viable and the high costs needed to manage these pollutants. **Looking at the global context of pharmaceutical micropollutant management, are there possible alternatives for the developing world?**[1]

In Brazil, the priority drugs for managing urban waters are unknown according to stakeholder groups involved in this chain and the sectorial management initiatives feasible for these groups. The integration of these various perceptions, priorities, and the discussion of feasible management initiatives for the problem needs to be debated and synthesized with all managers. This is a way to start moving towards a technical and political solution to this issue. But, **can this approach, already carried out in Europe, also lead to solutions to this problem in Brazil?**[2]

Negotiations between the academy and the sanitation sector need to be initiated since advances in the mitigation/removal of pharmaceutical micropollutants in water depend on their cooperation. The academy needs to act collaboratively with the sanitation companies aiming at the real structural solutions necessary for the water/sewage treatments towards urban sustainability. However, **in a country where only 53% of the population has access to sewage collection and 83% to water supply systems (SNIS, 2018), are there already economically viable technical solutions for reducing or removing these compounds in urban waters?**[3]

b. Hypotheses

1. Pharmaceutical micropollutant management strategies are technical and expensive, seeming unfeasible for the developing world, above all, due to the economic disadvantages and the distance from the universalization of sanitation in these societies (Chapter 2);

[1] This research question is answered in chapter 2.
[2] This research question is answered in chapter 3.
[3] This research question is answered in chapter 4 and 5.

2. In the scenario of Curitiba city, sectoral planning, and disarticulation between governmental spheres concerning public and environmental health policies, do not yet allow for it to be possible to establish a consensus among stakeholders from different sectors on the priority pharmaceutical micropollutants for intervention initiatives (Chapter 3);
3. The sustainability of cities is naturally related to the management of pharmaceutical micropollutants and greater resilience to climate change. However, it is not possible to envision for the city of Curitiba systemic solutions capable of advancing simultaneously in these faraway two fields of environmental management (Chapter 4);
4. At full scale, there are still no technical and economic conditions for the application of treatments in the region of Curitiba for the reduction of pharmaceutical micropollutants from the water (Chapter 5).

1.1 OBJECTIVES

The general objective of this research is to **propose viable paths**, with technical, political, and economic feasibility, for the management of pharmaceutical micropollutants in the urban waters of Curitiba.

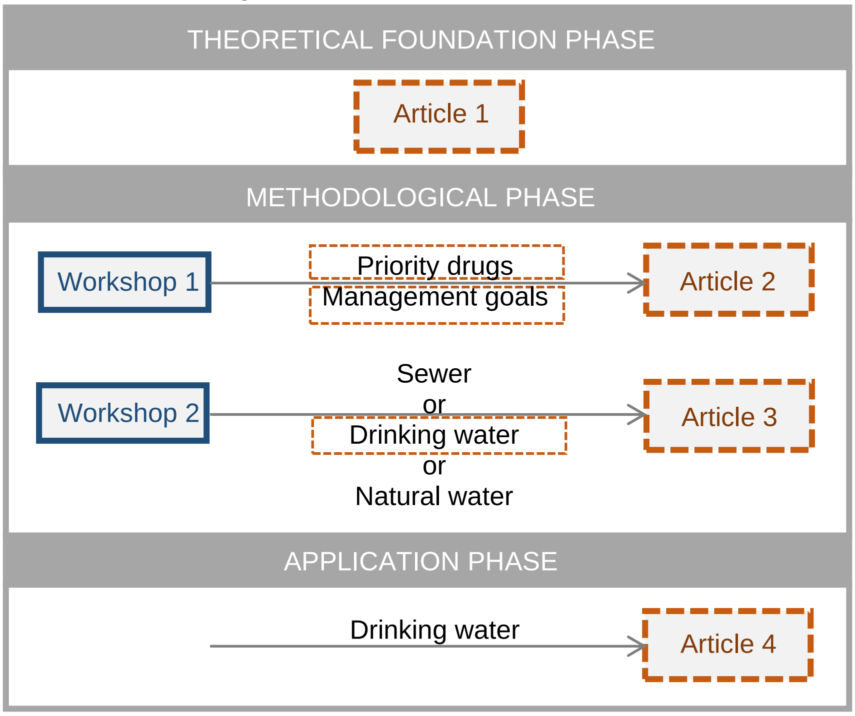
The specific objectives were defined as follows:

1. **Categorize approaches** used globally **and viable possibilities for developing countries in the management of pharmaceutical micropollutants** (Chapter 2);
2. **Identify the priority pharmaceutical micropollutants** for water management in the Curitiba region, from the perspective of the different stakeholders (academia, pharmaceutical sector, pharmaceutical industry, water industry, and policymakers) **and their management perspectives** (Chapter 3);
3. **Discuss Blue-Green Infrastructure** as a systemic alternative **to remove/reduce pharmaceutical micropollutants** from Curitiba urban waters (Chapter 4);
4. **Analyze water treatment solutions' technical and economic feasibility to remove/reduce drug residues** from urban waters in the Curitiba region (Chapter 5).

1.2 STRUCTURE

This research has six chapters. The first chapter is introductory and presents the research, showing the considered study design. Four chapters (from chapter 2 to 5) are related scientific articles (Figure 1) that meet the specific objectives, answering the research questions and allowing the hypotheses to be tested. The last chapter summarizes the research results, the ways of pharmaceutical micropollutant management for the Curitiba region, meets the general objective, bring the results of the research hypotheses, final considerations, and recommendations.

Figure 1. Structure of the research.



Chapter 2/ Article 1 has an <u>introductory</u> and <u>theoretical perspective</u> that presents several premises of this research, introducing the reader in-depth to the theme covered in the next chapters - the management of pharmaceutical micropollutants in urban waters. This article extensively reviews the scientific literature on idealized, planned, and executed management initiatives and strategies in developed countries (notably Europe and North America). This paper develops a macro-approach to manage pharmaceutical micropollutants composed of four micro-approaches, categorized from the global management context. We extract a series of opportunities to manage micropollutants in the developing world from this analysis. The objectives of this thesis were based on the assumptions described in this article -

the opportunities for managing pharmaceutical micropollutants for developing countries.

Chapter 3/ Article 2 is a targeting and prioritization article that brings a collective approach to management, which is often overlooked. Within the scope of this research, this is a methodological article since that indicates the towards of this study. After looking extensively at the literature (article 1), a management opportunity shown by developed countries is to unite the entire chain of stakeholders involved in the problem and seek a common agreement. This successful strategy held in Europe was one of the essential elements in making consistent progress in this direction. This article is the synthesis of a workshop with 37 stakeholders with an interface in managing pharmaceutical micropollutants in the region of Curitiba. At this event, the priority pharmaceutical micropollutants were established by consensus for intervention initiatives and sectoral management goals - for the water industry, pharmaceutical industry, academia, and the pharmaceutical sector. The event was planned with the support of specialized researchers in pharmaceutical micropollutants management from Glasgow Caledonian University (GCU)/United Kingdom, who are part of the pharmaceutical micropollutant management network in Europe and participated in the PILLS and noPILLS projects[4]. The event was also supported by the Paraná Sanitation Company (SANEPAR).

Converging sectoral management priorities across different sectors was a highlight in the workshop. These interfaces are promising aspects for management that can be explored collaboratively by the sectors involved. One of the points of convergence between the sectoral goals of academia and the water industry was to seek collaboratively viable alternatives for removing pharmaceutical micropollutants in water and sewage systems. A second workshop was held only with professionals from different departments of SANEPAR to discuss this point of the convergence of management goals between the academy and the water industry. This internal event was attended by eight professionals from different departments (water production,

[4] The PILLS and noPILLS projects were collaborative projects for the management of pharmaceutical micropollutants that included the participation of institutions from several countries in Europe. The PILLS project had a more technical approach (sewage treatments) and characterization (monitoring of polluting sources), however, its results showed the need to look at the entire pharmaceutical product chain. The PILLS project was succeeded by the noPILLS project, which brought a more educational approach involving the all population, specifically focusing on the rational use and the principle of precaution in the consumption of drugs, as well as the proper disposal of their residues to prevent them from reaching the waters.

research and innovation, sewage treatment and socio-environmental education). The meeting had the main of knowing which would be the targeting matrix priority (drinking water, natural water, or sewage) for the company in managing pharmaceutical micropollutants. This workshop intended to define with SANEPAR the direction of the research. In this second workshop, by vote, seven of the eight SANEPAR professionals prioritized the drinking water matrix, as they understand that it is the more accessible matrix to work with, and it has great importance for the company because it is directly linked to public health. This also considered that the sewage treatment coverage in Brazil is still deficient, and the universalization of this sanitary service is far from reality. However, one of SANEPAR's professionals defended the management of pharmaceutical micropollutants in sewage systems but focused on passive alternatives for treatment to remove them, such as constructed wetlands (CW).

Passive alternatives to remove pharmaceutical micropollutants are a real possibility and, depending on how they are used, can change the paradigm of city planning in Brazil. Towards the results of the discussions with SANEPAR, **Chapter 4/ Article 3**, like article 2, can be defined as methodological for being an unfolding of the methodological process of this research and pointing directions for an application stage. The directions and knowledge established by this chapter on filter gardens in urban riverbeds to reduce pollution by pharmaceutical micropollutants in Curitiba can be used in experimental and modeling studies. This article investigated and discussed the Blue-Green Infrastructure (BGI) to mitigate the problem of pharmaceutical micropollutants in urban waters. The use of BGI is not centered on a specific matrix - sewage, drinking water, or natural water - but focused on a systemic vision for this problem. The components of BGI can increase the resilience of cities to climate changes, making them less sensitive to water and improving their landscape quality. The entire background on the use of BGI in cities and their importance for the integrated management of water resources has been deepened with researchers from Deakin University/Australia who are experts on the subject.

Chapter 5/ Article 4 is an application article, which took the direction outlined by the first workshop with the 37 stakeholders and the second meeting with SANEPAR professionals. This paper seeks removal solutions, as it was the goals of the academy and water industry (1º workshop/article 3), for treatment alternatives in water supply systems to remove drugs (2º meeting). The article is an economic analysis implementation of a drinking water complementary treatment in the four main Drinking Water Treatment Plants (DWTPs) in Curitiba (which supply about 90% of the population served by the Integrated Water Supply System of Curitiba and Metropolitan Region - SAIC), to reduce pharmaceutical micropollutants. The collaboration and support of SANEPAR were essential for quantification and estimated of the costs of DWTPs and complementary systems.

1.3 RESEARCH METHODOLOGY

Although in Brazil, the territorial planning and management unit is the river basins for water resources management purposes (Brasil, 1997), urban planning and management generally use municipalities as a territorial unit. This conflict is particularly complicated in large cities permeated by several rivers with different functions, some used for public supply, others used for rainwater drainage, and others to receive urban wastewater. Municipal borders as a planning and management unit were considered most relevant for this study. Even though sometimes the river basins permeate only part of its territorial unit, municipal limits can provide a more comprehensive view of the possible and necessary management measures to control drug pollution in urban waters. The municipal borders would involve the urban rain drainage, wastewater, drinking water systems, and the city's urban environmental health. In contrast, only one river basin selection would probably be limited to one of these functions.

This investigation was used as a study area of Curitiba, the Parana State/Brazil capital. This city carries the legacy of having adequate urban organization among other large Brazilian cities (over 1 million inhabitants), approaching the standards established in the European cities. Curitiba has a worldwide recognized history of urban planning and management. It was the pioneer of the BRT (Bus Rapid Transit) urban transportation system in the 1970s, a system that is now widespread in the world's main cities. The capital of Paraná is also the Brazilian capital with the best basic sanitation in the country, with 94% of sewage coverage, 100% of treated water supply coverage, and 100% waste collection (SNIS, 2018). Recently Curitiba won several international awards in recognition of initiatives in favor of the environment and the quality of life of its residents: Clean Energy Project (C40 Cities Finance Facility, in 2018), Urban Agriculture Project (ODS Brasil, in 2018), Social Connectivity in the Health Sector (Latam Smart City Awards, in 2018), Inclusive Transport Project (Bloomberg Philanthropies, in 2018), among others. In this scenario, the city was selected because of the possibility of taking advantage of this orientation towards innovation in management technologies and environmental planning.

The urban rivers that permeate the city of Curitiba can be considered a model of what happens in large Brazilian cities. A large part of its rivers is channeled when they cross the urbanized area, receiving a sizeable organic load derived from domestic sewage, with a disorderly use and occupation of the soil and aimed at private interests, covering the most varied social stratum. This configuration also has similarities with several of the major urban centers globally since they generally grow around rivers and use their flow vector as a structural axis in the city's design (Baptista & Cardoso, 2013). On the other hand, Curitiba rivers have specific configurations of third-world urban rivers, such as Brazilians. In their course, the rivers of Curitiba come into contact with a great diversity of social and economic conditions population that coexists and disputes the city, and affected by precarious sanitary structures that result in water bodies with high levels of pollution[5]. These urban waters often end up entering water supply systems in diluted form.

Based on these assumptions, the research was divided into ten stages, which meet all specific objectives. The ten stages, the description of the stage, and its result can be seen in table 1, and in table 3 research methods are presented.

Table 1. Research steps

Objectives	**Stage**		**Description of stage**	**Chapter**
Background of research.	0	Introduce the research topic, describe pharmaceutical micropollutants' management experiences, categorize and present insights for developing countries.	A systematic review (Scopus and Web of Science) will be carried out about the pharmaceutical micropollutants management initiatives, which will be analyzed to obtain opportunities in this direction for developing countries, such as Brazil.	2
Categorize approaches used globally and viable possibilities for developing countries in the management of pharmaceutical micropollutants.	1			

[5] Although official data show that Curitiba has 94% sewage coverage, there are housing that are not connected to the public collection network, this is a citizen's obligation that must be fiscalized by the local government. Problems related to the collection network, especially in the old part of the city, also contribute to this situation. In these regions the collected sewage can go to the rain drainage network and reach rivers directly (this situation and the high concentrations of pharmaceutical micropollutants in Belém river, Curitiba main river, is described in detail in the chapter 4).

Identify the priority pharmaceutical micropollutants for water management in the Curitiba region, from the perspective of the different stakeholders (academia, pharmaceutical sector, pharmaceutical industry, water industry, and policy makers) and their management perspectives.	2	Identify 30 to 40 most used drugs in the region of Curitiba.	A literature review will be carried out on the pharmaceutical products that have already been monitored in the region and that are most used.	3
	3	Identify 50 to 60 stakeholders related to pharmaceuticals management in urban waters in the region of Curitiba.	A literature review and document analysis will be carried out to identify stakeholders.	
	4	Identify priority pharmaceuticals for urban water management according to stakeholders.	Two meetings will be held with 20 actors each to identify which are the five priority pharmaceutical products.	
	5	Identify feasible drug management initiatives for priority compounds according to stakeholders.	A meeting will be held with the group of 40 actors (who participated in the previous meetings) to learn about the feasible management initiatives for the priority compounds.	
Discuss Blue-Green Infrastructure as a systemic alternative to remove/reduce pharmaceutical micropollutants from Curitiba urban waters.	6	To know possibilities to reduce drug concentrations in Curitiba's urban rivers using Blue-Green Infrastructure.	A literature review will be carried out to verify the components of the Blue-Green Infrastructure that can be used to reduce the concentration of drugs in urban rivers.	4
	7	Discuss Blue-Green Infrastructure as a decentralized alternative to reduce pollution by micropollutants and make the city more resilient to climate change.	Using literature review data regarding the efficiency of Blue-Green Infrastructure to reduce pharmaceutical micropollutants, the possibilities of using this system in a decentralized manner will be analyzed and discussed.	
Analyze water treatment solutions' technical and economic feasibility to remove/reduce drug residues from urban waters in the Curitiba region.	8	Identify the priority matrix for the removal of drugs from the water.	Meeting with SANEPAR engineers to discuss technologies for removing drugs from water and defining the company's priority matrix (treated water, sewage, or natural water).	5
	9	To know the operational costs and implementation of technologies for and reduction of pharmaceutical micropollutants in treatment systems	Seek from SANEPAR the operating and implementation costs of water treatment systems capable of reducing drug pollution.	
	10	Analyze the full-scale economic and technical feasibility of technologies to remove/reduce pharmaceutical micropollutants in urban waters	It is analyzed and discusses the technical-economic feasibility of implementing a complementary treatment system in DWTPs in the region of Curitiba to reduce the concentrations of pharmaceutical micropollutants in drinking water.	

Table 2. Research methods

Article	Phase	Methods	Techniques	Journal
Management of pharmaceutical micropollutants discharged in urban waters: 30 years of systematic review looking at opportunities for developing countries	Exploratory, Descriptive and Analytic	Indirect information search - bibliographical and documentary	Literature review	Science of the Total Environment (Published)
Priority pharmaceutical micropollutants and feasible management initiatives to control water pollution from the perspective of stakeholders in metropolis of southern Brazil	Exploratory, Descriptive and Analytic	Indirect information search - bibliographical and documentary research - and direct information search	Literature review and workshop with stakeholders	Integrated Environmental Assessment and Management (Published)
Blue-Green Infrastructure in cities: climate change adaptation and reducing water pollution by pharmaceutical micropollutants	Exploratory, Descriptive and Analytic	Indirect information search - bibliographical and documentary	Literature review	Revista de Gestão de Água da América Latina (Published)
Economic impacts of complementary treatments for reducing pharmaceuticals in metropolitan drinking water in southern Brazil	Exploratory, Descriptive and Analytic	Indirect information search - bibliographical and documentary research - and direct information search	Literature review and economic analysis of implementation	In revision with authors

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CHAPTER 2: MANAGEMENT OF PHARMACEUTICAL MICROPOLLUTANTS DISCHARGED IN URBAN WATERS: 30 YEARS OF SYSTEMATIC REVIEW LOOKING AT OPPORTUNITIES FOR DEVELOPING COUNTRIES

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ABSTRACT

Pharmaceutical micropollutants' contamination of urban waters has been studied globally for decades, but the concentration of innovations in management initiatives is still in developed economies. The gap between the locus of innovations in pharmaceuticals and the relative stagnation in less developed economies to manage waste originating in this activity seems fruitful for investigations on innovation in integrated micropollutant management strategies. These tensions allow for advances in current knowledge for environmental management and, particularly, finding solutions for the contamination by pharmaceutical micropollutants of urban water bodies in developing countries. We aim to list the main strategies for managing pharmaceutical micropollutants discussed to point out opportunities for developing countries to advance in this direction. Methodologically, we conducted a systematic literature review from 1990 to 2020, covering 3,027 documents on "pharmaceutical micropollutants management." The framework formed by the macro-approach to integrated management operationalized by the dimensional micro-approaches: technical, organizational, community, and governmental allowed us to understand that (1) the management of pharmaceutical micropollutants tends to occur through a technical approach centered on the removal of aquatic matrices, green chemistry, and urine diversion; (2) management with an organizational approach has enabled removing drugs from water bodies by drug take-back program, collaborative projects, drug use reduction, and better organizational practices; (3) the community approach have helped minimize this type of pollution by reducing the consumption of medicines and the proper destination for medicines that are no longer in use. Finally, the government management approach emerges as a source of legal, economic, and informational instruments to reduce pollution by pharmaceutical micropollutants. Furthermore, these management approaches allowed us to identify 15 opportunities for possible adjustments for developing societies. These opportunities can be promising for practices and research and, in the medium term, contribute to minimizing pollution by pharmaceutical micropollutants in urban waters.

KEY-WORDS: Pharmaceutical micropollutants. Environmental management. Urban waters. Pollution control.

1. INTRODUCTION

The technological revolution of the 19th and 20th centuries impacted all scientific and practical knowledge areas practically, generating solutions and new problems. In this context, the “chemical revolution” (Colborn et al., 1996) started in the mid-twentieth century had a profound impact on environmental pollution, mainly due to the expansion of the production of synthetic chemical agents. In health, the emergence of the pharmaceutical industry was essential for the sanitary revolution based on large-scale drug production. The expansion of disease prevention and control has impacted life expectancy as a feasible reality for most nations. On the other hand, the growing generation and diffuse global distribution of residues originating from medicines adversely impact environmental matrices. The sharpening of the perception of these impacts occurs as increasingly more precise methodologies make it possible to determine the concentration levels of chemical pollutants in water. This deepening of knowledge allows increasing the relationship between pharmaceutical residues, generation of adverse environmental effects, and health risks. At this point, the drug literature is abundant in pointing out, for example, chronic toxicity, genotoxicity, and endocrine interference as effects of drug residues carried to aquatic environments (Halling-Sørensen et al., 1998; Kim and Aga, 2007; Kümmerer, 2009).

As collective impacts, investigations show the traces of pharmaceutical substances, as female sex hormones (estrone, ethinylestradiol and estradiol), as proven endocrine disruptors in aquatic ecosystems and potential drivers of the progressive decline in human reproductive health (Kidd et al., 2007; Skakkebaek, 2010; Gilbert, 2012; Jobling and Owen, 2013). While, the traces of antibiotics in the environment are related to the increase in the occurrence of resistant pathogenic bacteria (Kümmerer, 2009; Gilbert, 2012; Caban & Stepnowski, 2021). Since the mid-1990s, these problems have been driving studies on pollution by pharmaceutical micropollutants in aquatic environments (Kümmerer, 2009; Qian et al., 2015; Tiedeken et al., 2017). Currently, the amount of scientific material published is already considerable, but the focus of the reports is more to show efforts to manage this type of pollution in economically developed countries (Eggen et al., 2014; Bieber et al., 2018; Ingold et al., 2018; Reichert et al., 2019; Barcellos et al., 2020) and advances in artifactual technologies that mitigate the effects of this type of pollution.

Studies on the characterization, prioritization and management of pharmaceutical micropollutants are beginning to emerge in developing countries (Fernandez et al., 2015; Archer et al., 2017; Guo et al., 2017; Reichert et al., 2019; Böger et al., 2021). However, these studies tend to present a vision more focused on technical alternatives for removing these elements from water bodies, which does not seem to be very different from the past prescriptions to face this problem in the context of today's more developed economies. Alternatively, the state-of-the-art is bringing discussions, research, and applications of other management strategies from a holistic view on opportunities for reducing pollution by pharmaceutical micropollutants throughout the production chain (PILLS, 2011; Helwig, 2018; Caban & Stepnowski, 2021). These strategies developed in different contexts seem especially viable for societies with more fragile economies (Shalini et al., 2010; Udert et al., 2015; Pereira et al., 2017; Ariffin & Zakili, 2019; Barcellos et al., 2020), but with the need for some changes to adjust to the particularities and availability of resources locations. In different contexts, one of the common obstacles to advancing in the control of pharmaceutical pollution in waters has been the lack of information about these management and control strategies or the precipitate realization of the impossibility of application due to poorly understood local restrictions, such as link of the management to high costs or the requirement for universal sanitation.

In order to identify and analyze pharmaceutical micropollutant management opportunities specifically for developing countries, this systematic review investigates studies and management strategies over the thirty years of structuring this field of studies (1990-2020). Water pollution by pharmaceutical waste has deservedly been the target of several systematic reviews (e.g., Tiedeken et al. 2017; Urbina et al., 2018; Nassour et al., 2019; Rabello et al., 2019; Lyu et al., 2020), but none of these reviews dealt with the management of pharmaceutical micropollutants, indicating a significant gap in scientific knowledge. We aim to list the main strategies for managing pharmaceutical micropollutants discussed to point out opportunities for developing countries to advance in this direction. Our emphasis is on pharmaceuticals used by humans, the primary source of urban pollution by pharmaceutical micropollutants (Caban & Stepnowski, 2021).

2. METHOD

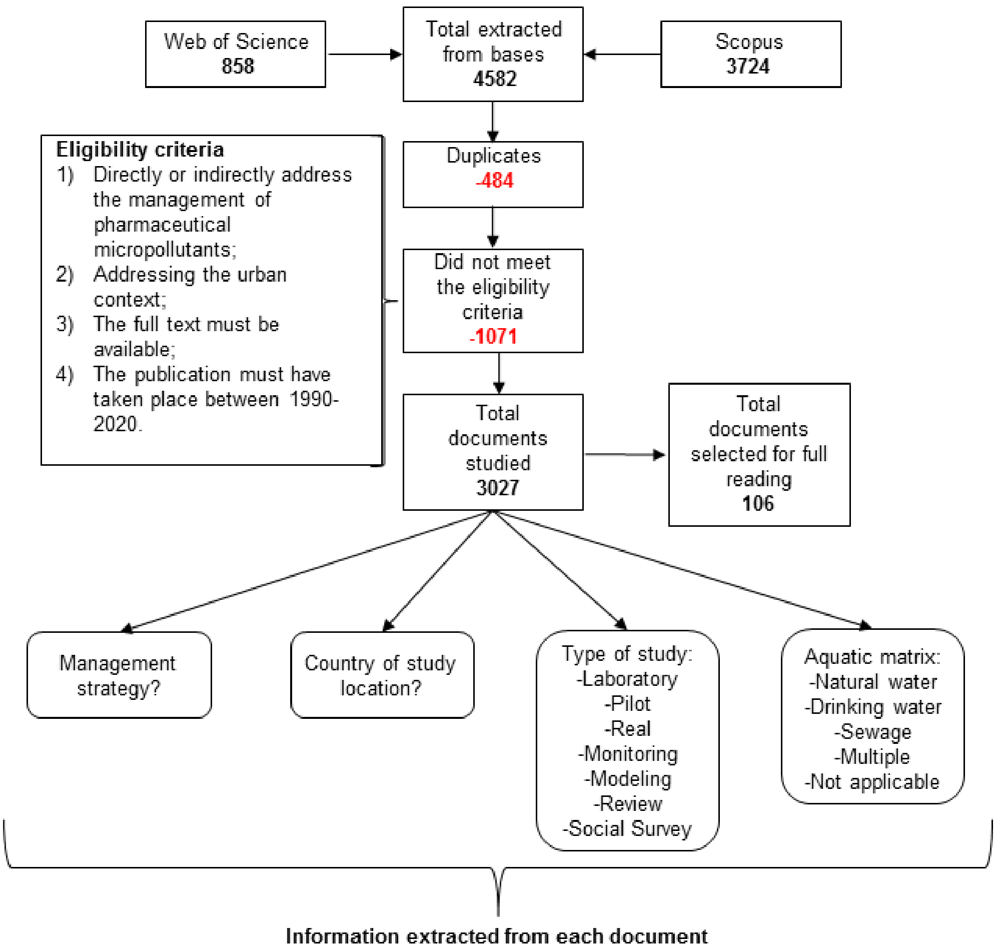
This systematic review seeks answers to four of the following research questions: Which aqueous matrix (supply water, sewage, and natural water) has prioritized studies on removing pharmaceutical micropollutants from water? What are the main control measures emphasized by pharmaceutical micropollutant management studies? What are the initiatives, and who are the stakeholders involved globally in managing pharmaceutical micropollutants? What are the management alternatives that could be feasible for controlling pharmaceutical micropollutants in developing countries?

The research protocol resulted from an adaptation of the Center for Evidence-Based Conservation's (CEBC) "Guidelines for Systematic Review on Conservation and Environmental Management" (Pullin and Stewart, 2006, Tiedeken et al., 2017). The research covered the period from 1990 to 2020, covering practically the entire evolution of investigations into pharmaceutical pollution, whose infancy is in the 1990s (Qian et al., 2015). The search was conducted by topics in Scopus and Web of Science databases, with searches performed with the combination of the following terms: "management AND pharmaceutical* AND water*". These searches covered any language and all types of scientific documents (books, book chapters, conference proceedings, and editorials).

The download of basic information (title, year of publication, authors, abstract, keywords, citation, and affiliation) from the databases to Microsoft Excel allowed the removal of duplicate documents. The analysis of the documents took place in three stages: (1) reading the title and abstract to verify if the document met the eligibility criteria (Figure 1) ; (2) reading of the title, abstract, keywords, and methodology to categorize documents based on management strategy, country of study, type of study (lab, pilot, monitoring, social research, modeling, and review), and identify the aquatic matrix focused on the study (natural water, supply water, and sewage); (3) complete reading of selected documents to describe the management strategies addressed.

The selection of full-reading documents included those dealing with integrated management strategies or brought an innovative perspective compared to conventional ones. The criteria for characterization of integrated management approaches were the solutions built to reduce such micropollutants in water, opening up opportunities throughout the production chain with its processes and actors. The counterpoint for delimiting the integrated approaches was the conventional approach, seen as strictly technical, generally excessively onerous, with practices or prescriptions for removing pollutants at the end of the water and sewage treatment process.

Figure 1. Sequential diagram of the systematic review



3. RESULTS AND DISCUSSION

Although the intensification of studies on pharmaceutical micropollutants took place in the 1990s, those about managing these elements did not exceed the annual average of ten until 2000. Until 2008, this number was less than one hundred, reaching 300 in 2018 (Figure 2). In the early 1990s, the management perspective was more concerned with removing drug residues in the effluents of pharmaceutical industries (e.g., Orhon et al., 1990; Seif et al., 1992; Frankin et al., 1992; Gulyas et al., 1995). In the second half of that decade, publications on monitoring pharmaceutical micropollutants gained intensity and breadth, starting to address the environment in general, domestic, hospital, and industrial effluents (e.g., Svenson et al., 1996; Kümmerer et al., 1998; Ahel et al., 1998; Buser et al., 1999). The integrated approach to the management of pharmaceutical micropollutants began to gain strength from the mid-2000s, with the inciting issues related to the environmental effects of pharmaceuticals in aquatic environments (e.g., Gross et al., 2004; Balmer et al., 2005; Lin & Reinhard, 2005; Reemtsma et al., 2006). At that time, discussions also arose about legal instruments to control this type of pollution (e.g., O'Brien & Dietrich, 2004; Frimmel, 2006; Adler et al., 2008; Fuerhacker, 2009), especially in the European Union, as well about studies on urine diversion as an alternative to reduce pharmaceutical pollution (e.g., Lienert et al., 2007; Winker et al., 2008; Larsen et al., 2009; Pronk & Koné, 2009). Another emerging question was about environmental drug classification systems to support physicians and patients choosing drugs with less polluting potential (e.g., Wennmalm & Gunnarsson, 2005; 2009; Oldenkamp et al., 2014). The consolidation of the integrated management approach with fundamental contributions to the management of drug micropollutants took place at the end of the years 2000 (Bound and Voulvoulis, 2005; Doerr-MacEwen and Haight, 2006; Lienert et al., 2007; Daughton & Ruhoy, 2008; Joss et al., 2008; Kümmerer, 2009).

Despite these advances and being consolidated in successful practices, the integrated approach to the management of pharmaceutical micropollutants still has a secondary perspective as a research field. Evidence of this is that 52% of management studies carried out between 1990 and 2020 dealt with removing aquatic matrices through water or sewage treatment. Another 37% dealt with the characterization, which is not a control step, but a diagnostic step for the control measures (Figure 3). Studies on management have reached greater intensity since 2000, with investigations on removal and characterization. The prioritized matrix has been sewage, with 48% of the investigations. Then comes multiple matrices (drinking water, natural water, and sewage), with about 28%, followed by natural water, with about 15% (Figure 4). About 4% of these studies are not directly related to an aquatic matrix, dealing, for example, with legislation or environmental classification systems for medicines. Drinking water ranks last, with only 2% of publications. The center of management attention was on the entry of pharmaceutical micropollutants into the urban water cycle and technologies to remove such pollutants from sewage systems. Most of these surveys were carried out in the laboratory (Figure 5), reaching 30%, while those on a full scale and pilot reached only 5% each. Monitoring and review were the subjects of 26% and 14% of the studies, respectively.

Figure 2. Studies related to the management of pharmaceutical micropollutants in the period 1990-2020, per year.

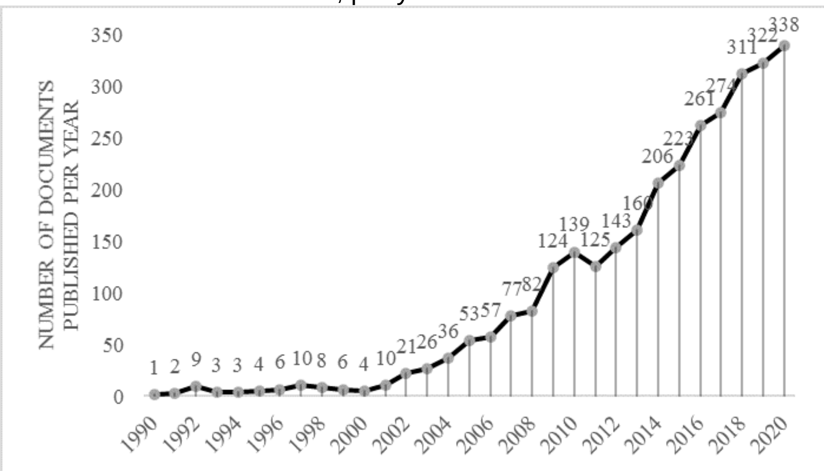


Figure 3. Pharmaceutical micropollutants management by category on the period 1990-2020.

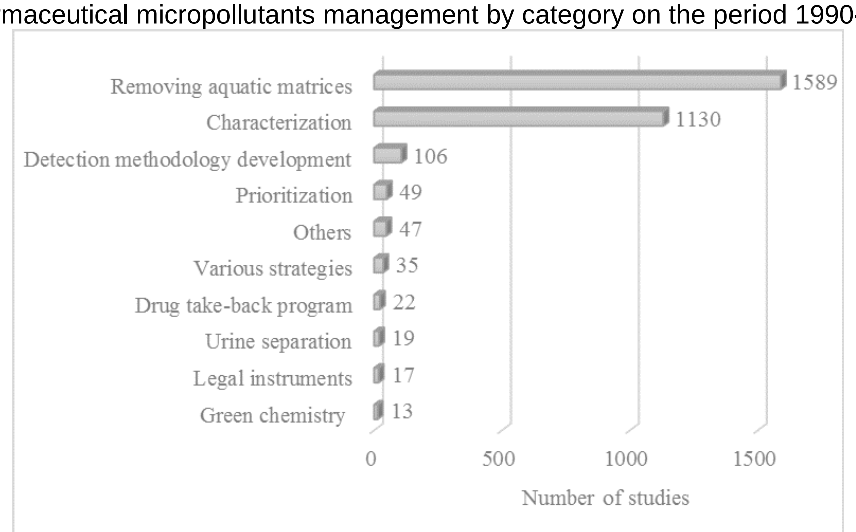
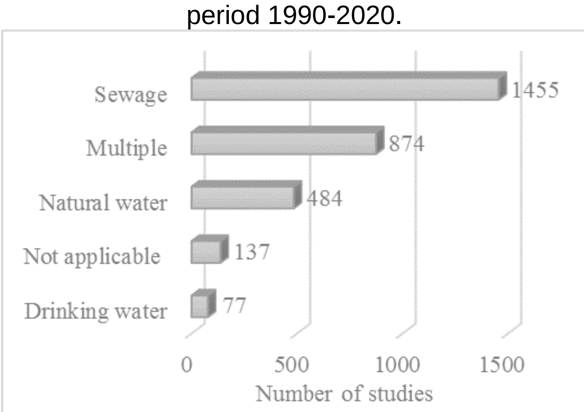
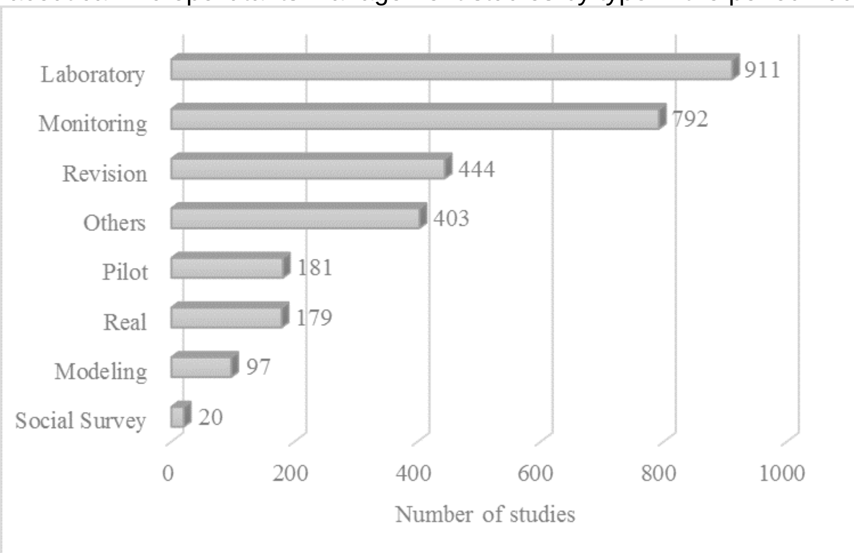


Figure 4. Pharmaceutical micropollutants management studies by aquatic matrix focused on the period 1990-2020.



Research on the management of pharmaceutical micropollutants predominates in regions with more developed economies, with exceptions being China, Brazil, and India (Table 1). Among the fifteen countries with the most publications on the integrated approach to managing pharmaceutical micropollutants, eight are in Europe. Out of 106, 64 publications on this management perspective are from the European continent and another 26 from North America. The USA prevailed with 23 published documents, followed by 22 German and 11 Swiss publications. Two Chinese studies deal with eco-pharmaco-vigilance (EPV) and the other with green chemistry. In the case of Brazil, both deal with the drug take-back program, with one of them bringing various management strategies. Among the Malaysian documents dealing with drug take-back, one on legal instruments for controlling water pollution and another on the risk management of pollution by pharmaceutical micropollutants.

Figure 5. Pharmaceutical micropollutants management studies by type in the period 1990-2020.



Of the total number of documents published on the integrated management of pharmaceutical micropollutants, only 14% originates in developing countries: China (3), Brazil (3), Malaysia (3), India (2), South Africa (1), Colombia (1), Romania (1) and Lebanon (1). In these countries, integrated management strategies seem to show promising results; but discussions persist in the idea that the management of micropollutants is necessarily an onerous and unfeasible field for the economic reality experienced. Integrated management is considered secondary to the search for some approximation with the universalization of sanitation services. Although there is no denying that this classic view can contribute from a practical point of view, it is essential to advance in understanding the potential of strategies centered on the integrated management of pharmaceutical micropollutants and how they can contribute to the context of emerging countries.

Table 1. Documents published by the fifteen countries with more studies on the topic.

Country	**Total/(%) of studies**	**Total/(%) of studies with the integrated approach of management**
China	453 (14.9)	3 (2.8)
United States	434 (14.2)	23 (21.7)
Spain	253 (8.3)	2 (1.8)
Germany	213 (7.0)	22 (20.7)
Canada	131 (4.3)	1 (0.9)
India	117 (3.8)	2 (1.8)
France	104 (3.4)	0
Italy	93 (3.0)	1 (0.9)
United Kingdom	87 (2.9)	6 (5.7)
Switzerland	71 (2.3)	11 (10.4)
Portugal	68 (2.2)	2 (1.8)
Australia	66 (2.2)	1 (0.9)
Brazil	65 (2.1)	3 (2.8)
South Korea	65 (2.1)	0
Sweden	62 (2.0)	**5 (4.7)**

3.1 Integrated approaches to managing pharmaceutical micropollutants in the world

There are several attempts to classify pharmaceutical micropollutant management strategies from an integrated management perspective. However, this has been a difficult task because the management of these pollutants involves a wide range of stakeholders in the pharmaceutical sector chains. Overcoming this difficulty seems to have been initiated by the European Start project (Kümmerer, 2007; 2009; Titz & Döll, 2009), which divided these strategies into three groups: (1) *technical approach* to advanced treatments with time to reduce pollution short to medium term;

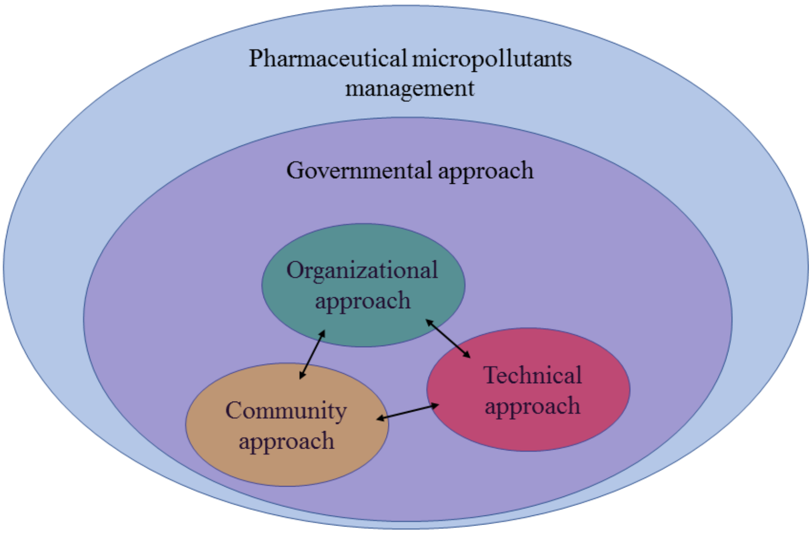
(2) *approach of educating and training* consumers, vendors, physicians, and others involved to reduce pollution in the medium term; and (3) *approach of developing environmentally benign compounds* to replace current damage-causing and health-hazardous compounds, with long-term pollution reduction time.

In this line of proposing solutions, Klatte et al. (2017) used the time to reduce pollution as a typology to classify pharmaceutical micropollutant management strategies. The European project noPILLS listed these strategies in seven phases of the production chain of these products (noPILLS, 2015). Following a similar line to this project, Kümmerer (2009) separated the opportunities to reduce the entry of drugs into the environment by professional categories involved in the production, distribution and consumption cycle of pharmaceutical products. Keil et al. (2008) separated the solutions to reduce pollution into three spheres: drug development, handling medications, and emission control in urban water management. Blair (2016) has defined these strategies in two groups: the end-of-pipe strategies (sewage and water treatments) and the other strategies, which have been under-emphasized. The classification proposed by Talib and Randhir (2016, 2017) considers three categories of strategies, with structural and non-structural approaches. The approach at source, such as urine diversion, green chemistry, conscious consumption, among others; the transfer approach, that is, in river-basin flows, such as wetlands, riparian vegetation, release limits, among others; and the sink level approach, with water and sewage treatments to remove these compounds.

In the present investigation, a conception of a new macro-approach for managing pharmaceutical micropollutants occurred through the composition of dimensional micro-approaches, which may overlap (Figure 6). These dimensions are based on the type of approach to the problem and the characteristics of the driving stakeholders. The definitions of these micro-approaches are as follows: (1) *technical* includes water and sewage treatments, urine diversion, and green chemistry; (2) *organizational* includes collaborative networks for management and initiatives to reduce pollution within organizations (NGOs, unions, industries, companies, hospitals, health and commerce facilities); the (3) *communitarian approach* includes the efforts of the population and professionals acting individually; and (4) *governmental* mainly involves public policies materialized by economic, legal, and informational instruments for the three approaches already mentioned, thus permeating the three previous approaches.

Each of these dimensional micro-approaches has its own relatively well-defined scope for the management of pharmaceutical micropollutants, as well as space for intersections between them. For example, the organizational and community interface has an interface, as occurs in reverse logistics initiatives for household medicines and reduced drug consumption. The technique has an interface with the organizational one, for example, in networks of researchers in collaborative projects for studies on the removal of these compounds from water. As for the government, it is not necessarily the government that induces management initiatives in other spheres of action since, in many cases, these efforts start in organizations and communities for later dissemination to other fields. A central aspect is an ascending and descending flow between these four dimensional approaches, which gives them a multilevel nature within the scope of the macro-approach of pharmaceutical micropollutants management.

Figure 6. Approaches for pharmaceutical micropollutants management



Based on this macro approach to micro-dimensional approaches, this research report advances to bring discussions, research, and practices in different global contexts from the selected published documents (106 documents).

3.1.1 Technical approach

The technical approach includes all ways of dealing with water pollution by pharmaceutical products when the solution involves technical-specialized knowledge and artifactual technologies. The practical application of this approach has substantial limitations even in more developed economies requiring high investments to implement initiatives with both short-term (e.g., water and sewage treatments or urine diversion) and long-term (e.g., green chemistry) results (Joss et al., 2008; Kümmerer, 2009 and 2010; Hrkal et al., 2019). Under this approach, treatments to remove drug micropollutants from water have merited many empirical investigations and comprehensive systematic reviews (e.g., Lajeunesse et al., 2012; Mohapatra et al., 2014; Taheran et al., 2016; Mirzaei et al., 2017). This research emphasizes alternative aspects of management linked to multidisciplinary knowledge, which have been relatively little studied and may offer opportunities for developing economies.

3.1.1.1 Removal from water

To avoid urban pollution in the hydrological cycle there is an urgent need to systematically track the leaks in sewage systems, find the intentional introduction of wastewater without treatment, investment in sewage systems to reduce the malfunctions (Caban & Stepnowski, 2021). Indeed, these are primary measures, as the universalization of sanitation, that any technical approach that focuses on removing pollutants in the urban water cycle must advocate. In the pharmaceutical micropollutant management strategies group, water/sewage treatments are the most studied in the scientific community and disseminated by the media, with about 28% of the reports, as shown by a survey carried out in the USA (Blair et al., 2017). The modernization of effluent treatment technologies carried out in the United States, Canada, and the European Union has a structural nature and a focus on contaminants (heavy metals, pathogens, and nutrients) and, at the same time, reduced environmental contamination by pharmaceutical residues (Doerr-MacEwen and Haight, 2006). In the European Union, Germany has tertiary level sewage treatment processes and fourth level for cases of removal of micropollutants from some plants (Jobling and Owen, 2013). Although it is possible to identify essential efforts to modernize WWTPs to remove micropollutants, mainly in Europe (Switzerland and Germany), these advanced treatments are still rare (Eggen et al., 2014; Bieber et al., 2018). The feasibility of these advanced treatments has generated significant discussions, especially considering economic issues as they involve high costs (Jones et al., 2007; Joss et al., 2008; Igos et al., 2012; 2013; Hrkal et al., 2019; Baresel et al., 2019).

The analysis of the life cycle of advanced treatments to remove pharmaceutical micropollutants shows still little significant gains because these systems depend on high consumption of chemical products and high energy consumption (Igos et al., 2012; Mousel et al., 2017). In decentralized stations, such as hospitals, after-treatments with ozone and activated carbon are more feasible than UV treatment. However, decentralized treatment does not seem adequate to remove pharmaceutical micropollutants in the urban water cycle (Igos et al., 2012;2013) because the central problem is in the environmental performance of post-treatments, which are unfeasible in centralized WWTP. Decentralized hospital stations have more optimization advantages when treating compounds other beyond pharmaceuticals, such as nutrients and metals (Igos et al., 2012;2013). The study of the life cycle of post-treatments shows that, among the four alternatives studied (solar photo-Fenton, ozone, nanofiltration, and granular activated carbon), nanofiltration followed by granular activated carbon has the lowest impacts (Zepon Tarpani & Azapagic, 2018). Implementing a new stage in the WWTP implies an increase in energy demand, lower with granular activated carbon than powdered activated carbon and ozone (Mousel et al., 2017). In addition to not being sustainable in the long term, the implementation of technologies specifically focused on micropollutants still tends to be economically unfeasible (Baresel et al., 2019).

The economic limitations for implementing quaternary treatment systems are illustrated, for example, by the case of the Czech Republic's WWTP to remove pharmaceutical micropollutants, which would generate an estimated 15% increase in water and sewage tariffs. A sociological survey pointed out that the values would be higher than the 10% increase in tariffs, which would be acceptable to the local population (Hrkal et al., 2019). In the case of Switzerland, the estimate of after-treatments was 5 to 20 euros per person/year, with feasibility for cases of low sewage dilution (Joss et al., 2008). In each country, region, and even WWTP, the environmental and economic performances present particularities and economic limits of the population willing to bear these costs. Nevertheless, the modernization of the WWTP and the requirements for the removal of micropollutants seems inevitable However, it is essential to address environmental and economic sustainability, considering a broader range of pollutants and improvements in advanced treatment options to increase their viability (Baresel et al., 2019).

As for the intensity of the modernization, the projects can go through a simple reconfiguration of current WWTP, such as increasing the hydraulic sludge detention time in aerobic systems to obtain greater efficiency in the general treatment and reach levels similar to those of advanced systems in drug removal. The challenge of these projects is not to significantly increase the cost and energy demand (Clara et al., 2005; Jones et al., 2007; Yu et al., 2009). The increase in the hydraulic sludge detention time has good levels of efficiency in removal and stability of several drugs and high rates for nitrogen removal (Clara et al., 2005; Yu et al., 2009). UV absorbance at 254 nm (UVA254) is a methodological innovation for evaluating removal efficiency that facilitates and reduces costs. Studies show that the reduction in absorbance at this wavelength is equivalent to the removal of pharmaceutical micropollutants and that it is possible to estimate their average removal rate (Wert et al., 2009; Nanaboina & Korshin, 2010; Zietzschmann et al., 2014; Chon et al., 2015). The anti-inflammatory drug ibuprofen and the anticonvulsant carbamazepine are emerging as indicators for some classes of micropollutants, with the potential to reduce removal costs (Jekel et al., 2015). In Germany and Switzerland, which implement advanced treatment systems, some substances were selected as indicators to assess the efficiency of removing groups of emerging contaminants (Bieber et al., 2018).

Green technologies to treat water are also possibilities under discussion to remove micropollutants from water, with multiple benefits for cities and greater public acceptance when faced with traditional alternatives (Schröder et al., 2007; Verlicchi & Zambello, 2014; Talib & Randhir, 2017; Franks et al., 2019). Technically, these technologies efficiently decompose organic pollutants in low concentrations, remove various combinations of pollutants, avoid chemical substances into the environment, and be applied with low operational and implementation costs on a small and large scale (Schröder et al., 2007). Constructed wetlands are among the most promising green technologies, with an efficiency equivalent to conventional WWTP. These solutions can act as a primary, secondary, and tertiary stage of treatment, playing a relevant role as a decentralized alternative, especially in small communities and for smaller users, such as health services, hospitals, and industrial units (Verlicchi & Zambello, 2014). The drug pollution removal in urban waters also can be performed silently as an unrecognized ecosystem service provided by riparian vegetation. Among these technologies, the sand willow (Salix exigua), a common shrub in riverside vegetation across North America, has shown the ability to quickly remove drug products from aqueous solutions (Franks et al., 2019).

3.1.1.2 Urine separation

As with other water pollutants, interventions at the source have also gained prominence for pharmaceutical micropollutants (Larsen et al., 2009). Despite being in the technical field, Urine source separation (NoMix technology) is a holistic alternative to reduce water pollution by nutrients and pharmaceuticals. The main drivers of this alternative are the recycling of nutrients and the reduction of water pollution (Larsen et al., 2004; Larsen et al., 2009; 2010; Pronk & Koné, 2009; Talib & Randhir, 2017; Boyer & Saetta, 2019). The integrative vision of this possibility can reestablish the nutrient cycle between nature and urban man. With the industrial revolution, cities assumed centrality and the nutrients extracted from the soil during food production no longer returned to their origin, through fertilizers generated from organic waste and excrement.

Modern NoMix technology toilets emerged in Sweden in the 1990s, but other versions with urine diversion date back to the 1970s (Larsen et al., 2009). Despite the scientific maturity of these systems (Talib & Randhir, 2016), their full-scale deployment is still limited and faces challenges. Traditionally, separation processes are most attractive in rural regions without sewage collection, but there are successful experiences in densely populated areas, such as Chinese and African cities (Medilanski et al., 2006; Udert et al., 2015). In China, there were about 700,000 of these toilets in 2003. In regions where flush toilets are unavailable, this solution has generated a notable sanitary improvement (Larsen et al., 2009). Several pilot projects of modern NoMix technology developed in Austria, Denmark, Germany, Luxembourg, Netherlands, Sweden, and Switzerland showed good acceptance levels, despite inconveniences with odors and time-consuming cleaning of these toilets (Larsen et al., 2009; Talib & Randhir, 2016). There are reports from 2010 on installing NoMix technology in South Africa to reduce environmental pollution and recover nutrients from urine to transform them into fertilizers (Udert et al., 2015).

Urine represents about 1% of the volume of wastewater (Larsen et al., 2004; Landry & Boyer, 2016; Talib & Randhir, 2017; Boyer & Saetta, 2019) but contributes considerably to a load of nitrogen (70 to 80%), phosphorus (50 to 70%), and pharmaceutical waste (60 to 70%) to a typical sewer (Lienert et al., 2007; Winker et al., 2008; Pronk & Koné, 2009; Jimenez et al., 2015). The separation process would remove nutrients in WWTP obsolete (Larsen et al., 2004). Urine separation is particularly important in reducing the effects of more aggressive drugs on the environment, with a low metabolization rate, such as oncological drugs and antibiotics (Lienert et al., 2007; Caban & Stepnowski, 2021). The excretion of drugs occurs mainly through the urine, on average about 64%, but these numbers vary according to each drug class - analgesics about 82%; antiepileptic drugs about 81%; antiviral drugs about 71%; antidepressants about 66%; antibiotics about 61%; antihypertensives about 50%; cytostatic and gestagens about 49% (Lienert et al., 2007). However, it would not completely solve the problem of pharmaceutical micropollutants in sewage because the most problematic drugs for this environment are usually associated with feces, generating about half of the ecotoxicological risks of this class (Larsen et al., 2009; Lienert et al., 2007). Reducing the high loads in undiluted urine WWTP would optimize the adsorption processes. The separation process removes about half of the pharmaceutical load and increases sludge production in non-nitrifying treatment plants, is an economic response to the growing problem of micropollutants (Larsen et al., 2009). The life cycle analysis of these technologies shows 90% lower environmental impacts when compared to conventional wastewater treatment systems. These impacts reduce potable water production for discharge water, electricity costs in the WWTP, and nutrient offsets (Landry & Boyer, 2016).

Urine treatment takes place locally or by transport to treatment plants. That first alternative is more viable because the latter incorporates the costs of piping or transport by truck, being an unattractive alternative for cities (Larsen et al., 2009). These two separation and treatment systems have similar costs to conventional wastewater treatment systems (Landry & Boyer, 2016). The most basic alternative to using urine is storage and direct application to the soil as a fertilizer. However, purification processing is essential to expand the possibilities of use and reduce environmental risks caused by micropollutants released with the direct application (Larsen et al., 2010). As for the recycling of urine nutrients, it is possible: (1) struvite precipitation, which is a rapid and straightforward process to recover phosphorus and other nutrients (e.g., nitrogen and potassium) from the effluent, but without the complete inactivation of pathogens; (2) the combination of nitrification and distillation, which is a more complex process to recover all nutrients in a concentrated solution, ensuring safe sanitation and production, as by-products, of only distilled water and a small amount of sludge.; and (3) the electrolysis, which is a simple operation but does not recover nitrogen and can generate dangerous chlorinated by-products (Pronk & Koné, 2009; Udert et al., 2015).

From the point of view of urban planning, urine diversion can be a strategic alternative because it links urban sanitation infrastructure with the provision of services and, thus, can ensure investments in works and resources for the operation and maintenance costs of these systems (Pronk & Koné, 2009). In addition to this benefit, there are contributions to the reestablishment of sustainability in the nutrient cycle. In this case, the nutrients recovered from the urine are used in urban or metropolitan agriculture, reducing costs and environmental impacts with chemical fertilizers. However, this practice still requires investments in studies and research, as it is considered immature and risky. Despite this potential contribution to sustainability, cities continue to allocate very few resources to develop a cheap, systemic, and inclusive alternative to urine diversion (Larsen et al., 2009).

3.1.1.3 Green chemistry

In addition to removing micropollutants at the destination (wastewater) and the source (urine separation), the chemical industry has created green chemistry as a strictly technical third way to deal with this problem (Larsen et al., 2004). This strategy reduces the impact of production on ecological performance, seeking cleaner production from new designs or redesigns of molecules without changing the application's functionality. Therefore, the challenges are manifold: it associates with reducing the global doses of drugs, maximizing the potential of metabolization by the body, increasing biodegradability, and reduced environmental effects (Kümmerer, 2010; Rastogi et al., 2015ab; Wang et al., 2015; Blair, 2016; Wang et al., 2019). This approach is a promising solution to the challenge of drug pollutants even in regions without health coverage (Rastogi et al., 2015ab; Blair, 2016). The motivations for the development of green chemistry can be ethical, legal, and economical due to marketing for sustainability (Larsen et al., 2004). A fundamental issue for maintaining the legitimacy of this strategy is the challenge of not reversing this order of motivations, that is, working with the marketing prioritization scale for legislation, leaving ethical issues as residual.

In the substantive dimension of development, one of the critical aspects of green chemistry is improving the biodegradation of pharmaceuticals to reduce the potential for degradation of water quality. The main barrier is that drugs tend to be resistant to biological degradation as the design premise is for their survival in the digestive system, which heightens the need for external removal (Khetan & Collins, 2007; Blair, 2016). As alternatives, the beta-blockers Propranolol and Atenolol are examples of molecules redesigned to be more bioavailable for biological treatment. The molecular alterations of these compounds increased their biodegradation capacity, reducing the potential for accumulation in the environment (Rastogi et al., 2015ab). As a modified cytostatic based on the old ifosfamide, glufosfamide with improved biodegradability is another example (Straub, 2016). In this direction, there are ongoing efforts to redesign ciprofloxacin antibiotics to facilitate the degradation process (Klatte et al., 2017).

On the other hand, the broad-spectrum antimicrobial agent from the group of fluoroquinolones, called ciprofloxacin, remains a challenge in the aquatic environment because it is highly stable. With future potential, the development of photoactive molecules seems promising because it allows for better molecular breakage by advanced treatment and transformation into less harmful or inactive substances. The concern with this technology lies in defining mechanisms for evaluating the toxicity of new metabolites, which does not prevent them from being considered in the development or redesign of pharmaceutical products (Khetan & Collins, 2007; Blair, 2016). Advances in this dimension depend, on the one hand, on technical capacities developed within corporate laboratories and research centers and, on the other, on pressure from consumers and society in general affected by the effects of waste.

Overall, green chemistry is an emerging and relatively underdeveloped field, but it has promising long-term potential for reducing pharmaceutical water pollution (Kümmerer, 2009; Wu & Janssen, 2011). One of the conditions for the development of this approach is that the productive sector reaches maturity and the expansion of investment capacity, as the costs to study and develop molecules with less environmental impact are considerably high (Adams & Brantner, 2006). On the one hand, there is a need for economic incentives to stimulate investment by pharmaceutical industries in this field of investigation (Straub, 2016; Klatte et al., 2017) Moreover, on the other hand, consider that, according to the 2015 Forbes magazine ranking, it is the performance of companies from 61 countries, with total annual revenues of US$ 39 trillion and $3 trillion in profits, with $162 trillion in assets and $48 trillion in market value. An exciting benchmark to measure the investment capacity of this sector is that, for example, annual revenues are practically equivalent, according to the Wordmeter survey (https://www.worldometers.info/gdp/gdp-by-country/), to the sum of US$ 40,288 in trillions of the 2017 GDP of the four largest economies in the world: United States (US$19,485), China (US$12,238), Japan (US$4,872) and Germany (US$3,693).

3.1.2 Organizational approach

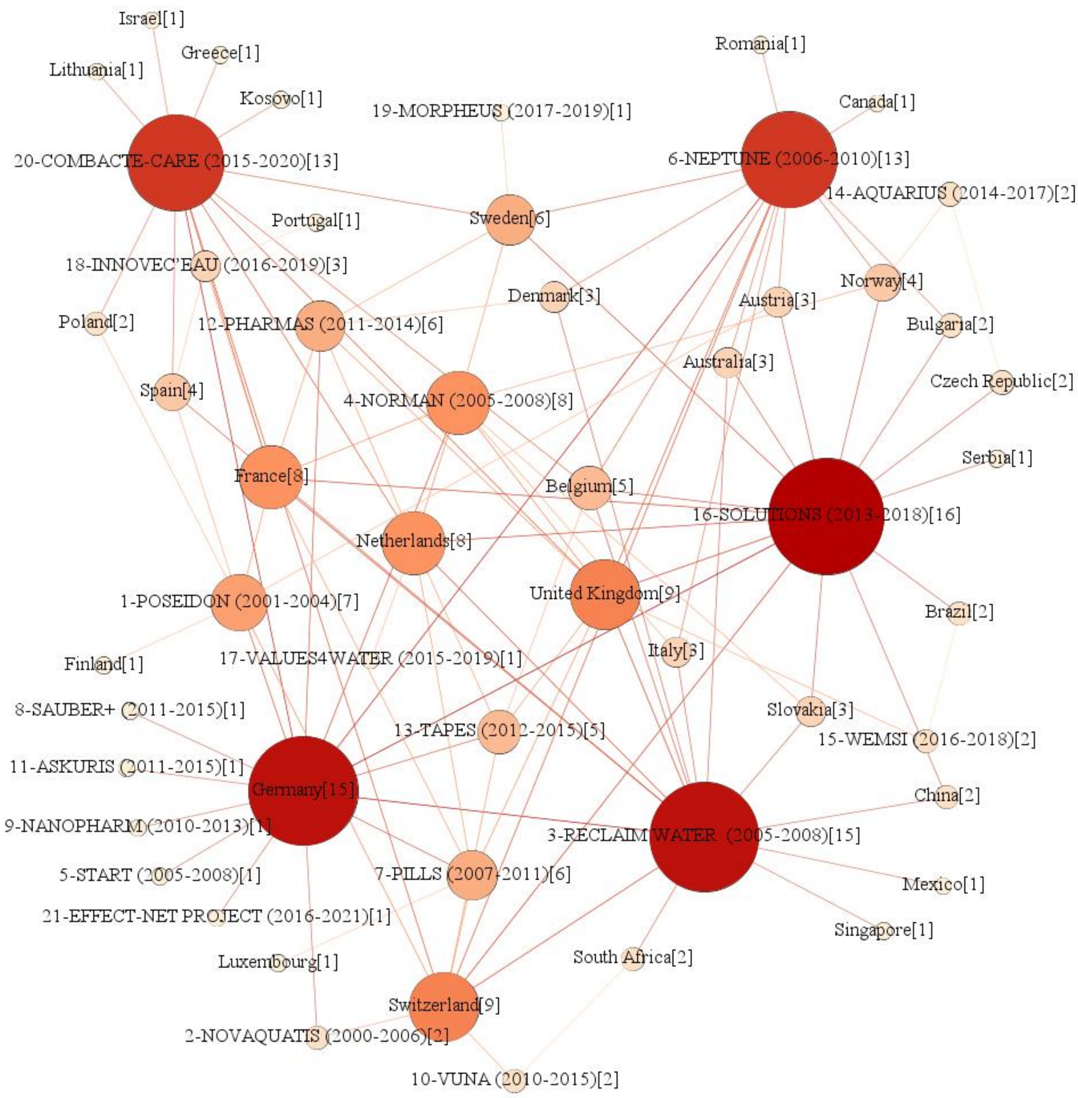
The organizational approach presupposes the co-responsibility of a broad spectrum of stakeholders, as the leading environmental solutions and problems faced by urban society arise from the interaction between multiple organizations and communities. Faced with a scenario of insufficient mechanisms for individual accountability for the management of pharmaceutical micropollutants, the concept of governance has a promising modus operandi for considering interventions involving both policymakers and other individual and collective stakeholders (Wuijts et al., 2017; Ingold et al., 2018). This approach to collecting the decision-making process is an essential alternative to the classic search for centralized solutions, whether technical or governmental. The underlying premise of governance systems is that complex problems demand comprehensive solutions that share responsibility and reflect on the action of multiple stakeholders (Keil et al., 2008). It is, therefore, a context in which the classical coordination capacities seem to extrapolate the technical-scientific and governmental spheres in the search for technical solutions for the diffusion of adverse effects of drug micropollutants, especially in light of the global diffusion of the production process, the effects of drug residues, and the economic power of the pharmaceutical industry. In this context of complexity, the concept of governance can encompass the articulations between different stakeholders, from local inter-organizational relations to international relations between nations.

Among the four micro-dimensional approaches to managing pharmaceutical micropollutants, this contextual tangle is the most challenging due to the difficulty of reaching agreements between stakeholders with multiple and contradictory interests involved in the environmental management of pharmaceutical waste. At the inter-organizational scale, a materialization of the efforts of this approach is the workshops (e.g., Rodriguez-Mozaz & Weinberg, 2010; Boxall et al., 2012; Furley et al., 2018; Barcellos et al., 2020). These events bring together stakeholders from different sectors to seek consensus and prioritization for management, facilitating collective constructions. In water quality management, the source of pollution and its effects may not be spatially connected, causing mismatches in the management process (Ingold et al., 2018; Widmer et al., 2019). The connectivity approach through collaborative multilevel organizational arrangements to create environments that allow institutional capacity seems promising to improve the potential for solving the mismatches generated by drug micropollutants (Wuijts et al., 2017; Ingold et al., 2018; Widmer et al., 2019). The mechanisms for substantively advancing these collective constructions are collaborative projects, disseminating best organizational practices, reducing the use of medication, medication return programs, among others.

3.1.2.1 Collaborative projects

In general, efforts to manage pharmaceutical micropollutants through the integrated management approach are collaborative, with the technical and community spheres of action having interfaces with the organizational sphere formed by private and governmental agents. Therefore, a fundamental characteristic of these efforts is the networking between different institutions that seek to share local, regional, national, and transnational efforts. In the practical dimension of the organizational approach to management, the consolidation of these efforts occurs mainly based on research projects and pilot network interventions. One of the ways to observe this dynamic is through scientific reports on evaluated practical experiences. For example, 27% (29) of the 106 publications analyzed in this investigation correspond to collaborative projects on integrated management approaches. As shown in Figure 7, these projects are initiatives led by European institutions, as indicated by 45% of documents reporting studies and experiences produced in that continent. Of these 29 documents, only two involve countries outside Europe, specifically Brazil and South Africa (Udert et al., 2015; Barcellos et al., 2020). The network shown in Figure 7 shows the 21 collaborative projects between countries and the duration of each one of them.

Figure 7. Collaborative projects to pharmaceuticals micropollutants management.



Note: In this figure, the first number on the left is code followed by the project name. In parentheses, there is the period of validity of the project. The number in square brackets on the right indicates the number of projects each country participates in or the number of countries participating in each project. The objectives of each project, according to the code, are in supplementary material 1.

Table 2 details the duration of each of the 21 projects presented in Figure 7. The gray color of the horizontal bars indicates projects involving countries outside Europe. Of the 21 collaborative projects (Table 2) identified, the following involve institutions outside Europe: (3) Reclaim Water Project (Water Reclamation Technologies for Safe Artificial Groundwater Recharge) is led by a German institution and has collaborators from institutions from China, Australia, Mexico, South Africa, and Singapore (Wintgens et al., 2008); (6) Neptune Project (New Sustainable

Concepts and Processes for Optimization and Upgrading Municipal Wastewater and Sludge Treatment) is led by a Swiss institution and has the participation of institutions from Canada and Australia (Joss et al., 2008); (10) VUNA Project (Valorisation of Urine Nutrients in Africa) is also led by a Swiss institution and involves the participation of institutions from South Africa (Udert et al., 2015); (15) WEMSI Project (Water Environment Micropollutant Science Initiative: Collaboration to explore emerging pollutants in Brazilian watercourses) has the leadership of a British institution and collaborators of Brazilian institutions (Barcellos et al., 2020); (16) SOLUTIONS Project (Solutions for present and future emerging pollutants in land and water resources management) is led by a German institution and counts on the work of collaborators from institutions in China, Australia, and Brazil (Kortenkamp et al., 2019; Van Gils et al., 2019); and (20) COMBACTE-CARE Project (Combatting Bacterial Resistance in Europe - Carbapenem Resistance) is led by a British institution and has the participation of collaborators from Israeli institutions (Roca et al., 2015). The other scientific documents investigated present results of the following 15 collaborative projects: (1) Poseidon Project (Clara et al., 2005; Joss et al., 2006, 2008, Ternes et al., 2007), (2) Novaquatis (Larsen et al., 2004, 2009; Lienert et al., 2007), (4) Norman Project (Farré et al., 2008), (5) Start Project (Titz & Döll, 2009), (7) PILLS Project (Igos et al., 2012, 2013), (8) SAUBER+ (Brandmayr et al., 2015), (9) NanoPharm (Rastogi et al., 2015ab), (11) ASKURIS (Zietzschmann et al., 2014; Jekel et al., 2015), (12) PHARMA (Oldenkamp et al., 2014), (13) TAPES Project (Fischer et al., 2017), (14) Aquarius Project (Hrkal et al., 2019), (17) Values4Water Project (Pigmans et al., 2019), (18) Innovec'EAU (Lima et al., 2020), (19) MORPHEUS (Kosek et al., 2020), and (21) Effect-Net Project (Tosun et al., 2020).

Table 2 shows that the overall average time for each project is 4.7 years, with internal projects lasting 4.5 years and those involving countries outside Europe having an average duration of five years. The last three numerical lines of this table show the number of projects in effect annually. Projects involving countries outside Europe started in 2005 and since then have varied between one and three projects. On average, there are about four projects in effect continuously, with a growth trend until 2017. Although they are essential to indicate the level of relationship between nations, this network of projects says little about the institutions of each country involved and budget. Promising opportunities for future researches are to precisely identify the knowledge generation centers on drug micropollutants and the amounts of resources invested. These collaborative initiatives identified in the European continent seek to understand the dynamics of pharmaceutical residues, propose management alternatives, identify priority pollutants, and bring together different sectors of society to search for ways to control of water pollution by pharmaceutical compounds (Joss et al., 2006; Lienert et al., 2007; Wintgens et al., 2008; Titz & Döll, 2009; Farré et al., 2008; Igos et al., 2012; Rastogi et al., 2015a; Jekel et al., 2015; Fischer et al., 2017; Van Gils et al., 2019; Kosek et al., 2020).

Table 2. Duration of internal and external collaborative projects in Europe.

Coverage in relation to Europe: Internal / External

Projects	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	General (Average 4,7)	Internal (Average 4,5)	External (Average 5,0)
1-Poseidon																							4	4	
2-Novaquatis																							7	7	
3-Reclaim Water																							4		4
4-NORMAN																							4	4	
5-Start																							4	4	
6-Neptune																							5		5
7-PILLS																							5	5	
8-SAUBER+																							5	5	
9-NanoPharm																							4	4	
10-VUNA																							6		6
11-ASKURIS																							5	5	
12-PHARMAS																							4	4	
13-TAPES																							4	4	
14-AQUARIUS																							4	4	
15-WEMSI																							3		3
16-Solutions																							6		6
17-Values4Water																							5	5	
18-Innovec'EAU																							4	4	
19-MORPHEUS																							3	3	
20-COMBACTE-CARE																							6		6
21-Effect-Net Project																							6	6	
Average 4,5 General	1	2	2	2	2	4	5	5	5	2	4	6	6	7	7	8	7	8	7	5	2	1			
Average 3,1 Internal	1	2	2	2	2	3	3	3	3	1	2	5	5	5	5	5	4	5	4	4	1	1			
Average 1,4 External	0	0	0	0	0	1	2	2	2	1	2	1	1	2	2	3	3	3	3	1	1	0			

Years / Duration of each project / Current projects at the same time

Note:The projects identified are those that made up the sampling of 106 scientific documents selected for full reading. However, unfortunately many other relevant collaborative projects were left out of the sample, some even for not sharing their results by scientific journals, as: noPILLS (http://www.no-pills.eu/conference/BS_NoPills_Final%20Report_long_EN.pdf),NonHazCity (https://thinkbefore.eu/en/) and Less is More (https://southbaltic.eu/-/less-is-more).

The set of cooperation initiatives identified in Figure 7 is part of an environmental governance model in European countries, forming articulation networks involving different sectors of society (Lee, 2006). Among its various functions, this model contributes to management innovation, giving visibility to pharmaceutical micropollutants' problems and putting pressure on the government to structure public policies and corrective structural measures (Lee, 2006). These efforts come from stakeholders articulated in a network and spread throughout society, enabling the community and authorities to influence the organizations' routines to adapt to new or potential demands. These networked initiatives for managing water resources have also shown successful experiences in managing other water pollutants (Metz & Ingold, 2014). Due to their continuity seems to have an important role also for pharmaceutical micropollutants (Table 2). In several cases, this autonomous type of networked institutional arrangement can be characterized as an information tool to develop research to raise the understanding of problems, encourage voluntary actions, improve the content of environmental education campaigns, and improve environmental practices in different organizations (Metz & Ingold, 2014). In addition to these functions, these project networks are fundamental instruments for the training of researchers and dissemination of scientific knowledge around the world, which, according to the relations between countries shown in Figure 7, seems to have great potential for expansion, especially in the context of developing economies beyond the European continent.

3.1.2.2 Drug take-back

Among the management tools that make up the organizational approach, drug take-back of disused domestic medicines has been one of the most studied and prescribed (Figure 3). This management tool is, for example, the second most cited in the US media, with 23% of the total news linked to the management of pharmaceutical micropollutants, second only to water and sewage treatments (Blair et al., 2017). In practical terms, 19 member states of the European Union, Australia, USA, Canada, and New Zealand have adopted this pharmaceutical waste collection strategy. In general, the return of drugs through drug take-back systems is not the most common destination in most of these countries, with exceptions being Germany and the Netherlands (Tong et al., 2011; Alnahas et al., 2020). In developing economies, this strategy is at an early stage of implementation as in Brazil, Colombia, and Mexico (Tong et al., 2011; Bergen et al., 2015; Pereira et al., 2017; Barcellos et al., 2020). Despite the pressure of public opinion and advances in adoption in different global contexts, take-back has only a marginal structural capacity to mitigate pollution by drug residues, as a small portion (5% to 15%) of drug sales goes to the condition of drug sales disuse and disposal. Therefore, this strategy does not cover the larger volume of excreted drugs after passing through the body (Guidotti, 2009; Tischler et al., 2012).

The main destination for medicine waste is household waste, but the most relevant problem is when disposal is done in kitchen sinks and bathrooms, the most undesirable means for this purpose from a technical and economic point of view (Tong et al., 2011; Alnahas et al., 2020). Regarding the portion liable to be discarded due to disuse, the trend is the progressive reduction of drug residues proportional to the intensity of diffusion and institutionalization of drug take-back programs, as evidenced by studies carried out at different times in the United Kingdom and the USA. Studies show that the return to pharmacies or collection points for medicines used in homes depends on individual habits and social awareness. This awareness and habits are related to the community approach subject to regulating the legal environment built under the government approach (Massoud et al., 2016; Bungau et al., 2018; Ariffin & Zakili, 2019; Rogowska et al., 2019; Barcellos et al., 2020). In general, the drug take-back system depends on collective efforts involving multi-stakeholders for its institutionalization and, therefore, gaining reach and long-term feasibility (Massoud et al., 2016; Bungau et al., 2018; Kinrys et al., 2018; Ariffin & Zakili, 2019; Barcellos et al., 2020). The conclusion is that this solution is an early stage and has structurally limited effectiveness for the treatment of drug residues (Tong et al., 2011) due to the volume of micropollutants covered by the possibility of return and the level of efficiency being dependent on community awareness and legal regulation.

In awareness and institutionalization, the great challenge of take-back systems is the necessary involvement of several stakeholders, defining procedures, and constructing a unitary design complex. The absence of legislation and government coordination to assign responsibility for costs are essential elements that hamper the advancement of these systems in many regions (Massoud et al., 2016; Bungau et al., 2018; Ariffin & Zakili, 2019; Rogowska et al., 2019; Barcellos et al., 2020). In addition to these elements, low population adherence is another crucial point that creates a discrepancy between actual practices and best practices (Massoud et al., 2016; Kotchen et al., 2009; Fenech et al., 2013; Bungau et al., 2018; Kinrys et al., 2018). Implementing this solution demands organizational efforts to raise the level of knowledge and awareness of the population and, on the other hand, the search for balance in the distribution of costs and responsibilities of those involved in the waste collection and treatment system pharmaceuticals.

The low adherence of the population also reflects the lack of guidance from medical professionals and educational programs to promote these systems (Fenech et al., 2013; Kinrys et al., 2018; Bungau et al., 2018; Ehrhart et al., 2020). For example, a survey showed that only 7% of Maltese and 21% of Irish received professional guidance on how best to dispose of pharmaceuticals (Fenech et al., 2013). Surveys show that a small number of consumers (20%, 24%, and 8%) in the USA receive instructions from medical professionals or on medication packaging about the correct disposal for expired validity or disuse cases (Kinrys et al., 2018). From a more general perspective of guidance, the percentage of drug collection in pharmacies in Romania rose from 1% to 87% after an educational campaign for the population over six months (Bungau et al., 2018). Schools can also play an essential role in educating for proper disposal and constituting possible collection points for pharmaceutical waste. In this sense, a pilot project in a school district in the USA showed the feasibility and success of implementing a drug disposal protocol in schools (Taras et al., 2014). The efforts of health professionals, education, and the press appear to be an indispensable organizational perspective approach to drug take-back.

In the case of distribution of responsibilities, the costs of the treatment and collection systems for medical substances used in households are not borne by pharmacies in most European countries, being extended to cover the producer and, in some cases, local authorities (Bungau et al., 2018). The transfer of costs directly to the consumer has occurred in contexts with institutional and legal frameworks that are still premature, which create difficulties in allocating responsibilities to the productive and public sectors. A sociological survey carried out in the USA showed that the population is willing to pay a surcharge for prescription drugs, which would reach annual amounts of US$14 to fund the drug return system (Kotchen et al., 2009). Although it seems promising, this transfer of costs directly to the consumer needs to be evaluated in the regional context and implemented by stakeholders or public authorities. Another critical point is that these decisions do not allow ethical issues involved in purchasing medications to be relegated to the background. When purchasing medicines, consumers will not have the freedom to choose products without significant consequences but will face the weight of an evaluation to acquire an essential input to preserve their own life. Taking on a policy of attributing cost decisions to each individual can lead to an escape from the confrontation between the economic interests of the drug industry and the social forces that define limits between costs that must be borne individually or collectively in each society.

As with any other management strategy, the effectiveness of drug take-back depends on the feasibility in each regional context. For example, the life cycle analysis of three disused medication disposal options (sink, take-back, and household waste) in the USA showed that the emission of micropollutants would have similar between disposal in household waste and collection by return programs (Cook et al., 2012). However, the authors show that drug return programs, in addition to their high costs, have low adherence by the American population and generate a significant increase in the generation of study effect gases. As 60% of the population in the USA disposes of disused drugs in household waste, the level of compliance with this option would also be higher, thus disposal in household waste would be the most convenient option to rapidly reduce drug pollution in the environment (Cook et al., 2012). Estimates in the USA show that the disposal of expired or unused medications in landfills effectively eliminates medication pollution in surface waters, as around 99.7% to 99.94% originates from excreta (Tischler et al., 2012). In this situation, if the objective is to reduced water pollution, the decision to dispose of it in household waste seems proper even is limited to simply directing the micropollutants to the landfill environment, therefore, without facing the cause of pollution.

3.1.2.3 Reduction in use

Reducing use is an organizational approach with the potential to minimize drug pollution, which advocates responsible and functional consumption of medications. The objective is to minimize use without increasing the therapeutic effect and reducing the environmental impact (Shalini et al., 2010; He et al., 2017). This approach can bring significant results because one of the main ways of eliminating drug residues is by excretion (Straub, 2016). Reducing use presupposes the participation of health professionals and educational programs at all levels of education (kindergarten, elementary, secondary, and university), including subjects in academic curricula (Daughton & Ruhoy, 2008; Becker et al., 2010; Rodriguez-Mozaz & Weinberg, 2010; Brandmayr et al., 2015; Kümmerer et al., 2019; Ehrhart et al., 2020). The objectives are to avoid over-prescribing, prioritize minimal therapeutic doses, produce fractional medications, maintain disposal instructions on medication packages, promote preventive and systemic health at a local scale (e.g., schools, work environment), select medications considering environmental impacts, evaluate the excretion profile of drug residues (Keil et al., 2008; Rodriguez-Mozaz & Weinberg, 2010; Wu & Janssen, 2011; Boxall et al., 2012; Brandmayr et al., 2015; Blair, 2016; Barcellos et al., 2020). In addition to choosing the right drugs, there are possibilities for dose customization to optimize the combination of drug profile, effects on the patient, and impact on the environment.

Usually, an abstract figure of the “average patient” is the reference used to define the pharmaceutical dosage, which can influence the effectiveness of the medication by disregarding the particularities of each individual. The consequences can be overdosing or underdosing (Straub, 2016). The scaling of drug doses results in risks for patients with low metabolic capacity and high drug residues in excretion. The drug may also be ineffective because it does not reach treatment for patients with rapid metabolism. Therefore, healthcare must advance to personalized and dedicated assessments to consider the individual characteristics of patients. This knowledge involves genetic inheritance, phenotypic expression, concomitant therapy, age, sex, and other physiological factors (Straub, 2016).

Another problem is the use of antibiotics for infectious diseases not associated with bacteria, which requires rapid diagnoses to exclude the prescription of antibiotics as a treatment option for these infections (Roca et al., 2015). Advances in this direction require educational programs to inform medical professionals about undifferentiated antibiotic prescriptions, which should also seek to raise awareness of patients and consumers about antibiotics' inappropriate uses and risks (Roca et al., 2015; Straub, 2016).

Among the ways to face these problems, the Swedish classification introduced by the Stockholm County Council (https://www.fass.se/LIF/startpage) allows a comparative analysis of the risks and adverse environmental effects of the medicine, helping to reduce the use of harmful ones for the environment (Wennmalm & Gunnarsson, 2005;2009; Oldenkamp et al., 2014). The criteria for the analysis show effectiveness in evaluating the potential for accumulation of drugs in surface waters and the interference of residues in aquatic ecosystems. In these assessments, the producer provides biodegradation, bioaccumulation, and ecotoxicity data for each drug to calculate the PEC/PNEC, which allows the generation of an environmental risk scale to measure the insignificant, low, moderate, or high potential of the generated risk (Oldenkamp et al., 2014). In addition to increasing awareness of the harmful environmental effects generated by drug consumption, this classification allows considering the multiple factors involved in choosing a particular drug (Wennmalm & Gunnarsson, 2005). When therapeutic options exist, these assessments can direct use towards the most ecologically friendly option. The system is interactive and open for access by medical professionals and the population. This opening motivates the increase in demand for medicines with less environmental impact and encourages manufacturers to invest in more ecological medicines (Wennmalm & Gunnarsson, 2009). This system appears to have a good level of consolidation on a national scale but presents opportunities for improvement as its use by physicians increases. There are still initiatives to develop similar solutions to cover the whole of Europe (e.g., Oldenkamp et al., 2014).

3.1.2.4 Best organizational practices

The so-called organizational "best practices" is a pharmaceutical micropollutant management approach used by institutions that operate with high volumes of drugs with the potential to generate pharmaceutical pollution and adversely influence their production chain, as is the case, for example, in chains formed by pharmaceutical corporations, hospitals, and health centers. Including hospitals, facilities, and health systems, The Global Green and Healthy Hospitals network, created in 2011, is an organization that aims to reduce the environmental impacts of medicines and to promote public and environmental health. Networking uses strategies and operations management spanning public health and environmental health to connect global and local initiatives to encourage environmental health, equity in access to health, and the green economy in different contexts (Morales et al., 2019). This network has 1,350 members spread across 72 countries, representing the interests of more than 43,000 hospitals and health centers (GGHH, 2021).

In addition to this joint action of organizations involved with health issues, technical advances are essential to operationalize efficient environmental classifications of medicines and transparent performance by pharmaceutical corporations. In this direction, it is possible to see some advances in transparency in several companies in providing environmental data on pharmaceuticals, which occurs in some cases on the respective institutional websites (Holm et al., 2013; Caldwell et al., 2015). A potential for advances in corporate practices lies in responses to meet the demands of medical professionals for transparency about the environmental impact of products and production processes (Joakim Larsson & Fick, 2009). For example, in Sweden, which has one of the strictest environmental legislation globally, numerous marketed pharmaceuticals originating from Indian producers using inadequate wastewater treatments have been identified. This example expresses the need to expand individual and corporate action to the scope of shared responsibility between societies to deal with the unsustainable production of pharmaceutical drugs. In this process, professionals in the medical field need to create informational bases to educate consumers (Joakim Larsson & Fick, 2009).

Some large pharmaceutical corporations have been working on extensive and diversified analyses of their products to understand the environmental and social impacts and minimize risks in production and use processes (Caldwell et al., 2015). These practices can be an essential source of dissemination of ethical and sustainable principles among organizations through protocols. The basis of these product administration protocols usually is in the following three pillars: (1) expansion of environmental risk assessment; (2) expansion of the scientific knowledge base (Evaluation of Medicines in the Environment), and (3) control of effluent emissions (Caldwell et al., 2015). The materialization of the results obtained with the application of these protocols usually occurs by developing more efficient technical safety sheets to provide chemical, physical, biological, and toxicological data for each drug (Caldwell et al., 2015). It is also possible to identify efforts by a set of pharmaceutical corporations that have set shared goals to reduce the incidence of antimicrobial resistance and help ensure that antibiotics are used only by patients who need them (Tell et al., 2019).

3.1.3 Community approach

The mention of drug take-back occurred in the organizational approach, but the functioning of this system necessarily depends on the population's adherence. Reducing drug use also has aspects related to the organizational and community approach. The government (government approach) and stakeholders in a network (organizational approach) can lead and structure the reduction and correct disposal of medicines. It is up to the population the essential role of participating, being involved, and contributing to disseminating these systems. In this sense, the community approach contributes to the reduction of drug consumption and drug take-back through practices such as avoiding the use of over-the-counter medications; discard unused or expired medications at collection points; spread the intended use and correct disposal of medications; avoid improper disposal of medications in the bathroom or sink; adopt a healthy lifestyle with the use of fewer medications (Kümmerer, 2009; Shalini et al., 2010; Zorpas et al., 2017).

3.1.4 Governmental approach

The governmental approach is transversal and fundamental for the effectiveness of the others to face the problem of pharmaceutical micropollutants (Ingold et al., 2018; Widmer et al., 2019). This approach relies on economic, legal, and informational instruments (Metz & Ingold, 2014). In the management of organic micropollutants, there is no evidence of ubiquitous approaches in the contexts of more developed or developing economies, although there are possibilities for critical approaches to government strategies and management (Bieber et al., 2018). Societies use legal instruments as force enforcement mechanisms to prohibit or restrict the use of substances, determine ways and means for disposal, prioritize environmental monitoring, define mandatory emission limits, and establish minimum technical standards for the structuring and functioning of the WWTP (Meisel et al., 2009; Metz & Ingold, 2014; Kuster & Adler, 2014; Bieber et al., 2018). Economic mechanisms enable subsidies, encourage behavior change to reduce discharges of pollutants into the environment, and control pollution via overcharging products, substances, or effluent discharges (Metz & Ingold, 2014; Bloomer & McKee, 2018). Informational instruments are the means to disseminate codes of conduct, discard practices, promote information campaigns, support research, and induce articulation in collaboration networks between various types of organizations (Titz & Döll, 2009; Wennmalm & Gunnarsson, 2009; Metz & Ingold, 2014; Bloomer & McKee, 2018). Collaborative projects (Figure 7) dealt with in the organizational approach can be promising examples of information tools, which, in several cases, were induced or financed by governments. Legal instruments are the most discussed in the governmental approach and tend to have greater social and political visibility.

The European Union obliges its member states to dispose of unused or expired pharmaceutical products by appropriate methods. Although that local reality is quite different, several European countries have relatively well-established collection systems (Alnahas et al., 2020). For example, Italy, Greece, Norway, and Belgium made it mandatory to return medication to pharmacies. Austria, Croatia, Hungary, Ireland, Latvia, Luxembourg, France, and Portugal created possibilities to take expired or unused drugs to pharmacies or recycling points (Alnahas et al., 2020). Poland, Finland, and Germany have collection systems in municipal level organizations. The Maltese and French governments have established agreements to coordinate collections by non-governmental organizations (Alnahas et al., 2020). In 2017, the US government agencies Food and Drug Administration (FDA) published guidelines for the disposal of household drugs at collection points or disposal in household waste (Haughey et al., 2019). In 2019, the Australian Government's Department of Health issued instructions for the safe disposal of unused or expired drugs by returning them to pharmacies (Alnahas et al., 2020). In Brazil, drug take-back structuring is still incipient. The conduct of the initiatives is under the joint responsibility of the Ministry of Health, the National Health Surveillance Agency (ANVISA), and stakeholders (Pereira et al., 2017; Barcellos et al., 2020).

Emerging micropollutants do not yet have solid and pervasive legal approaches to setting water concentration limits. The European Union and the USA have comprehensive prioritization systems stipulated by law to periodically monitor potentially hazardous compounds, which can become mandatory concentration limits in the future (Bieber et al., 2018). The US prioritization basis is the Safe Drinking Water Act (SDWA), which applies only to drinking water sources based on the Contaminant Candidate List (CCL) (Bieber et al., 2018). In the European Union, the so-called “watch list” of the “Water Framework Directive” focuses on water quality and its possible effects on aquatic life (Bieber et al., 2018). Countries in the European Union, such as Germany, have quietly advanced towards advanced treatments to meet legal goals defined by that Directive (Bieber et al., 2018). Some German states are starting to implement advanced treatment systems in WWTP to measure the potential for removing organic micropollutants indicators.

Switzerland has new policies to control micropollutants in waters instituted by legislation in place since 2016, which resulted from a comprehensive legislative process involving the public and stakeholders (Bieber et al., 2018). This legislation requires, for example, the implementation of advanced processing processes in WWTPs that serve more than (a) 80 thousand people with the potential to reduce the load of micropollutants; (B) 80 thousand people and contribute with more than 10% of the flow of the receiving bodies; (c) 24 thousand people discharging their effluents insensitive or critical areas for supply (Eggen et al., 2014). The forecast is that around 100 WWTPs under these conditions will be updated by 2040, out of more than 700 existing. This upgrade will allow 50% of the country's sewage to undergo advanced treatment processes, removing more than 80% of the country's proposed organic micropollutant indicator compounds (Eggen et al., 2014). As in other cases emerging in the systematic review, innovations dependent on government action are recent and whose results tend to emerge in a long-term perspective. An important point to be considered is that all state public policy tends to originate from the reflection of the internal political contexts of each society, whose manifestation occurs through the defense of one of the infinities of interest by different stakeholders. So it seems to make little sense to assess what governments do and consider what societies intend to do in choosing their respective governments over time. The challenges, especially for environmental issues, are perhaps much more in progress to capture the implicit intentions of each society than looking for signals in the "smoke clouds" generated by each of its governments and organizations that defend sectoral and corporate interests.

3.2 Opportunities for the developing world

The results reported up to this point in the work show that the problem of water pollution by compounds of pharmaceutical origin still prevails even in ideal scenarios of universal sanitation (e.g., Switzerland, Austria, Germany, United Kingdom, Netherlands, Spain, Italy, and Sweden), which occurs in more advanced countries in the fight against pharmaceutical micropollutants, as is the reality in the USA and from European countries. In essence, the problems seem to lie in the inability to altogether remove these pollutants by conventional technical sewage treatment systems, the society's lack of mobilization to define investment priorities and limitations by legal instruments, and the relatively low concern of the pharmaceutical production sector. Given these limitations, there are promising opportunities to focus on behavioral management strategies as alternatives to complement what a strictly technical nature cannot solve for structural reasons dependent on technology and economic capacity to create definitive solutions.

The relative slowness of progress in technical management approaches seems to prioritize other strategies to overcome barriers of high cost and energy demand for technical solutions. In this context, essential experiences are developed alternatively in developed economies that can generate opportunities for other contexts to advance in drug residue management strategies even before reaching universal sanitation levels. Table 3 summarizes these pharmaceutical micropollutant management opportunities identified by this systematic review.

The opportunities to innovate in the management of pharmaceutical micropollutants presented in Table 3 can be applied individually or jointly by the management approaches categorized in this review: technical, organizational, community, and governmental. The socio-technical nature of these possibilities indicates that the management of these pollutants is a multidisciplinary task involving multiple stakeholders. These fifteen management strategies can be applied in more developed economies, which seek to increase the efficiency of managing pharmaceutical micropollutants, and other economies with more outstanding weaknesses in developing infrastructure bases dependent on intensive technologies and economic resources. In general, these strategies offer returns in the medium and long term, requiring continuous articulation in networks and demanding relatively lower costs when compared to traditional technical solutions. Therefore, these strategies deserve greater attention from both managers and researchers to create mechanisms that facilitate implementation to achieve effectiveness and efficiency in short periods, especially in emerging economies that present intense difficulties in managing pharmaceutical micropollutants. It is also essential to consider the environmental and infrastructural conditions of developed economies that tend to have a higher consumption of medicines. This favorable market condition can bring opportunities for the socialization of environmental costs with the drug sector and large beneficiary economies of this production system, such as sharing technologies and resources that allow significant proximity to social justice and environmental justice principles.

Table 3. Pharmaceutical micropollutant management opportunities for developing countries.

Approach	Strategy	Stakeholders
Governmental, organizational, and community.	Develop a proper drug take-back program.	Policymakers, pharmaceutical sector, medical sector, and population.
	Reduction in drug consumption.	
	Promotion of preventive and systemic approaches to health.	
Governmental and organizational.	Guidelines from health professionals to the population for the proper disposal and correct use of drugs.	Policymakers, medical sector, and pharmaceutical sector.
	Educational programs at all levels of education for the proper disposal and correct use of drugs.	
	Promotion of personalized medical practice.	Policymakers and the medical sector
	Best organizational practices.	Policymakers, the medical sector, pharmaceutical companies, hospitals, and health centers.
	Development of economic, information, and legal instruments to encourage the management of pharmaceutical micropollutants (e.g., for incentive drug take-back, research, and best organizational practices).	Policymakers, medical sector, pharmaceutical sector, hospitals, health centers, sanitation companies, and research institutions.
Technical, governmental, and organizational.	Environmental classification system developments for pharmaceuticals.	Policymakers, the medical sector, and pharmaceutical companies.
	Collaborative projects for pharmaceutical management.	Policymakers, pharmaceutical sector, medical sector, sanitation company, and research institutions.
	Studies on the development of drugs with less environmental impact.	Policymakers, the pharmaceutical sector, and research institutions.
	Pilot studies on the feasibility of urine separation in regions where there is still no sanitary coverage.	Policymakers, sanitation companies, and research institutions.
	Prioritization of pharmaceutical micropollutants.	Policymakers, the pharmaceutical sector, sanitation companies, and research institutions.
	Selection of appropriate indicators to indicate pharmaceutical pollution.	
	Evaluation studies on green technologies and the reconfiguration of WWTPs.	

4. CONCLUSION

This systematic review covered most of the period of studies on the management of pharmaceutical micropollutants, showing research trends and revealing feasible solutions both for improving the management of these micropollutants in developed economies and for implementing more intense structural limitations in terms of availability in other contexts financial resources and advanced technologies. The results show that sewage is the most frequent aquatic matrix in the reports and that the most significant emphasis on the removal of aquatic matrices is the management strategy. There is, therefore, a relatively small set of studies in the field of integrated environmental management that deal with alternatives in addition to technical ones.

Investigations in the perspective of the integrated management of pharmaceutical micropollutants deal more intensively with the drug take-back system, urine separation, legal instruments, and green chemistry. Regarding the countries with the highest number of studies, the results showed the predominance of developed economies, which, as a rule, host the big drug companies. As exceptions, China, India, and Brazil configure the most attractive drug markets in developing economies. The predominance of research reports published in these two contexts is on studies of a strictly technical approach. This picture indicates that the management of pharmaceutical micropollutants seems to be more motivated by the economic interests of producing nations and companies than by other interests more related to the diffuse adverse effects generated by these components on life across the planet.

The analysis centered on studies on the integrated macro-approach to management evidenced the predominance of the USA (21.7%), Germany (20.7%), and Switzerland (10.4%). This perspective articulately brings together the technical, community, organizational and governmental micro-dimensional approaches, which are the component pillars of the management of pharmaceutical micropollutants. The support of the *technical approach* is in reports on the removal of these pollutants from the water, urine diversion, and green chemistry. Support for the *community approach* is in reports on drug use reduction and the drug take-back system. The basis of the *organizational approach* is in studies on collaborative projects, drug take-back, reduction in drug use, and organizational “best practices.” Finally, the *governmental approach* supports the discussions and evaluations of political, legal, and economic instruments used for control and incentives to reduce the collective effects of pharmaceutical micropollutants.

The deepening of research based on these four dimensional micro-approaches to the management of pharmaceutical micropollutants allowed us to contextualize how the most developed economies use the integrated macro-management approach. This research opens the discussions on advances in applying this management perspective, both to improve management in those economies and serve as a basis for initiatives in economically and technologically disadvantaged economies. The scenario unfolded with the investigation shows promising opportunities with medium-term effects to improve management practice and reduce environmental pollution in different social and economic contexts and at a relatively low cost compared to traditional technical alternatives. The nature of these strategies shows possibilities for advancing in managing these pollutants concurrently with efforts towards the universalization of basic sanitation.

The implementation of integrated management systems is, at the same time, less dependent on heavy investments in technological solutions incorporated by material bases and more dependent on social technologies, initiatives, and convergence of interests in networks formed by multiple stakeholders involved in the chain of these compounds. Along these lines, two directions for the work of researchers and practitioners interested in contributing to face the problem generated by drug micropollutants seem to emerge: the continued focus on infrastructure solutions based on the incorporation of "hard" technologies and, at the same time, innovation to from the adoption of strategies to mobilize and direct behavioral resources based on investment in "soft" technologies. Therefore, it does not seem to be the case to maintain the cleavage between these two possible advances. It's necessary to expand the list of initiatives to address environmental problems by acting at the interfaces of technical-scientific knowledge and socioeconomic and socio-technical efforts internalized and developed in each urban society.

If, on the one hand, these possibilities do not seem to emerge as significant innovations for the management of drug micropollutants in studies over the past three decades. On the other hand, the geographic concentration of investigations in environmentally and economically less problematic contexts associated with the scarcity of decisive emerging innovations of scientific thinking seems worrisome. This apparent stagnation in the generation of solutions seems to be worrying given the growing globalized diffusion of pharmaceutical micropollutant impacts that affect the environment with potential risks to public health. If the fundamentals are well understood, this concern can open paths for deeper discussions on the role and responsibilities of corporations that produce and diffuse these pollutants, as well as on economically wealthier societies that benefit from the returns of these practices and on how they are willing to contribute with less technologically sellable solutions.

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CHAPTER 3: PRIORITY PHARMACEUTICAL MICROPOLLUTANTS AND FEASIBLE MANAGEMENT INITIATIVES TO CONTROL WATER POLLUTION FROM THE PERSPECTIVE OF STAKEHOLDERS IN METROPOLIS OF SOUTHERN BRAZIL

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ABSTRACT

The search for common agreement between stakeholders is one of the biggest challenges for solving environmental problems. There are different views, perceptions, knowledge and sectoral goals for these stakeholders. In complex environmental problems, such as the management of pharmaceutical micropollutants, it is essential to establish the intersectoral and individual sector priorities for a collective approach to the problem. This research aimed to identify priority micropollutants for intervention initiatives, and the management goals of the stakeholders involved in the ‘product chain’ of pharmaceuticals, in the region of Curitiba, Brazil. First, the most consumed pharmaceutical micropollutants in the region and those previously detected in water were identified and a ‘long list’ with 40 pharmaceuticals was drawn up for prioritization by stakeholders. Stakeholders of region were selected by intentional sampling and were invited to a workshop that was designed to list, by consensus, priority micropollutants and objectives for their management. The event was attended by 37 stakeholders from different sectors. It was divided into two stages: the first stage was a multisectoral discussion to select the priority pharmaceutical micropollutants; the second stage a sectoral discussion to establish management objectives to control and reduce the presence of these pollutants in waters. The meeting generated a coherent prioritization of pharmaceuticals where ethinyl estradiol, ciprofloxacin, ibuprofen, diclofenac, estradiol, caffeine and fluoxetine were prioritized and their importance was justified. The main sectoral goals prioritized were related with the drug take-back program, characterization of the presence of pharmaceuticals in the sanitation cycle and the creation of a permanent multi-sector discussion environment for the theme. The multisectoral definition, established collectively by consensus, of management priorities is promising and this strategic approach can be replicated in other developing countries.

KEY-WORDS: Pharmaceutical micropollutants. Prioritization process. Water management. Water pollution control. Stakeholder engagement. Urban environmental management.

1. INTRODUCTION

Pharmaceuticals are absolutely essential to the medical demands of animals and humans, but paradoxically, the same properties that ensure the therapeutic effects of these substances are those that can cause the toxicity or bioaccumulative potential of their traces in the environment (Halling-Sørensen et al. 1998; Santos et al. 2010). Exposure to traces of medical substances, intentionally or unintentionally released into the environment, has received attention worldwide. The problem was initially highlighted in the 1970s in the USA and about a decade later in the United Kingdom, with advances in analytical techniques for detection and laboratory measurement (Santos et al. 2010). But it was from the mid-1990s that investigations on the subject were intensified, showing cause-effect responses of these residues on the environment and human health (Kümmerer 2009; Qian et al. 2015; Tiedeken et al. 2017). At present, the focus is primarily on urban rivers, since the characteristics of the ‘product chain’ (Helwig 2018, p.200) of pharmaceutical production and consumption are most likely to result in high concentrations of residue where high population densities and low environmental dilution co-occur (Helwig 2016). Since in Brazil only 46% of the sewage is treated and only 21 municipalities, all located in the 100 largest cities in the country, treat more than 80% of the sewage (SNIS 2018), the priority of the sanitation sector is still focused on the removal of macropollutants, i.e. dissolved organic carbon, nitrogen and phosphorus, from industrial and household effluents. Among the group of micropollutants, the demands of the productive sector (agriculture and industry) for agrochemicals and metals has led to those residues being considered priorities for the national context. A previous study (Barcellos et al. 2019a, p. 76), carried out with 32 stakeholders from different sectors of society (community, academia, government and productive sector) in the Curitiba/Brazil region, showed that the most important aquatic micropollutants are pesticides, followed by heavy metals and then pharmaceuticals.

There are already management initiatives for agrochemicals and heavy metals in the waters in Brazil, implemented via legal instruments that establish limits for the maximum permissible concentrations of these compounds both in natural waters (Brazil 2005) and water supply systems (Brazil 2017). Despite an emerging scientific consistency in the international literature on the environmental effects of some pharmaceutical compounds, such as 17-alpha ethinylestradiol (Owen and Jobling 2013; Gilbert 2013), there are as yet no regulations and standards to drive monitoring, control and minimization of its residues in Brazil. This is largely true elsewhere in the world as well, although several pharmaceuticals are on the EU ‘Watch List’ and Article 8c of Directive 2008/105/EC (amended by Directive 2013/39/EU) obliges the European Commission to develop a strategic approach to water pollution from pharmaceutical substances and some countries have started putting in place national regulations (Küster and Adler 2014). As the concentrations of pharmaceuticals reported in Brazilian surface waters have been relatively high, and certain pollutants have indeed also been found in the water supply in significant concentrations (Dias 2014; Böger et al. 2015; Lima et al. 2017; Reis et al. 2019), there is a need to prioritize pharmaceutical substances for monitoring and intervention. Efforts to establish a comprehensive prioritization of pharmaceuticals in Brazil and in developing countries are still incipient (Barcellos et al. 2019b).

Where a lack of data on the range, volume and toxicities of pharmaceuticals consumed hinders a strictly risk-based approach, a mix of published data and ‘expert input’ can be used as a starting point (Helwig et al. 2013) for the prioritization of pharmaceuticals for monitoring or intervention. In this study, we explore firstly how local stakeholders prioritize pharmaceuticals for the management of urban waters, and from there, we explore options for management initiatives.

The entire management process can be considered collective and needs to be negotiated among the stakeholders. This is no different in the case of pharmaceutical micropollutants. The various groups involved in this issue have distinct and complementary overviews, responsibilities and knowledge about the processes involved in the product chain of these pollutants. In order to validate such a collective approach, it is essential that the integration of these perceptions, priorities and manageable initiatives is discussed jointly by all these stakeholders. The topic of pharmaceutical pollution has not been widely discussed in Brazil so far, and in the incipient discussions that have been established, the sectorial nature of approaches and decisions remains (Barcellos et al. 2019a, p. 142). This study sought to bring stakeholders together to further this integration of perspectives in order to bring about a collective approach to management.

2. MATERIALS AND METHOD

This study was conducted in the metropolitan region of Curitiba, the ninth largest metropolitan region in Brazil, with about 3.5 million inhabitants (IBGE 2016). Curitiba and the metropolitan region have an integrated water supply system, so that the city's drinking water also comes from the metropolitan region (SANEPAR 2013). Water management in Brazil is the responsibility of Union (national authority) and States (regional authority) while the land use and "to combat pollution in all its forms" is the responsibility of municipalities (Brazil 1988). The city of Curitiba is the capital of the Parana State, has around 2 million inhabitants, is the largest city of southern Brazil and the eighth most populous in the country (IBGE 2019). The city has a world-renowned history of urban planning and management and has won several international awards in recognition of the initiatives in favor of the environment and the quality of life of its citizens (Mega 2010; Macedo 2013). It is also the Brazilian capital with the best basic sanitation in the country, with 94% sewage coverage, 100% of treated water supply for the population and 100% waste collection (SNIS 2018). As such, the city was selected for the possibility of exploring the potential for innovation in management technologies and environmental planning.

A workshop was organized with stakeholders to prioritize pharmaceutical micropollutants, as well as to jointly identify feasible management initiatives. Prior to this workshop, two selection processes was take place: a ‘long list’ of possible priority pharmaceutical products was drawn up to begin the selection and classification process and presented to stakeholders, and, of course, the stakeholders in the Curitiba region themselves have been identified and approached as potential workshop participants.

2.1 Initial pharmaceutical micropollutants long list

The ‘long list’ of pharmaceuticals was established with a view to selecting pharmaceuticals that might be likely to be ‘priorities for intervention’ by participants. Establishment of a ‘long list’ from thousands of pharmaceuticals available on the market is not straightforward and various criteria, including consumption level, ‘expert choice’, previous detections, and known toxicities can be used in this process (Helwig et al. 2013). In the current research, two separate approaches were used.

Firstly, in order to represent ‘expert choice’ and include an element of (perceived) risk to the environment, the literature was reviewed to determine which pharmaceutical micropollutants had been monitored in the rivers of the Metropolitan Region of Curitiba and to identify minimum and maximum concentrations for these compounds. It was established that only 27 compounds from 8 different classes (hormones, antihypertensives, anti-inflammatories, analgesics, psychotropics, metabolites, lipid regulators, stimulants and food/cosmetics preservatives (Ide et al. 2013; Kramer et al. 2015; Osawa et al. 2015; Böger et al. 2018; Barcellos et al. 2019a, p. 66) had been monitored in this region. Several shortcomings to this first approach are acknowledged. Firstly, the list of pharmaceutical products resulting from review included only those already monitored and detected in surface waters, which represents a tiny fraction of all pharmaceuticals on the market. This constraint is exacerbated by the fact that many researchers, for reasons of convenience, select analytes that have already been reported in the environment - a phenomenon known as the ‘Matthew effect’ (Merton 1988) – or for which there is a readily available analytical method. Secondly, beyond their detection, there is no attempt to prioritize these substances or to establish their actual environmental risk. Thirdly, the list does not represent in any way the multisectoral interests or concerns of the various stakeholder groups. Nevertheless, as a starting point for discussions, a list of pharmaceuticals detected in the local environment was thought to be useful.

The second approach was based on pharmaceutical consumption patterns and sought to establish which pharmaceuticals are most commonly consumed in the region. Pharmaceuticals may be bought by the general population, freely dispensed by medical staff in Municipal Health Units (MHU) or dispensed and used in hospitals (the pharmaceuticals used and dispensed by hospitals were not considered in this analysis, as there are no data available). The pharmaceutical consumption data in Curitiba used in this research refer to the period of 2016 and 2017 and were extracted from a research already published (Barcellos et al. 2019a, p. 78-99). The level of consumption of a pharmaceutical is a poor indicator of the environmental risk posed by its residues in the environment, which depends on many factors including metabolism (including the extent to which the pharmaceutical is excreted as parent compound or as metabolites), persistence in the environment, potential for bioaccumulation and toxicity. But just like the previous list of compounds already found in water bodies, the list of top-selling and distributed pharmaceuticals is an important starting point, not only because it may allow inference of which pharmaceuticals are likely to be present in the waters but also because they are likely to be familiar to workshop participants.

From these two initial lists, 40 active ingredients of pharmaceutical products were identified as potential priorities for stakeholders (this list can be found in Supplemental Data). The pharmaceuticals selected were those: 1) with a relevant position in the consumption ranking (sale in pharmacies + free distribution in health units); 2) present in the waters of the region in concentration and with possible environmental effects (information evaluated from the study of each molecule by Wiki Pharma data base). Among the 40 selected, 10 active principles had already been monitored and detected in the waters of the region. For the 40 pharmaceuticals selected, information was sought on the percentage excreted unchanged via urine (Bernareggi 1998; Johnson and Williams 2004; Ashley and Currie 2009; Lucena 2013; Cunha 2014; EMC 2017) and the ecotoxicological LOEC - lowest observed effect concentration - (Wiki Pharma 2018) of each compound to make available to stakeholders. This list was sent to all invited stakeholders, who were asked to indicate, in their own view, which 10 compounds they considered to be a priority and to bring this list of the 10 along to the workshop. The use of these initials list was designed to guide the discussion, but stakeholders could select other pharmaceuticals that were not included in the lists.

2.2 Selection of Stakeholders

The stakeholders were selected by intentional sampling, following a procedure similar of previous research (Doerr-MacEwen and Haight 2006), we sought participants from two broad groups: those who have contributed to the literature on micropollutants in the region, and those who play a role in the production and consumption of pharmaceuticals and their subsequent management in (waste) waters.

To identify them, an exploratory research was initially carried out for academic papers published by researchers from institutions located in the region of Curitiba. The curricula vitae of these researchers were accessed by 'Lattes Platform' (a system that reports academical and scientific information of researchers working in

Brazil) and, through the personal list of publications and research projects, other research collaborators were identified who were listed as possible participants.

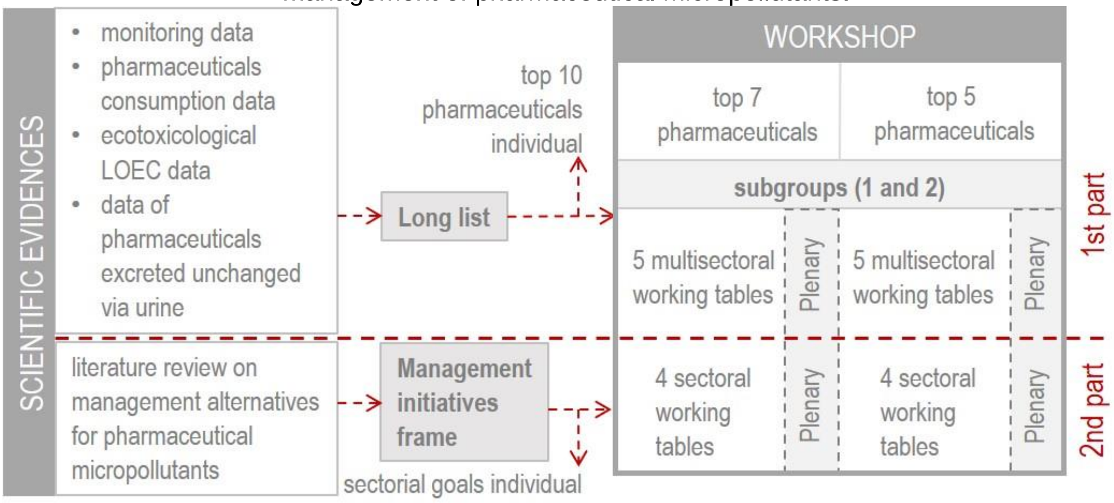
Secondly, governmental institutions with interest in the management of water resources were identified based on previous work (Bracht 2008; Lara 2014; Barcellos et al. 2019a, p. 74). Additionally, other institutions were identified through internet research, including those related to the productive sector and the hospital and pharmaceutical sectors.

The representatives of the selected institutions were divided into 5 groups: decision makers, generally representing local and state government; researchers, belonging to the 4 main local universities; pharmaceutical sector (unions, class councils and institutions representing the category) and representatives from a hospital (healthcare workers appointed by the manager); pharmaceutical industry and finally the water industry, represented by the Parana State Sanitation Company - SANEPAR (a list of institutions and the number of invitees of each group stakeholders can be found in Supplemental Data).

2.3 The Prioritization Process

A workshop was held involving all stakeholders. This was divided into two phases: the first phase sought to identify 5 pharmaceuticals prioritized for monitoring and management to reduce their residues and to justify this selection; in the second phase, possible management objectives and initiatives for pollution control were identified, whereby stakeholders also indicated the stages and temporal scale to implement these. The discussions in both the first part of the event and the second were based on scientific evidence (Figure 1). In the first phase of the event, the 'long list' was sent to participants by email, two weeks before the event. While at the end of the first part of the event, the dynamics of the second phase were explained and participants were given the frame of management initiatives, adapted from the literature (Supplemental Data). Based on this frame, as the 'long list' in first phase, the participants were asked to bring a list of goals that, in their perception, could be achieved by their own sector to reduce the concentration of pharmaceuticals in rivers. These materials (long list and frame of management initiatives) were useful to guide the discussion and enriched it at the working tables, where individual perceptions could be further developed.

Figure 1. Sequential diagram of the collective approach developed for prioritization on the management of pharmaceutical micropollutants.



In order to allow more effective management of the discussions and to encourage a more productive participation of each participant, the initial group of 55 invitees was divided into 2 subgroups in the first phase of the workshop, maintaining proportionality of each sector in each group of stakeholders. The two subgroups met on November 19 and 20, 2018, respectively for the first phase events. At each subgroup meeting, the guests were divided into four working tables. The composition of the tables was planned so that each table could count on the participation of a representative from each sector, allocated prior to the event with a random number generator (both in the first and second round), although this was not quite achieved as not all invitees attended: each of the subgroup meetings was attended by 17 participants each, totaling 34 guests out of 55 stakeholders initially invited. Once consensus was obtained in working tables, the results were presented and discussed in a plenary session. The second phase of the process occurred on November 27, 2018. This phase followed the same methodology as the previous phase, but with the formation of sectoral working tables, instead of multisectoral negotiation. This phase was designed to be carried out with all 34 stakeholders who participated in the first phase (subgroups 1 and 2), but only 22 participants attended the second phase. Of these 22 participants, 3 had not attended the first phase of the event. The stakeholders this phase represented four sectors and were accordingly arranged at four working tables.

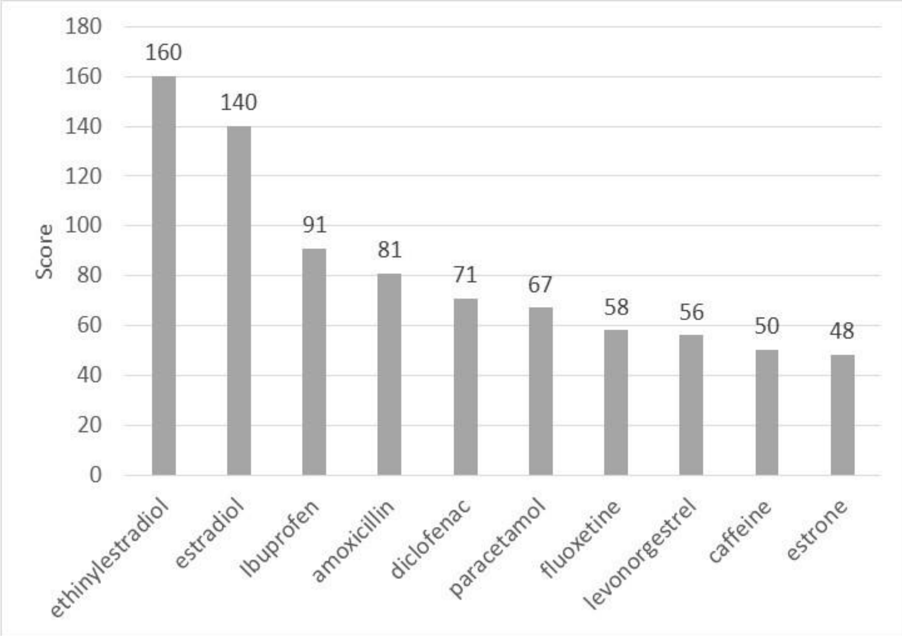
Both in the second and in the first phase of the event, each working table had a mediator / rapporteur. They had the function of leading the discussion, if necessary, and reporting on its most important points. In the two phases of the event, one of the participants at each table was responsible for filling in a standard sheet with the results of the table by consensus. In the plenary sessions there was also a rapporteur. At the start of the plenary session of the first phase of the event, a free discussion was established. In the meantime, the support team calculated the values of the top seven (first round) and top five (second round) – seven and five points were assigned to the first in the ranking each table, six and four to the second and so on - of the four work tables, creating a single ranking for each round. It should be noted that the scoring systems were merely illustrative so that reflection and discussion could be established; consensus was the basic principle of the entire event. In the plenary sessions of the second phase of the event, the most important goal agreed by each sectoral table (first round), the ways to achieve it and the timeframe (second round) were read aloud to allow a moment for reflection and multisectoral discussion. At the end of the second plenary sessions at both the first and the second phase of the event, the Mentimeter® software was used to perceive the individual opinion of the participants.

3. PRIORITY PHARMACEUTICAL PRODUCTS FOR WASTE MANAGEMENT

The first result obtained was derived from the individual lists brought in by the invited stakeholders. For the construction of a classification, a scoring system was assigned to the individual lists, following the same logic as those developed for the top 7 and 5. Scores in individual lists were summed by compound resulting in a ranking (Figure 2). It should be noted that exercise of classification of individual lists was carried out after the meetings, only in an exploratory way, and participants not have access this ranking. The lists were used in the working tables and delivered at the end of the event.

A total of 65 different pharmaceuticals were mentioned on the individual lists. Those most frequently prioritized belonged to the following therapeutic groups: hormones, with four compounds (ehinylestradiol, estradiol, estrone and levonorgestrel), two of which were first and second in the ranking; anti-inflammatories (diclofenac and ibuprofen); antibiotics (amoxicillin and ciprofloxacin); an analgesic (paracetamol); a psychotropic (fluoxetine) and a stimulant (caffeine). Ciprofloxacin, which was not on the 'long list', was selected in many individual lists and ranked 11 in this initial exercise.

Figure 2. Top 10 priority pharmaceuticals of according to the individual perceptions.



The results of the first round of negotiation (Figures 3 and 4) – the closed meeting where working tables attempted to identify 7 pharmaceuticals as priorities - show that the second subgroup (Figure 4) of stakeholders had more difficulty to agree on the most important compounds compared to the first subgroup (Figure 3), with the final list of the subgroup 2 showing 13 pharmaceuticals whereas the of subgroup 1 showed only 8. The score of the first placed in the ranking was significantly lower in the subgroup 2, and there were also pharmaceuticals tied in the fourth, fifth and seventh position of the final list.

In the subgroup 1 plenary, the focus of the discussions was what pharmaceuticals should be prioritized and what would be the criteria for choosing them. On the other hand, in the subgroup 2, the discussion was focused on the paradox: prioritizing specific pharmaceuticals based on their individual importance or identify markers for the various therapeutic groups. In this subgroup, virtually every working tables agreed that it would be better to prioritize markers rather than specific pharmaceuticals. Perhaps this is the most logical explanation for the greater balance in the list of the priority pharmaceuticals pointed out by subgroup 2.

In the plenary session of the round, the results of the prioritization of each working table and the pharmaceuticals with the highest aggregated score (adding up the values of all working tables) were presented for general discussion. After the plenary, the groups returned to the working tables in order rank the top 5 pharmaceuticals, based on the general ranking of the pharmaceuticals prioritized in the first round.

Figure 3. Top 7 priority pharmaceuticals of according to stakeholders (First Round) subgroup 1.

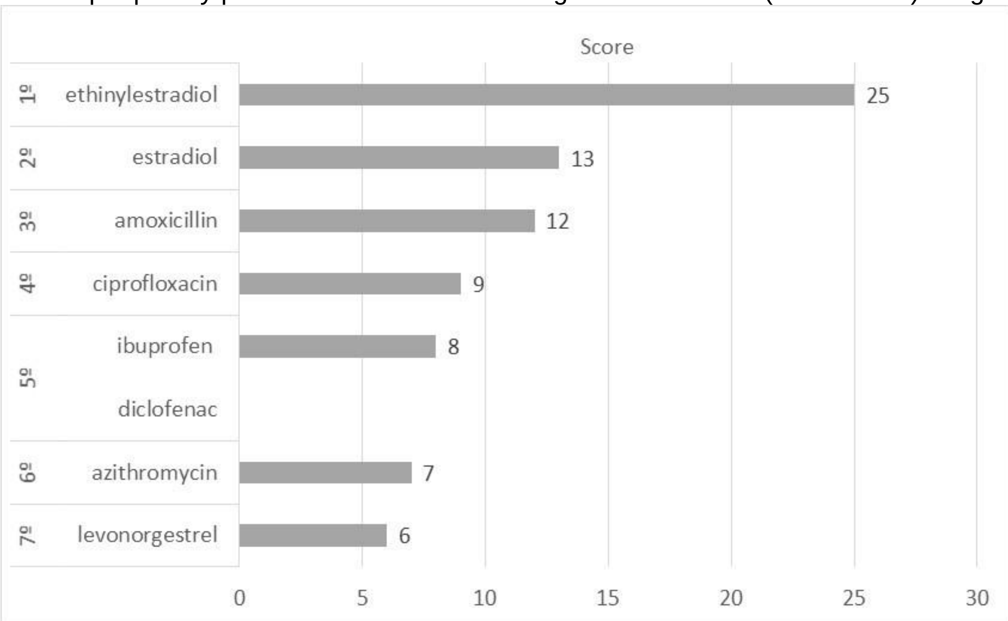
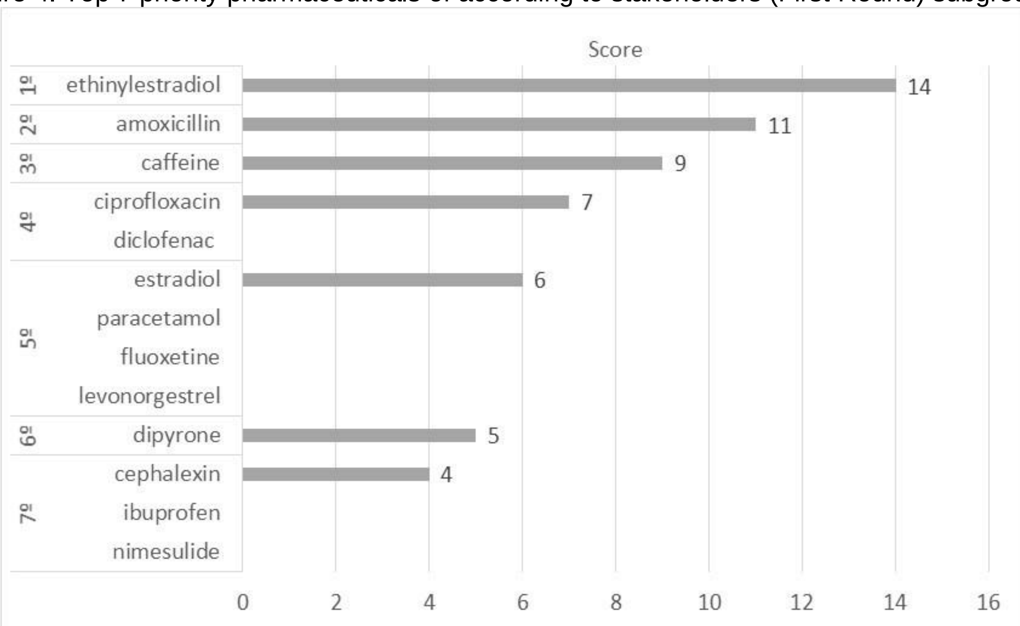
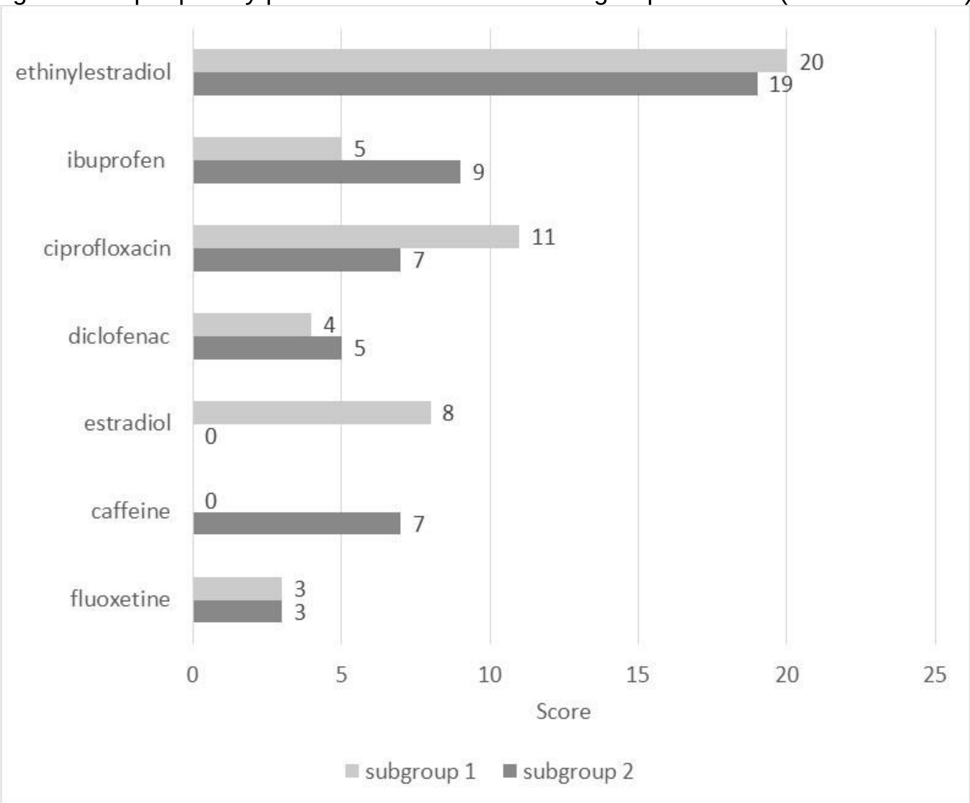


Figure 4. Top 7 priority pharmaceuticals of according to stakeholders (First Round) subgroup 2.



With a second round of discussion in the working tables, each table was able to produce a consensual ranking of five of the most important pharmaceutical products for the management of the waters of the region of Curitiba. The results of the second round of discussion were tabulated with the scoring system that was used to present the aggregated results of the four tables working in the plenary (Figure 5).

Figure 5. Top 5 priority pharmaceuticals for the subgroups 1 and 2 (Second Round).



Subgroup 1 agreed that antibiotics should be included as a group because antibiotic residues may represent important environmental and public health problems. It was agreed that the detection of antibiotics can be done indirectly, measuring the effect of bacterial resistance to pharmaceuticals, since this methodology has a low cost and an easy analytical procedure unlike the chromatographic methods. Ciprofloxacin was the antibiotic most indicated by the stakeholders, because its molecule remains active after treatment (it is persistent). Beta-lactam antibiotics, despite being listed as a priority in the literature, were discarded by stakeholders because they degrade easily in the environment (Mitchell et. 2014; Timm et. 2019). Fluoxetine was not indicated as a priority because, according to stakeholders, there are other pharmaceuticals whose impacts are more relevant. The anti-inflammatory nimesulide, widely used in Brazil, was mentioned by this subgroup in plenary, as it is a molecule that needs to be further studied regarding its potential risks to the environment, but is currently not recognized by the group as a priority. In the end, the subgroup 1 agreed that the order of prioritization was established more by the potential risks to the environment than by frequency of use.

After the plenary session that identified the 5 priority pharmaceuticals for the management in subgroup 1, according to the aggregate score of the work tables (Figure 5), a survey was carried out using the software Mentimeter®, in which the stakeholders were invited to answer, with their smartphones, a question about their satisfaction with the ranking produced. The results showed a high degree of satisfaction regarding the final ranking: 14 out of the 17 participants answered the question (three participants had to leave before the end of the discussion and so they did not answer the question), whereby four stated they were very satisfied, eight were satisfied, two were not entirely satisfied, and no one answer for the option "unsatisfied" or "very unsatisfied". The two stakeholders who were not entirely satisfied were a representative from the pharmaceutical industry and hospital. For the hospital representative, the dissatisfaction was due to the fact that the management of some priority molecules would require a very specific investment and a more macro view was needed. In the case of one of the representatives of the pharmaceutical industry the dissatisfaction was due to the fact that only two pharmaceuticals prioritized in their individual list were in the top 5 of the group.

In the subgroup 2 plenary, one participant stated that in their perception it seemed reasonable and feasible to introduce legislation requiring monitoring of pharmaceutical micropollutants in urban river waters, with one representative compound for each pharmaceutical group. For him, the monitoring procedures would be feasible financially, since some institutions already have equipment to carry out the measurements. However, this was not the consensus among the various sectors represented at the meeting. In the working tables of this subgroup, participants frequently suggested caffeine for inclusion in the list of priority pharmaceuticals, since it is an indicator pharmaceutical for the presence of sanitary effluents, which is the main vehicle of several pharmaceuticals for rivers (Figure 5). Caffeine has been shown to being a good indicator for the presence of other pharmaceutical compounds because, in addition to be a persistent molecule in the environment, it is present in many pharmaceuticals as an auxiliary substance (Daneshvar et al. 2012; Montagner et al. 2014; Baz-Lomba et al. 2016; Alygizakis et al. 2016; Korekar et al. 2019). Another substance mentioned that could be used as an indicator was Carbamazepine: some experts have already used this compound as a monitoring alternative to Caffeine since it is also a persistent molecule and widely used in the pharmaceutical industry (Guo and Krasner, 2009; Wang and Wang, 2017; Dinis et al. 2017; Dvory et al. 2018). It was discussed by the group that it might be interesting to include as a priority the pair of anti-inflammatory pharmaceuticals, diclofenac and ibuprofen, as both are widely used at all times of the year.

Again, with use of the software Mentimeter®, applying to the audience a final question about the overall satisfaction with the aggregated prioritization results (Figure 5), most of the participating stakeholders agreed with the final ranking. Of the 17 stakeholders 9 answered the question (eight participants had to leave before the end of the discussion and so they did not answer the question), where seven respondents said they were satisfied and two indicated the option "I am not entirely satisfied" with the priorities highlighted by the group. For stakeholders who were not entirely satisfied were a representative from academia and a hospital. For the hospital representative the dissatisfaction was because two anti-inflammatory pharmaceuticals (ibuprofen and diclofenac) on the priority list would be too much - should be one or the other. In place of one, his would include an antineoplastic. For the academic stakeholder the dissatisfaction was because triclosan should be on the medication prioritization list, as it is an endocrine disruptor, bioaccumulative and in many countries, such as the USA and some European countries, it is already banned, while in Brazil it is still used as a preservative in hygiene products (shampoos, soaps, etc).

There was a clear similarity (Figure 5) between the two lists of 5 priority compounds as identified in the two subgroups, which demonstrates the validity of the method since the stakeholders who participated in the two subgroups were different, with no contact between the groups.

Table 1 shows the final score of the ranking pharmaceuticals identified as priorities by the stakeholders in this first phase of the workshop and the justifications that were given for their prioritization. Ethinylestradiol, ibuprofen, ciprofloxacin and diclofenac were identified by both subgroups as the four most important pharmaceuticals for water management. Regarding the fifth priority pharmaceutical, the hormone estradiol had a higher score (8), however, caffeine (7) and fluoxetine (6) had a very close score. Therefore, there are still doubts about the fifth substance to be prioritized.

Table 1. Priority pharmaceuticals for water management according to the stakeholders' perception.

ACTIVE PRINCIPLE	SCORE	JUSTIFICATION
1- Ethinylestradiol	39 out of 50	Detected in waters at high concentrations, high consumption, continuous use, impact at low concentrations on several types of organisms, endocrine disrupter, causes infertility, carcinogenic, good marker for the synthetic hormones and difficult to remove in both sewage and water treatment.
2- Ciprofloxacin	18 out of 50	Broad-spectrum antibiotic, induces bacterial resistance, high environmental stability, large percentage excreted unchanged via urine.
3- Ibuprofen	14 out of 50	High sales and consumption, proven toxic effects in fish, low LOEC*, genotoxic effects, persistent in the environment and resistant to the treatment, effects in low concentration and detected in waters.
4- Diclofenac	9 out of 50	Immunotoxic, genotoxic, immunosuppressive, high environmental impact, causes renal failure in birds, low LOEC*, high consumption, frequently found in waters and resistant to biological degradation.
5- Estradiol	8 out of 50	High consumption, causes endocrine disruption, low LOEC* and resistant to degradation.
Caffeine	7 out of 50	Marker of the presence of anthropogenic emerging contaminants and high consumption.
Fluoxetine	6 out of 50	Widely used pharmaceutical with environmental effects in low concentration, low LOEC* and difficult to remove in treatments plants.

*Ecotoxicological LOEC - Lowest Observed Effect Concentration.

4. FEASIBLE MANAGEMENT GOALS

The feasible goals for the management of the pharmaceutical micropollutants in the Curitiba region were discussed at the second phase of the workshop that took place on November 27, 2018. As mentioned, participation at this event was significantly lower, with only 22 participants out of about 34 expected stakeholders in attendance. One important and significant lack was the absence of the government sectoral group (policy makers): no representative of that sector attended the event.

Not surprisingly, the individual goals were quite diverse, although they pointed in converging directions. Frequently suggested individual goals were:

1. The full implementation of a drug take-back program of expired or obsolete pharmaceuticals. The scope of this initiative varied in the lists, which sometimes indicated a state scale of coverage (in the cities of Parana State), sometimes local (pharmacies and medical centers in Curitiba) and sometimes sectoral (encompassing pharmaceutical distributors);
2. Periodic monitoring of pharmaceutical micropollutants in water supply and river basins. With regards to monitoring, the individual lists pointed out two directions: a) to monitor those of greater consumption; b) to create a working

group to discuss and make feasible this activity, in terms of infrastructure and equipment, partnerships, costs and analytical methodologies;

3. Development and testing of efficient treatments for the removal of priority pharmaceutical micropollutants in water and sewage. The scope of the proposal was to find efficient treatment for water industry, responsible for municipal water and sewage treatment, and pharmaceutical industries. In this goal, it was evident that participants saw this as academic research at this stage, because little was thought to be known about the viable and effective techniques of removal of these compounds;
4. Multisector partnerships: academia, pharmaceutical sector, pharmaceutical and water industry as well, for the identification of priority compounds, development of analytical methodologies and the removal of these compounds;
5. Universalization of sanitation systems including sewage networks and treatment plants;
6. Implement a limit concentration for priority pharmaceutical micropollutants in rivers and water supply systems in the coming years;
7. Evaluation of the internal processes of the pharmaceutical industry to reduce the generation of waste and consequently lower the concentration of emerging micropollutants in the effluents;
8. Environmental education for the correct disposal of pharmaceuticals, rational use, and reduction of self-medication: this educational process would occur through recommendations on the packaging of pharmaceuticals and advertisements (newspapers, television, bus stops, etc.).

In the individual goals, as well as in those discussed at the sectoral working tables, the absence of public policy was a clear consequence of the absence of the government sector.

The lists of individual goals presented a preview of what would be discussed at the sectoral tables, but the robustness and originality of the goals discussed at the table far outstripped those highlighted by the individual goals.

The general discussion on management goals was quite comprehensive bringing several new elements to the discussion. From the hospital and pharmaceutical perspective, addressing and solving the problem of pharmaceuticals in the environment is very difficult, since much of the problem is related to human excretion, requires specialized treatment plant and cannot be solved by the sector.

Although reconsidering of packaging sizes of pharmaceuticals is not in the sectoral goals, this goal was highlighted in the general discussions as a simple and efficient management measure, which in Brazil is not considered, there is no legislation that requires this of industry. It is known that packaging size can influence consumption, better serving users' needs and preventing the generation of unused and expired pharmaceuticals (BIO Intelligence Service 2013), for this some insdustries have already been working on this direction. The pharmaceutical sector stressed that the federal regulation should be modified in favor of this measure. In this way, the pharmaceuticals would not be stored unused at home.

Collection of expired or discontinued pharmaceutical products was a much-mentioned and discussed management initiative, both in sectoral goals and general discussions. Although there is clear progress in this regard, Brazil is still in an early phase of this management initiative (Aquino et al. 2018; Barcellos et al. 2019, p. 126; Rebehy et al. 2019). The feasible management goals that were agreed upon by each one of the four sectors participating in the event are presented in Tables 2, 3, 4 and 5.

The pharmaceutical sector stressed that through the Parana State pilot drug take-back program, which ended in 2017, 9.6 million kilograms of unused pharmaceuticals were collected. The participation of drugstores in Foz do Iguaçu, a city around 600 km far from Curitiba, where the population's adherence to the project was high, was highlighted as a success. In Paraná, the law that regulates the drug take-back program came into force in July 2018, with, 270 collection points in operation and the goal for 2019 is that further 500 points be installed. As State legislation covering drug take-back programmes is recent, the project under development is considered as pilot and is still in the test phase. The collection of pharmaceuticals is carried out for 60 consecutive days at each location, after which the collection point is moved to another pharmacy. Collected pharmaceuticals are transported to an incineration plant in São Paulo, with support from the Union of Pharmaceutical Products Industry in the State of São Paulo (SINDUSFARMA).

Table 2. Distributors and pharmaceutical industries goals.

Goal for minimization / mitigation	How to reach it	Time scale (envisaged completion time) (short - up to 5 years, medium - 5 to 10 years or long term - over 10 years)
Implement drug take-back program of overdue or obsolete pharmaceuticals in at least 50% of pharmacies in each municipality of Paraná*	Establish partners among trade peers to optimize the drug take-back procedure	Up to 5 years
	Use drug take-back program for the marketing of partner companies as ‘environmentally friendly’	5 years to 10 years
	To form associations between the companies interested in fomenting and influencing public policies for fiscalization and fiscal incentives the drug take-back	5 years to 10 years
Raise awareness amongst the public the importance of drug take-back through the packaging material of the pharmaceutical itself	Change the patient information leaflet of pharmaceuticals and / or cartridges to including guidance on drug take-back program	Up to 5 years
Monitor the presence of pharmaceutical residues in industrial effluents from the production of pharmaceuticals	Make an initial study to identify the worst cases	Up to 5 years
	Validate analytical methods	Up to 5 years
	Monitor critical compounds	More than 10 years

*Goal nominated by sector as more important.

The pharmaceutical industry, on the other hand, reported having developed a separate, smaller scale project support with Union of the Chemical and Pharmaceutical Industries of the State of Paraná (SINQFAR-PR) whereby 60 pharmaceutical collection points have been established on a permanent basis in the State of Paraná. In the State of São Paulo, laws regulating the drug take-back program are of municipal scope, but are at a more incipient stage than what occurs in Parana State. The Federal Law Project that will be regulating this topic, and is currently in discussion in the National Congress, was also cited as essential for the expansion of drug take-back in Brazil.

The representatives of the water industry suggested to the group, especially to the representatives of the pharmaceutical sector, that it would be useful to include in product packaging information about the impact of pharmaceutical residues on the environment and on human health.

Table 3. Water industry goals.

Goal for minimization / mitigation	How to reach it	Time scale (short - up to 5 years, medium - 5 to 10 years or long term - over 10 years)
Carry out an environmental education campaign on the correct disposal of pharmaceuticals	Partnerships between prefectures and pharmaceutical industry	Up to 5 years
	Environmental education activities in communities, churches, etc	Up to 5 years
	Illustrations on boxes of pharmaceuticals, leaflets and posters in pharmacies doing propaganda	5 years to 10 years
Improve understanding of the behavior of pharmaceuticals in the sanitation cycle*	Seek support from academia and the pharmaceutical industry to define priority pharmaceuticals, tolerance limits, methodology and standard.	5 years to 10 years
	Development of methodologies and research	Up to 5 years
	Monitoring of the active principles defined as priorities	More than 10 years
Identify actions of the internal programs of control of irregular connections and diagnosis of the integrity of sewage collection networks	Partnerships with inspection bodies for intensive campaigns to identify irregular connections	Up to 5 years
	Update of registration of activities (hospital, industrial, commercial, etc.) that launch effluents	Up to 5 years
	Identification by telediagnosis, improve equipment and better equipping the teams	5 years to 10 years
Promote research looking for viable alternatives for the removal of these compounds	Partnerships with universities and the pharmaceutical industry to investigate ways of removal	More than 10 years
	Partnership with society to encourage the pharmaceutical industry to develop biodegradable products	More than 10 years

*Goal nominated by sector as more important.

Participants from all sectors noted the absence of government stakeholders in the discussion. This constituted a gap in the intersectoral dialogue, as government institutions have a fundamental role in the introduction of public policies. It was noted that many of the measures targeted by the sectors can only be implemented if there is effective participation of the government. The need for synergy among sectors (government, water industry, pharmaceutical industries and distributors, hospitals and pharmacies, and academia sectors) was evident in the discussion for effective progress in the management of pharmaceutical micropollutants in Brazil.

Table 4. Pharmaceutical and hospital goals.

Goal for minimization / mitigation	How to reach it	Time scale (short - up to 5 years, medium - 5 to 10 years or long term - over 10 years)
Raise awareness about minimizing pharmaceuticals use as well as correct disposal*	Carrying out publicity campaigns in class councils - professionals (Regional Council of Medicine, Regional Council of Pharmacy, etc.)	Up to 5 years
	Campaigns to inform the population through the media, in general, in schools and universities	Up to 5 years
	Creation of a recognisable logo for a campaign	Up to 5 years
Implement a legal requirement setting out allowable concentrations (for rivers and sewer) for pharmaceutical micropollutants	Supporting public bodies to develop relevant legislation in conjunction with the class councils and universities	Up to 5 years
Periodically monitor the use of pharmaceuticals with its distributors	Encourage meetings with the medicinal chain to carry out the survey of the market numbers (sales report)	Up to 5 years
	Establish indicators that show the amount of pharmaceuticals sold versus pharmaceuticals unused (drug collection program)	Up to 5 years

*Goal nominated by sector as more important.

The water industry, represented by the Parana State Sanitation Company (SANEPAR), showed that these collaborative actions are indispensable for the sector due to the need for research technological advances that can only be developed with at least the support of academia. Its representatives also added that they would be very interested to open a more effective dialogue with the pharmaceutical sector to facilitate information exchange and enhance understanding of risk from pharmaceutical residues to the environment and to human health.

Another discussion that was emphasized by the representatives of the water industry, considered the importance of establishing specific legislation to establish the monitoring of pharmaceuticals along with the establishment of safe concentration limits in river waters. A government representative in the first phase of the event also positioned himself in a favorable way to this, arguing that the periodic monitoring of these molecules is already financially viable, thus feasible.

Table 5. Academic goals.

Goal for minimization / mitigation	How to reach it	Time scale (short - up to 5 years, medium - 5 to 10 years or long term - over 10 years)
To develop methods and processes that improve techniques of identification and detection of micropollutants	Develop and validate analytical protocols that suit the needs	Up to 5 years
	Reduce analytical costs	5 years to 10 years
Improve methods of collection and treatment of sewage and water	Create prototypes, simulators and the like (test new materials)	Up to 5 years
	Transfer technologies to other sectors	5 years to 10 years
Train academics and other stakeholders to deal with the problem (micropollutants)	Form research groups	Up to 5 years
	Empower potential leaders	Up to 5 years
Create a permanent environment for discussion of micropollutants among different sectors*	Map the areas of expertise (visibility and resources) internally or externally	Up to 5 years
	Capitalize resources and public and private partners	Up to 5 years
	Identify key interests, perspectives and opportunities	Up to 5 years

*Goal nominated by sector as more important.

At the end of this second phase of discussions, Mentimeter® was used to assess stakeholders' perception regarding the timeframe necessary achieve a similar level of control over pharmaceutical residues in the environment as is the case in some developed countries in Europe (United Kingdom, Germany, Netherlands, etc). Twelve out of the 22 participants answered the question (ten had to leave before the end of the plenary). Of the respondents, one answered that it would take "5 years", five answered "5 to 10 years", another 5 indicated that it would take "10 to 20 years" and one responded "more than 20 years". At this point, the pharmaceutical sector spoke up and said that the pharmaceutical industry must modify its production system in order to reduce pharmaceuticals in the environment. Another point touched was that the treatment of sewage is significant and should be prioritized because it reduces the pharmaceuticals in the environment.

5. CONCLUSION

The compounds prioritized (seven clearly had more importance) by the stakeholders in the workshop reflect the sectoral interests related to pharmaceutical pollution in the water and its management. The multidisciplinarity and multisectorality of the stakeholders present at the meeting ensured a comprehensive view of the problem, indicating which are the most important pharmaceuticals for management in the region of Curitiba and why they should be prioritized. On a national scale, these compounds are also likely to be important, but it is necessary to make efforts of prioritize in other regions because each region will have a different consumption pattern and, consequently, a different pollution pattern.

The management goals are also important to think about and act towards the management of pharmaceutical micropollutants on the national scale and these are more generalizable than a list of priority substances. The multisectoral discussion about feasible actions showed that some initiatives priority have already started but are still emerging, as is the case of drug take-back program. Raising awareness amongst the population on the correct disposal of pharmaceuticals was defined as a priority goal, as were the technical and political aspects of implementation of the drug take-back program in Brazil. This issue is still a major challenge on a national scale and, due to its shared attribution, it is necessary to construct multisectoral networks and also have the participation of the population. Monitoring efforts to characterize the behavior of pharmaceuticals in the sanitation cycle and the creation of a permanent multisectoral environment for discussion on pharmaceutical micropollutants were the other two management goals prioritized. The new fronts of action and the challenges of each sector were also important elements of multisectoral discussion for enabling each sector to recognize the complexity of the problem and understand the need for a collective approach of problem, as already occurs in Europe (NOPILLS, 2015).

However, the workshop represented an important initial step towards the management of pharmaceutical micropollutants in the Curitiba region and Brazil, being the first meeting with this multisectoral character in the country to discuss this type of pollution. In addition to the knowledge produced collectively, the most important legacy of this event was the formation of a network to discuss this problem and advance its management. The 37 stakeholders who participated in the event have great engagement in their sectors and relevant capacity for action. It is hoped that the established network can be maintained and work collaboratively for the management of pharmaceutical micropollutants, as is it done successfully in Europe.

The methodology used to conduct the workshop reached its objectives, producing collective knowledge in an interactively way, as well as informing and connecting people towards a common goal. This approach has shown promise for developing countries, such as those in Latin America, which are general still taking the first steps towards managing this kind of problem.

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CHAPTER 4: BLUE-GREEN INFRASTRUCTURE IN CITIES: ADAPTATION OF CLIMATE CHANGE AND REDUCING WATER POLLUTION BY PHARMACEUTICAL MICROPOLLUTANTS

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ABSTRACT

In the context of climate change, city planning needs to seek holistic solutions that, in addition to mitigating the effects of climate change, can move towards the solution of other urban environmental problems. The pollution of urban waters is a critical problem in Brazilian cities that still have a deficient sanitary infrastructure. While emerging pollutants in developed countries have already occupied a prominent place in discussions, these pollutants have not received attention in Brazil. This paper discusses using the Blue-Green Infrastructure (BGI) as a systemic solution for cities, discussing its potential to remove pharmaceutical micropollutants, its feasibility, and possible scenarios for implementation in the region of the main river basin of Curitiba city, Brazil. The first part of the paper discusses the effects of climate change on the water regime of cities, conceptualizes BGIs, and discusses pollution by pharmaceutical micropollutants as a new urban challenge. In the second part of the paper, the scenarios for implementing BGIs in Curitiba, available areas, costs, urban potentialities, and the most suitable types of plants are investigated and discussed. BGIs, with their multifunctionality and low cost, have the potential to spread across the developing world, pointing to the future of cities and urban planning.

KEY-WORDS: Water quality management; Blue-Green Infrastructure; Emerging pollutants; Urban planning; Climate change adaptation; Resilience cities.

1. INTRODUCTION

The growing and competing demands of society for water have increased the complexity of water management, especially in cities where water resilience is a goal. This is the case in both developed and developing countries. Climate change adds a further layer of complexity. Climate change is changing the hydrological cycle with an intensity that differs from place to place but shows the general behavior of intensifying droughts and heavy rains (MacAlister & Subramanyam, 2018). Although climate change has global causes, cities need adaptation measures to mitigate its effects. Therefore, it is necessary to implement monitoring, planning, and control measures in relation to both extreme weather (rainfall deficits and high precipitation volumes), depending on the scenarios for each region.

For developing countries such as Brazil, there are other variables that make water management challenging. Unlike much of Europe or developed countries such as Canada, the USA, and Australia, discharge of sanitary effluents into urban rivers is still common in Brazil. The developed world is already responding to new urban water quality issues such as micropollutants (Gilbert, 2012; Cunha et al., 2016), but the focus in Brazil is still on achieving universal sanitation. Therefore, in the developing world, cities need to deal with global problems such as climate change while simultaneously solving local issues such as water pollution. Efficient technologies that mitigate floods and water scarcity, improve water availability and water quality management (such as minimizing micropollutants concentration and presence) are emphasized in the plan for cities in developed countries.

In this paper, we propose a nature-based approach for the removal of pharmaceutical micropollutants from urban waters, a type of pollution for which management strategies are still lacking in the developing world. The methodological approach is new for Brazil and Latin American but perfectly feasible for any developing country where funds are tight, emphasizing the possibilities of these technologies to mitigate the challenging problem of pharmaceutical micropollutants. The object of analysis was the city of Curitiba, the capital of the Paraná state and the biggest city of southern Brazil. The paper's main objective is to discuss the applicability of Blue-Green Infrastructure (BGI) as means of supplementing water quality management systems while also providing multiple co-benefits for cities. In the first part of the paper, we present some cases of extreme weather events in cities; we conceptualize systems of BGI with an emphasis on removing micropollutants and; we outline the problem and management strategies of pharmaceutical micropollutants. In the second part of the paper, we contextualize the pharmaceutical pollution in Curitiba by its main river basin and propose possible BGI solutions. This paper discusses a new way for urban planning in Brazil already scattered for the developed world, fundamentally based on natural capital, where even controversial and challenging problems like pharmaceutical micropollutants can be mitigated with a systemic and feasible approach.

2. BACKGROUND

2.1 Climate extremes and urban water management

Climate extremes represented by heavy rains and prolonged droughts are a significant problem for cities, especially in terms of sustainable and resilient water management. In addition to quantitatively affecting local water availability for multiple human activities, they also cause substantial oscillations in the water quality, making it difficult to treat. These vulnerabilities are a reality in several countries where problems for water supply in major cities have been reported recently.

Australia is highly susceptible to flooding. Data show that, in the period from 1967 to 1999, about AU$ 314 million was spent each year to minimize its effects (Gentle et al., 2001). Comparing post-disaster expenditure, considering different climate events shows that floods were the most expensive type of natural disaster in Australia, followed by severe storms and tropical cyclones. Heavy rains are the predominant cause of floods, usually combined with other elements such as rainfall distribution and, soil imperviousness, among other factors (Ghofrani et al., 2016). Therefore, the need to prepare Australian cities for extreme weather events, such as heavy rains causing floodings, is strategic for water management in the urban context.

Droughts have also caused water rationing in large urban centers due to depleted water supply reservoirs. Three of the most recent cases are in Cape Town in South Africa, Barcelona in Spain (Martin-Ortega & Markandya, 2009), and São

Paulo in Brazil (Otto et al., 2015, Zuffo, 2015, Muller, 2018). In all of these cases, the main point of discussion was whether climatic extremes could be attributed as the primary driver of these events. There is evidence of deficiencies in urban planning and water management in some cases too.

In the case of Barcelona, historical records show that the 2007-08 drought was the most severe of the century and was therefore an exceptional climatic event (Martin-Ortega & Markandya, 2009). In the specific case of São Paulo, historical precipitation data in the Southeastern region of Brazil do not demonstrate a robust temporal anomaly in the rainfall regime for the period 2014-15 (Zuffo, 2015; Otto et al., 2015), although hydrological models predicted the risk of severe drought (Muller, 2008). On the other hand, in the Northeast region of Brazil, a climatic evaluation of the period 1981-2016 showed that this region presented the most severe and prolonged drought between 2011 and 2016 (Brito et al., 2018). In Cape Town, the 2016-17 drought was indicated in 2009 by hydrological models, which pointed to the need to increase water reserves for human supply. However, authorities dismissed these recommendations (Muller, 2018). These case studies, which are three of many, show that water supply problems caused by droughts in large cities are a combination of the effects of extreme weather events and problems of city management and preparedness for climate change.

In addition to the problems related to the amount of water, whether it is excessive, causing floods, or scarce leading to shortages, extreme climatic events also cause oscillations in urban water quality by concentrating or diluting the aquatic pollutants. For example, in the São Paulo water crisis, pumping the volume near the bottom of the city's reservoirs was announced as an emergency measure (Soriano et al., 2016). This was a point of much debate by specialists since the concentration of some pollutants, mainly inorganic micropollutants such as heavy metals, could be higher near the bottom of the reservoirs. In drought events, urban rivers can also increase the concentration of pollutants by reducing their base flow, significantly increasing pollution levels.

2.2 Blue-Green Infrastructure and the environmental sustainability of cities

In developed countries that are in the "sustainable" phase of sanitation management (Tucci, 2008), there are advances in solving problems of water management with the use of systems known as Green Infrastructure (GI) or Blue-Green Infrastructure (BGI). The term BGI evolves from the Australian concept of Water Sensitive Urban Design (WSUD) and refers more particularly to "green" that temporarily turns "blue" during rain and flood events (Everett et al., 2015; O'Donnell et al., 2020). The ideas and practices related to these systems have been used for a long time, although this overarching concept is relatively new. Internationally, BGIs has been applied under various terms or programs, such as Stormwater Best Management Practices (BMPs) and Low Impact Development (LID) in the USA, Sustainable Urban Drainage System (SUDS or SuDS) in the United Kingdom, Alternative techniques (ATs) or Compensatory techniques (CTs) in France, Water Sensitive Urban Design (WSUD) in Australia, Low Impact Urban Design and Development (LIUDD) in New Zealand, ABC (Active, Beautiful and Clean) Singapore Water Program, and Sponge City Initiative in China (Fletcher et al., 2015; Liao et al., 2017). BGI “is an interconnected network of natural and designed landscape components, including water bodies and green and open spaces” (Ghofrani et al., 2017) that provide multiple functions: water purification, flood control, water storage, treatment, and wetlands for wildlife habitat, among others (Ghofrani et al., 2017; Brears, 2018). These systems are the green roofs that are numerous in some European cities, the rain gardens or bio-retention ditches common in several cities in the United States, and the various wetland systems and retention/detention basins spread across Australia’s metropolises.

The BGI systems offer natural solutions for urban water management, with costs equivalent to those of traditional systems (Lloyd et al., 2002), and important examples of their efficiency are reported in the literature: to control urban floods, such in Belgium; increased water infiltration, reduced surface runoff, decreased urban heat island effects, and coping with climate change, such in Japan (Ghofrani et al., 2017); reduction of excessive load in the drainage systems and frequent overflow events in the combined systems, forcing the discharge of sewage and rainwater directly into rivers and causing flooding, such in USA (O'Donnell et al., 2020); reduced risk of flooding, due to the inability of drainage systems to receive large volumes of precipitation, such in United Kingdom (Ellis, 2013) improvement of water quality, and ecological destination for drainage water to reduce the burden on the unit system and guarantee water security for cities, such in Australia (Wong, 2006; Liao et al., 2017). Using BGI systems to improve urban water quality can remove the most diverse aquatic pollutants (Table 1).

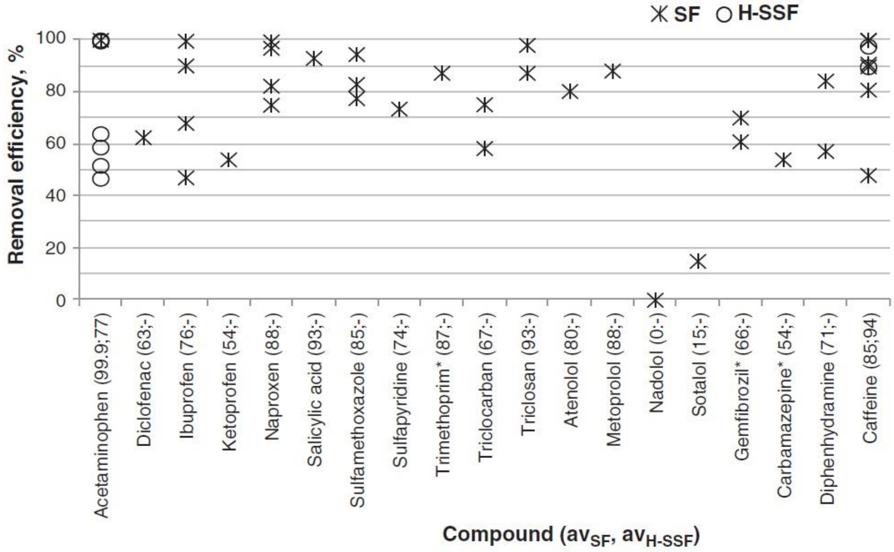
Table 1. Relative improvement in water quality, reduction volume, and recharge performance of Green-Blue Infrastructure practices.

Green Infrastructure Practice	Quality and Quantity Benefit										
	Bacteria	Metals	Organics	Sediment	Pesticides	Nutrients	Oil and Grease	Trash	Flow rate	Volume reduction	Groundwater recharge
Bioretention cells	+++	++	++	+++	++	+++	++	+++	+++	+++	+++
Bioretention strips/swales	+++	++	++	+++	++	+++	++	+++	+++	+++	+++
Infiltration basins/swales/trenches	+++	++	++	+++	++	+++	++	+++	+++	+++	+++
Planter boxes	+++	++	++	+++	++	+++	++	+++	++	++	++
Constructed wetlands	+++	++	++	+++	++	++	+++	++	+++	++	++
Rainwater capture	++	++	++	+++	++	++	++	++	+++	+++	+++
Permeable pavement	+++	++	++	+++	++	+++	+	+	+++	+++	+++
Dry wells	+	+	+	+	+	+	+	+	+++	+++	+++

Source: adapted from USEPA, 2013.
Note: +++=primary benefit; ++=secondary benefit; +=little or no benefit

The use of wetlands, especially for water quality improvement, is already a well-established solution and an alternative with public acceptance (Schröder et al., 2007). Experiences of the implantation of these systems in urban water bodies are numerous. Some of these systems focus on treating waters derived from urban drainages, such as in Melbourne, Australia (Allinson et al., 2015), and the Welsh Harp Reservoir in London, England. While others also treat wastewater such as Lake Enäjärvi, Vihti in Uusimaa in Finland (Wahlroos et al., 2015), Parc du Chemin de I'lle in Nanterre in France - where there are processes of de-pollution of the Senna River - and Putrajaya Lake in the city of Putrajaya in Malaysia (Shutes et al., 2001). However, regarding the ability of these systems to remove emerging micropollutants, especially pharmaceuticals, the information is early because it is still the subject of recent studies (Li et al., 2014; Gorito et al., 2017) and a new problem for urban water quality management. The results of some studies that tested the effectiveness of wetlands in removing pharmaceutical products (Figure 1).

Figure 1. Reported removal efficiencies in constructed wetlands acting as a primary step.



Source: Verlicchi & Zambello, 2014
Note: Circle = H-SSF (horizontal subsurface flow) bed, asterisk = SF (surface flow). *Negative percentage removal efficiencies reported for trimethoprim (−283%), gemfibrozil (−68%) and carbamazepine (−44%, −177%, −316%).

2.3 Pharmaceutical pollutants in urban waters and management challenges

The problem of pharmaceutical residuals in rivers and other water bodies in urban areas has been emphasized internationally because of its importance to the natural environment and public health (Fent et al., 2006; Owen & Jobling, 2012). This class of pollutants originates in sewage since, after use, they are excreted by the body in unchanged form or as metabolites and many exist as compounds that are resistant to the treatment of sewage and water (Aquino et al., 2013; Dias, 2014). Additionally, the pharmaceutical sector generates a significant part of this residual itself (Cue & Zhang, 2009).

The same wastewater produced in cities often returns to the water supply systems by the common “indirect and not planned reuse of wastewater” (Hespanhol, 2014). Once conventional water treatment systems and sewage treatment systems cannot altogether remove these compounds, the presence of traces of medical substances in supply water has been reported worldwide (Dias, 2014; Sun et al., 2015). Their presence has already been observed in drinking water in the USA, Canada, France, Spain, the Netherlands, South Korea, and China (Sun et al., 2015). In the drinking water provided in the three most populous Brazilian metropolitan areas - São Paulo, Rio de Janeiro and Belo Horizonte - significant concentrations of medical substances have also been found (Ghiselli, 2006; Gerolin, 2008; Moreira, 2008; Dias, 2014; Barcellos et al., 2019; Böger et al., 2020). Prolonged exposure to small doses of these pollutants is a potential public health problem, both directly (by water intake) and indirectly (by the presence of these compounds in urban rivers), as the adverse environmental effects of several of these residuals are proven (Bila & Dezotti, 2003; Gilbert, 2012; Cunha et al., 2016).

Among the numerous traces of medical substances in urban rivers, some drugs have attracted more attention because of their significant environmental effects, such as Diclofenac, Ethinylestradiol, Fluoxetine, and Ibuprofen (Boxall et al., 2012). In general, the most recurrent effects of these drugs on living organisms are acute toxicity (compound effect on mortality), chronic toxicity (compound effects on reproduction and growth), behavioral, biochemical, genetic, and histological effects over cells and tissue (Boxall et al., 2012). However, these effects are known only for a small group of compounds and their impacts are understood only in an isolated and non-synergistic way (Kummerrer, 2009).

For human health and environmental authorities throughout the world, two principal classes of pharmaceuticals are indicated as strategic for monitoring and reducing their concentration in natural waters: antimicrobials and hormonally active compounds (WHO, 2000; Bila & Dezotti, 2003; Kummerrer, 2009). The presence of antibiotics in urban waters may be contributing to the development of resistant pathogenic bacteria. The development of bacterial resistance to antimicrobials is a significant medical issue identified by the World Health Organization (WHO) and considered one of the major public health problems of the 21st century (WHO, 2000). Another paramount concern of the presence of these pollutants in the environment is their toxicity to living organisms (Locatelli, 2011). The toxicity limit of some antibiotics in the aquatic environment is relatively low, as in cases of Sulfamethoxazole (0.025 $\mu g.L^{-1}$), Erythromycin (0.010 $\mu g.L^{-1}$), Clarithromycin (0.070 $\mu g.L^{-1}$), Ciprofloxacin (0.060 $\mu g.L^{-1}$) (NoPills, 2015). Concerning the direct effect on public health (water intake), the hormonally active compounds have worried health authorities for their potential to cause disorders in the endocrine system of living animals (Ghiselli &

Jardim, 2007) and the aquatic communities (Bila & Dezotti, 2003; Gilbert, 2012; Cunha et al., 2016).

Among the hormonally active compounds derived from pharmaceuticals, the synthetic hormone 17-α-Ethinylestradiol is the first on the list of the health authorities in Europe and North America (Owen & Jobling, 2012). The 17-α-Ethinylestradiol is an active ingredient present in almost all oral contraceptives and estrogen used in hormone replacement therapy, and is one of the most widely used pharmaceutical products in the world (Cunha et al., 2016). This compound has been commonly found in natural waters because it persists through water and wastewater treatment processes. Researchers point out that it is responsible for endocrine disruption in aquatic organisms (Gilbert, 2012). In Europe and North America, efforts have been undertaken to reduce and control this compound in waters, but little has been done in Brazil.

Several studies have pointed out the opportunities for managing pharmaceutical residuals in urban waters and involve all sectors that somehow integrate the productive chain of these products (Doerr-Macewen & Haight, 2006; Kummerrer, 2009; Metz & Ingold, 2014). In the developed world, there are several consolidated strategies such as the drug take-back program (Carazza et al., 2014), advanced sewage treatments (Doerr-Macewen & Haight, 2006; Owen & Jobling, 2013), collaborative projects for rational use and discard of pharmaceuticals (Start, 2008; Pills, 2012; NoPills, 2015) and monitoring efforts in waters, etc. (Cunha et al., 2016). For the waters of the large Brazilian cities (over 1 million inhabitants), the main problem is still low urban sanitation coverage or problems in the network of sewage collection that end up taking the sanitary effluents directly to the urban rivers. In Brazil just 46% of sewage is treated (SNIS, 2018).

3. CHALLENGES AND SOLUTIONS FOR CURITIBA

3.1 The context of water management and pollution by pharmaceutical residuals in Curitiba

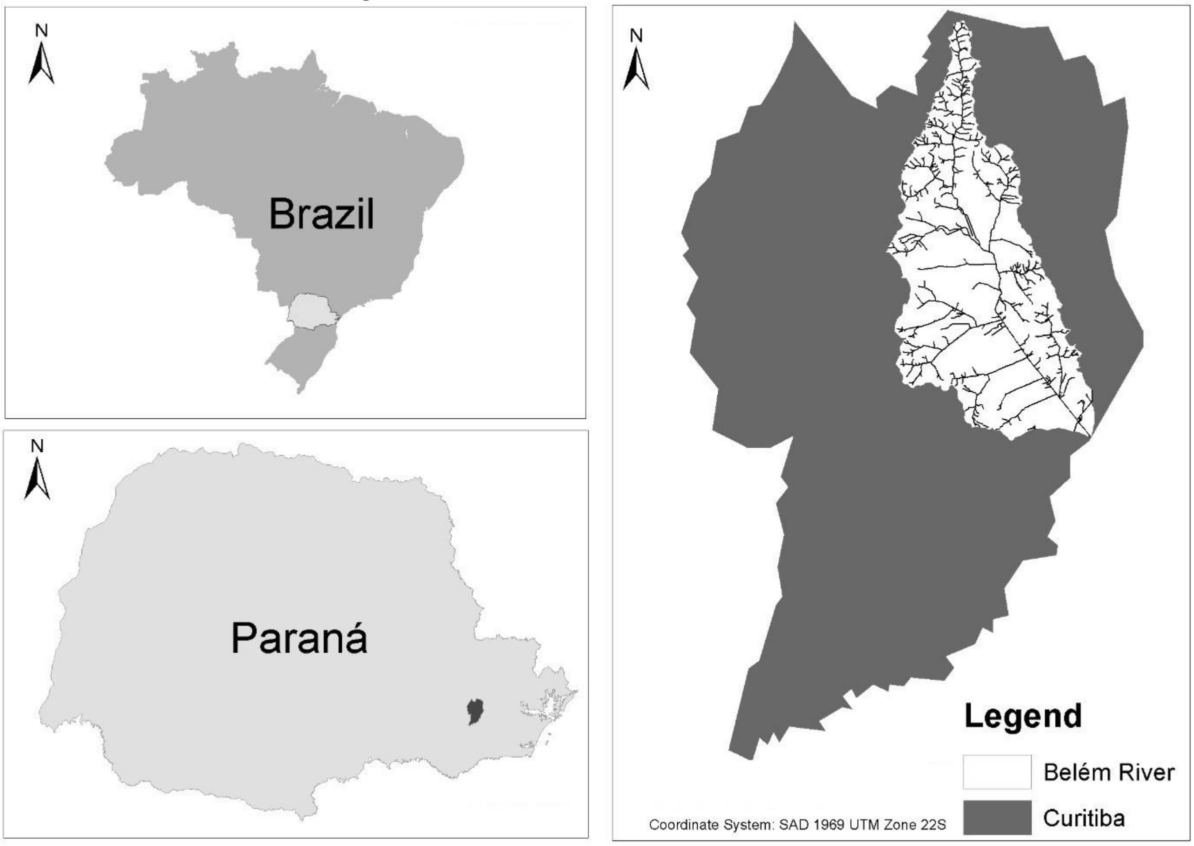
Curitiba is the eighth-most populous city in Brazil, with over 1.9 million (IBGE, 2020). The city is known worldwide as a reference in urban planning, especially regarding the environment and urban mobility policies. Curitiba is considered sustainable and called an "ecological city" (Macedo, 2013, Mega, 2010). As far as transport is concerned, the city was the pioneer of the BRT (Bus Rapid Transit) system that is now used in many cities worldwide. As the urban management model in Brazil, the city was selected to explore the potential for innovation in management and environmental planning, such as emerging pollutants management and BGI systems.

However, in terms of urban river pollution, Curitiba is similar to other large Brazilian cities, where urban rivers have high levels of contamination by domestic sewage. Curitiba has the best basic sanitation indices among Brazilian capitals, with 94% sewage coverage, 100% water supply and 100% garbage collection (SNIS, 2018). However, the high water pollution levels in the city's urban rivers demonstrate problems in the sanitary structure (Bollmann & Edwiges, 2008; Barcellos et al., 2019; Böger et al., 2020). The sewage system of Curitiba suffers from three types of problems. The first problem is lack of connection by households despite the system being available to them, and as a result they discharge their effluents directly into the rivers. The second type is lack of coverage and therefore sewage is dumped into the drainage system or even directly into the rivers. The third type of problem is mainly related to the central part of Curitiba that has, an old sanitary network with unauthorized connections between sewerage and drainage systems, and sometimes directs the sewage together with rainwater to the rivers. The central river basin in Curitiba, the Belém River, is an excellent example of this reality.

The area of the Belém River basin is typically urban and is entirely within the municipality of Curitiba (Figure 2). It has an area of 87.85 km², occupying 20% of the city territory. Considering that in 2017 the population of Curitiba reached 1,908,359 inhabitants (IBGE, 2020), the number of inhabitants of the basin of the Belém River reached about 518 thousand inhabitants. According to Lara (2014), about 43% of the properties in the basin are not correctly connected to the sewage network, which consequently reflects high levels of pollution from domestic sewage. Regarding the general water quality in the Belém River, there is a progressive degradation from the originating springs through to the mouth due to punctual and diffuse sources of pollution. About 90% of this pollution is derived from domestic sewage discharged directly to the river or drainage networks (Bollmann & Edwiges, 2008).

Due to the intensity of pollution by domestic sewage in the Belém River waters, the presence of pharmaceuticals is also significant. Table 2 shows the pharmaceutical residuals already monitored and the concentrations found in the Belém River. It is possible to observe substantial concentrations of several medical substances with environmental impacts, such as the Diclofenac, 17-α-Ethinylestradiol, 17-β-Estradiol, and Estrone. But the highlight is the synthetic hormone 17-α-Ethynylestradiol, derived from birth control pills and medications used in hormone replacement therapies. The safe concentration of this compound in natural waters, according to European toxicologists, is 0.035 $ng.L^{-1}$ (Gilbert, 2012). A concentration 17-α-Ethynylestradiol as low as 6 $ng.L^{-1}$ can cause irreversible damage to aquatic communities due to endocrine interference. Concentrations ranged from <48 to 5,830 $ng.L^{-1}$ were found in the waters of the Belém River.

Figure 2. Location of the Belém River basin.



Source: Authors, 2021.

Table 2. Pharmaceuticals in the waters and the sediment of the Belém River.

Class	Compound	Concentration Water P0% - P100%	Concentration Sediment P0% - P100%	Reference
Hormone	17β-estradiol	<25 – 20,987 ng L^{-1}	12,710 – 16,690 ng kg^{-1}	Padilha & Leizke, 2013, Ide, 2014, Mizukawa, 2016, Barcellos *et al.*, 2019
	17α-ethinyl oestradiol	<48 – 5,830 ng L^{-1}	31,650 – 33,890 ng kg^{-1}	Padilha & Leizke, 2013, Ide, 2014, Mizukawa, 2016, Barcellos *et al.*, 2019
	Estrone	<26 – 2,420 ng L^{-1}	58,080 – 128,080 ng kg^{-1}	Padilha & Leizke, 2013, Mizukawa, 2016, Barcellos *et al.*, 2019
Antihypertensive	Metoprolol	61.1 – 2,125.9 ng L^{-1}		Osawa et al., 2015
	Propranolol	68.7 – 299.7 ng L^{-1}		Osawa et al., 2015
	Nadolol	<14.1 - 30 ng L^{-1}		Osawa et al., 2015
Anti-inflammatory	Naproxen	<9.5 - 640 ng L^{-1}		Ide,2014
	Ketoprofen	<5.0 – 2,540 ng L^{-1}		Ide,2014
	Ibuprofen	<31 - 729 ng L^{-1}	<1,200 ng kg^{-1}	Kramer et al., 2015
	Diclofenac	<31 - 61 ng L^{-1}	<1,900 ng kg^{-1}	Kramer et al., 2015
Analgesic	Paracetamol	120 - 261 ng L^{-1}	<1,260 ng kg^{-1}	Kramer et al., 2015
	Acetylsalicylic acid	<36.1 – 8,570 ng L^{-1}		Ide,2014
Metabolite	Salicylic acid	<33.7 – 1,550 ng L^{-1}		Ide,2014
Lipid Regulator	Genfibrozila	<0.92 - 217 ng L^{-1}		Ide,2014
	Fenofibrate	<0.77 - 395 ng L^{-1}		Ide,2014
Stimulant	Caffeine	100 – 59,810 ng L^{-1}		Ide,2014
Antibiotic	Amoxicillin	180 - 1,210 ng L^{-1}		Böger et al., 2021
	Azithromycin	80 - 500 ng L^{-1}		Böger et al., 2021
	Ciprofloxacin	<20 ng L^{-1}		Böger et al., 2021
	Doxycycline	<200 ng L^{-1}		Böger et al., 2021
	Norfloxacin	110 ng L^{-1}		Böger et al., 2021
	Sulfamethoxazole	1,090 – 1,320 ng L^{-1}		Böger et al., 2021
Psychotropic	Carbamazepine	209 – 856 ng L^{-1}		Böger et al., 2018
	Diazepam	435 – 763 ng L^{-1}		Böger et al., 2018

3.2 Blue-Green Infrastructure for the improvement of water quality rivers in Curitiba

An alternative to the emerging need to reduce pharmaceuticals concentration in the Curitiba rivers is Blue-Green Infrastructure. The possibility of using these urban infrastructures to minimize water pollution would be a municipal strategy since the use and occupation of land is a municipal responsibility. Constructed wetlands can efficiently mitigate this problem and still bring many co-benefits, contributing to the mitigation of extreme climatic effects such as floods in the urban context. According to experiments reported in the scientific literature, wetlands provide the same general efficiency in removing pharmaceutical products from sewage compared to conventional treatments (Li et al., 2014; Verlicchi & Zambello, 2014). The scenario proposed here uses the Belém River basin as a case study for water management due to the wide availability of information and data about the population the river supports and its environmental condition. It is also the most representative basin in the city and has great symbolic importance to Curitiba because of its touristic, economic, and city marketing features.

Considering the problems of urban sanitary infrastructure in the central region of Curitiba, where the Belém River basin is located (Bracht, 2008; Lara, 2014), one possibility to improve the natural water quality is to implant constructed wetlands in available areas. These systems can treat the raw sewage still being directed to the river or even the heavily polluted river waters themselves. The Belém River basin already has some systems of BGI constructed to mitigate floods that also can be used to improve the water quality. But the first challenge is to identify areas with availability for installing these systems in a completely urbanized basin.

We have identified six different areas in the Belém River basin that can install filtering gardens (wetlands) and one outside the watershed. These areas have space available for these systems and are located at strategic points in the basin (Figure 3 and 4):

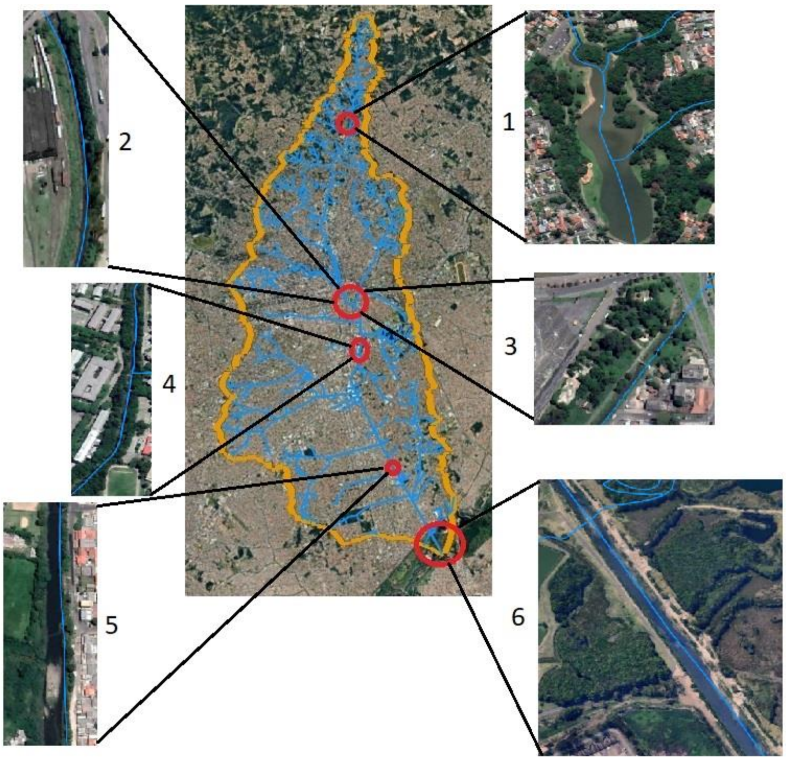
1. The first viable intervention point is the pond of São Lourenço Park (22 J 674373.82 m E; 7191306.90 m S), in the upper part of the Belém River basin. In this region, there are already significant amounts of sewage. As there is already a retention basin created in the riverbed - the São Lourenço pond was designed to minimize urban flooding in the region - it would be possible to use the lagoon to treat the water.
2. After the Belém River passes over the central part of the city of Curitiba fully channeled, it returns to the surface next to the city bus station (22 J 675005.05 m E; 7185589.25 m S); this is the second stretch of possible intervention for

the insertion of wetland systems. This place is important because it is next to the bus station and is a city's business card.

3. After the Belém River passes through the bus station area, it receives water from three of its most polluted tributaries, the Ivo River, the Água Verde River, and the Juvevê River. The third point of intervention is in the same mesoregion of the bus station next to the mouth of the Juvevê River (22 J 675577.20 m E; 7185351.51 m S). This stretch and the previous are strategic for the city due to their central and representative locations. In this stretch, besides the water's foul smell, there are constant floods in periods of intense precipitation, problems that could easily be solved using BGI systems. The region also is in the neighborhood of a peripheral area of the city that needs a rejuvenation project.
4. Despite the Forest Code (Law No. 12,651 of May 25, 2012) requiring riparian forest even in urban rivers, one of the few stretches of the Belém River that actually has riparian vegetation and refuges for biodiversity is where the river crosses the Pontifical Catholic University of Paraná (PUCPR). This area is the fourth stretch with availability for the installation of wetland systems on the riverbed (22 J 675894.17 m E; 7184245.17 m S).
5. The fifth stretch of possible intervention is just before the bridge on Street Rodolfo Bernardelli, in the neighborhood of Uberaba (22 J 677886.99 m E; 7179531.49 m S). This stretch is also impacted by floods when heavy rains occur, and the BGI systems could also contribute to mitigate the floods.
6. The last stretch of intervention with an available area is just before the mouth of the Belém River, in the neighborhood of Boqueirão (22 J 679584.10 m E; 7177424.28 m S). This area is the region of the Náutico of Iguaçu Park. The installation of filtering gardens, further reducing the pollution load that the Iguaçu River receives - the Belém River flows into an Urban Drainage Channel and then reaches the waters of the Iguaçu River - could be another attraction for the park and also minimize the risk of flooding events that occur in the region.
7. The Urban Drainage Channel is an artificial channel built up to ensure that the polluted waters of the urban streams like the Belém River reach the Iguaçu River with lower impact. This channel was constructed in a region that is not yet urbanized between São José dos Pinhais and Curitiba (Figure 4), where

other wetland systems can be developed outside the Belém watershed (22 J 679364.99 m E; 7176308.19 m S). Additionally, this alternative can receive the effluents of the Belém Wastewater Treatment Plant for a post-treatment in this wetlands system.

Figure 3. Possible areas available for the installation of wetlands in the Belém River basin.

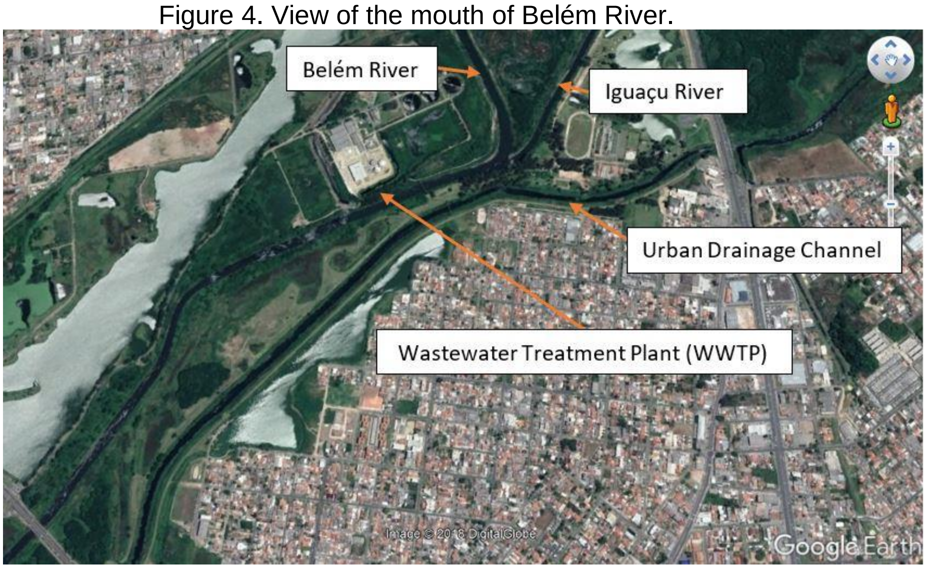


Source: Authors, 2021.

The seven proposed intervention points, six within the Belém River basin and one outside the basin, would be multifunctional investments. BGIs have great acceptance by the population (Schröder et al., 2007) and create iconic spaces because the environments that compose them can be used as social and leisure spaces. Still, these works may represent projects of urban rejuvenation for abandoned parts of the city and efforts to renaturalize the city and create spaces for biodiversity. Filtering gardens can be research areas for universities and urban parks with the potential to stimulate environmental awareness for audiences of various ages. These opportunities present at all proposed intervention points.

In addition to the availability of the area, two other challenges for the installation of these systems in urban areas are 1) their implementation costs and 2) political and bureaucratic issues. Intervention area 3 (Figure 3) was recently proposed to create a filter garden in a collaborative effort by SANEPAR (Paraná Sanitation Company) and the Government of the State of Paraná, which unfortunately was blocked by bureaucratic and political obstacles. The project proposed for this area had a direct estimated cost (IAT, 2021) of R$ 2.5 per inhabitant (considering the population of Curitiba) to create an urban park that could significantly improve the quality of the waters of the Belém River, reduce the risk of floods, and promote the urban rejuvenation of the region. Due to the multifunctionality of a project of this type, it is difficult to economically value all the benefits associated with several areas of urban management, such as sanitation and urbanism. However, strategic and alternative interventions like this in important regions of Curitiba have the potential to benefit the entire population of the city with their environmental and social content, which makes them cheap in terms of cost per inhabitant.

Figure 4. View of the mouth of Belém River.



Source: Authors, 2021.

In Brazil, several wetland experiments can be identified in the literature to treat domestic and industrial effluents. The diversity of plant species that can be used is quite large for multiple purposes. The comprehensive bibliographic review of Machado et al. (2017) pointed out 28 different species of plants, including native, naturalized, and exotic plants, being used in Brazil. The pollutants removal efficiency is naturally related to the plant species used. Some researchers argue that wetlands can remove a broad spectrum of pharmaceuticals (Verlicchi & Zambello, 2014). This is not so with advanced treatment technologies, which in general can remove only certain types of compounds (Kummerrer, 2009). According to Verlicchi & Zambello (2014), this is due to the coexistence of several microenvironments in the wetlands, such as anoxic, aerobic, and anaerobic, and different mechanisms involved in the treatment process, such as biodegradation, sorption, absorption, and also photodegradation.

Based on studies about the use of constructed wetlands to remove pharmaceuticals (Conkle et al., 2008; Breitholtz et al., 2012; Giang et al., 2013; Li et al., 2014; Verlicchi & Zambello, 2014; Gorito et al., 2017), and the most common species used in wetlands in Brazil (Machado et al., 2017), the most suitable plants for Belém River basin are likely *Typha spp*, which is native to Brazil, and *Phragmites australis*, which is naturalized. Both could be used for effluent treatment and have also been tested internationally to remove pharmaceuticals with good efficiency for a wide range of medical substances.

4. CONCLUSION

Climate change is a new challenge for urban management, which requires the paradigms of preparedness for cities and a resilient and preferably interconnected urban water system. Holistic alternatives such as BGIs can reduce concentrations of polluting pharmaceuticals and make the city more resilient to the effects of climate change. In the Curitiba region, the BGIs with wetlands are economically more feasible than traditional technologies (grey infrastructure) to reduce pharmaceutical residuals pollution in water. It can be used centrally - by the local sanitation company to treat sewerage - and decentralized - by the government in water bodies to treat several kinds of water. In addition to reducing these pollutants, the use of these systems would undoubtedly result in a significant improvement in general water quality. It also provides an opportunity for the sanitation companies to evaluate the possibility of constructed wetlands implementation as a post-treatment of the existing wastewater treatment plants or even as an alternative to expanding the current system. We suggested experiments with pilot systems in the Curitiba region using the species *Typha spp* and *Phragmites australis* so that the best operational parameters for the wetlands can be defined and the removal efficiencies of the priority pharmaceutical pollutants for the region evaluated.

Paradoxically, small budgets can act to promote alternative solutions such BGI in urban water management. Proposals and solutions such as BGIs have already been implemented in several countries and, for their cost-benefit, are a promising alternative for the developing world. Indeed, there is a receptivity on the part of the population for these types of projects. Public policies are implemented not only for the quality of what is proposed and for the social interest that they must contain but also because of their public acceptance. BGIs can create iconic features within a city and suggest sustainable characteristics in a mixed urban space, all while solving critical urban problems, such as floods and water pollution. This combination of attributes, the good acceptance of the population, and the low cost in comparing traditional alternatives can enhance public water management policies and motivate projects with this interest.

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CHAPTER 5: ECONOMIC IMPACTS OF COMPLEMENTARY TREATMENTS FOR REDUCING PHARMACEUTICALS IN METROPOLITAN DRINKING WATER IN SOUTHERN BRAZIL

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ABSTRACT

Many research has addressed treatment solutions for removing pharmaceutical micropollutants from water. However, few investigations aim to understand and discuss the real feasibility of these solutions, especially related to the economic sphere in developing countries. In this article, we investigate the direct economic impacts of complementary treatment systems to reduce pharmaceutical micropollutants from the water supply of a metropolis in southern Brazil. The complementary system studied was a powder activated carbon (PAC) dosing system recently installed at the inlet of a conventional Drinking Water Treatment Plant (DWTP), but which is not yet operating. Its implementation costs were taken from its public bidding and estimated operating costs. These prices were proportionally extrapolated by the nominal flow for three other DWTPs in the city and compared with the costs of a conventional DWTP. The DWTP compared had its operation and maintenance costs provided by the local sanitation concessionaire and its implementation costs estimated. The results showed that the system's operational costs are high mainly due to the required high daily PAC dosage. In thirty years, this system's direct cost per capita is Brazilian real 5.57 a year higher than that of a DWTP. The direct costs per m³ of water produced represent approximately 78.52% of the costs of a DWTP in thirty years, and proved to be higher than those of ultrafiltration and granular activated carbon systems. The high economic impacts demonstrated the financial infeasibility of installing complementary systems to reduce micropollutants, even if there is technical feasibility. The modernization of water and sewage treatment systems in developing countries to reduce pharmaceutical micropollutants seems to require a new financing model in which pharmaceutical companies and their host countries provide economic and technical solutions.

KEYWORDS: Economic analysis. Pharmaceutical micropollutants. Water treatment costs. PAC. DWTPs. Environmental management.

1. INTRODUCTION

The management of pharmaceutical micropollutants is an emerging challenge in the field of water quality management in cities. In urban rivers with high population density and low environmental dilution, this type of pollution is more likely to be representative (Helwig et al., 2016). Several studies demonstrate the environmental effects of these pollutants on sewage receiving waters and potential risks to public health (Halling-Sørensen et al., 1998; Skakkebaek, 2010; Kümmerer, 2009; Jobling & Owen, 2013; Qian et al., 2015; Tiedeken et al., 2017). The European Union (EU) already has legal instruments that oblige the periodic monitoring of organic micropollutants in rivers and the USA in supply waters (Bieber et al., 2018). Efforts and studies to modernize WWTPs (Wastewater Treatment Plants) are increasing in developed countries. However, aspects related to economic and environmental feasibility are the main controversies (Jones et al., 2007; Gilbert, 2012; Mousel et al., 2017; Zepon Tarpani & Azapagic, 2018; Baresel et al., 2019).

The feasibility of modernizing water and sewage treatment systems is a particular aspect of each region or country. In Switzerland, the estimated costs for implementing complementary sewage treatment systems were considered viable in WWTPs where there is low sewage dilution (Joss et al., 2008) and resulted in a policy of updating the WWTPs that is being implemented (Bieber et al., 2008). al., 2018). In the United Kingdom, the economic and environmental impacts (energy consumption and CO_2 emissions) of modernizing WWTPs have been widely questioned in terms of feasibility, especially by the water and pharmaceutical industries (Jones et al., 2007; Gilbert, 2012; Zepon Tarpani & Azapagic, 2018). While, in the Czech Republic, the costs of implementing a complementary treatment system, in the largest WWTPs in the country, with activated charcoal were estimated as above what was acceptable for the population (Hrkal et al., 2019). In the context of developing countries, discussions on the real feasibility of implementing complementary treatment systems to remove pharmaceutical micropollutants are not yet consolidated (Reichert et al., 2019; Barcellos et al., 2020).

In Brazil, studies on environmental monitoring (Barcellos et al., 2019; Santos et al., 2020; Böger et al., 2021; de Almeida Brehm Goulart et al., 2021) and sewage and water treatment, on a scale of laboratory, to remove pharmaceutical micropollutants (Fröhlich et al., 2018; Pompei et al., 2019; Gonçalves et al., 2020;

Starling et al., 2021) are already emerging. Due to the still deficient sanitary coverage in Brazilian cities, concentrations of pharmaceutical micropollutants in urban rivers are much higher than in developed countries in Europe (e.g., Switzerland, Austria, Germany, United Kingdom, Netherlands, Spain, Italy, and Sweden) and the USA, where the drugs that remain in the water are those resistant to sewage treatment. In the context of the unplanned indirect reuse of sewage, which occurs in Brazil, where untreated or poorly treated sewage is collected by Drinking Water Treatment Plants (DWTP) and subjected to conventional treatments, there is an emerging concern about the possible effects of pharmaceutical micropollutants on drinking water (Hespanhol, 2014; Barcellos et al., 2021). Studies have identified trace concentrations of pharmaceutical micropollutants in Brazilian supply waters that may pose risks to public health (Machado et al., 2016; Caldas et al., 2018; Reis et al., 2019; Santos et al., 2020).

An important question is whether the application of treatment technologies can be feasible for the Brazilian situation, where only 53% of the population has sanitary coverage and 83% access to water supply systems (SNIS, 2018). In the Brazilian context, where there is a short budget and a current scenario of worsening social inequalities and poverty, it is necessary to question the economic feasibility of solutions proposed to manage pollution. The economic sphere is one of the essential aspects that need to be considered in decision-making. But in no way can it be attributed to this greater relevance than the social and environmental spheres. However, in the specific case of pharmaceutical micropollutants, the economic sphere seems to be a determining factor that has prevented even countries with well-developed economies from modernizing their water and sewage treatment systems.

Many resources have been spent on research that emphasizes strictly technical solutions to reduce the input of pharmaceutical micropollutants in the environment, but few investigations discuss the economic scenarios and their feasibility on a full scale. In the developing world, investigations into the real feasibility of these technologies are still not reported in the techno-scientific literature. In this article we investigate the economic impacts, in a scenario of implementation of complementary treatment technologies in DWTP, to reduce the concentrations of pharmaceutical micropollutants in the drinking water of a metropolis in southern Brazil. In the first part of the article, the starting point of this investigation is discussed, which begins through the intersectoral dialogue with the local sanitation concessionaire through a prioritization process. Then we discuss the direct economic impacts per capita and in m³ of water produced from the implementation of complementary water treatment systems to reduce concentrations of pharmaceutical micropollutants in drinking water in Curitiba, considering a payback period of up to thirty years. The last part of the article discusses this alternative's economic, political, and technical feasibility.

1.1 Pharmaceutical micropollutants management: where to start and what water to treat?

The management of pharmaceutical micropollutants is already a consolidated field of scientific knowledge, with at least thirty years of research and discussion (Kümmerer, 2009; Qian et al., 2015; Tiedeken et al., 2017; Caban and Stepnowski, 2021; Barcellos et al., 2017; Caban and Stepnowski, 2021; Barcellos et al., 2015; al., 2022). Although there are many possible management approaches (technical, organizational, community and governmental), the strictly technical approaches have been most emphasized to date. This trend is also consistent with the feasible reality of the locus of innovation in management, the developed countries with resources, technology and, coincidentally, the largest pharmaceutical industries (Barcellos et al., 2022). In the Brazilian context, one of the first challenges is to create a network of stakeholders for the discussion and management of these micropollutants, something that is already consolidated in the scenario of several European countries (e.g., Switzerland, Germany, France, United Kingdom and Spain) (Titz & Döll, 2009; PILLS, 2011; Helwig, 2018; Bieber et al., 2018; Barcellos et al., 2020; Barcellos et al., 2022). It is necessary to prioritize target trace substances in urban waters and discuss and work collaboratively on feasible management strategies. These collaborative efforts have already emerged in Curitiba, the largest city in southern Brazil, and an important locus of innovation in urban management.

In Curitiba, priority pharmaceutical micropollutants were defined through a collective prioritization approach. The micropollutants indicated as most important for urban water management were established by consensus in a workshop with representatives from different sectoral groups (academics, water industry, pharmaceutical industries and distributors, pharmaceutical sector and government). These prioritized pharmaceutical pollutants were: ethinylestradiol, ciprofloxacin, ibuprofen, diclofenac, estradiol, caffeine, and fluoxetine (Barcellos et al., 2020). At this same meeting, which resulted in the creation of this multisectoral network of stakeholders, the management goals for each sector were defined. The synergy between the different sectoral groups is notable for the established targets. These goals are possible areas of work and partnerships to achieve them are essential. It was established at this meeting that academics and the water industry sector needed to work collaboratively in search of feasible treatments to remove pharmaceutical micropollutants from sewage and water supply systems (Barcellos et al., 2020). This was one of the converging sectoral goals pointed out by these two sectors.

In order to continue this collaborative work with stakeholders, started by Barcellos and collaborators, the local sanitation concessionaire in Curitiba was contacted and a workshop was proposed with professionals from different departments of the company, to discuss the priority matrix (natural water, drinking water and wastewater) in the removal of pharmaceutical micropollutants. The professionals selected for this workshop were strategically chosen by the company's Research and Innovation Management team. In this meeting held with eight professionals from the sanitation company, drinking water was the priority matrix to remove pharmaceutical micropollutants. Seven professionals chose drinking water as a priority and only one chose sewage as a priority matrix, advocating post-treatment with passive technologies and solutions based on nature, such as wetlands. Nature-based solutions are indeed a feasible solution for the developing world, due to their urban multifunctionality, public acceptance and cost-effectiveness (Schröder et al., 2017; Barcellos et al., 2021).

The matrix prioritized by the local sanitation concessionaire in Curitiba to remove micropollutants presents an important contrast with what has been advocated by developed countries in terms of micropollutants management. Removing pharmaceutical micropollutants from sewage seems to be the most coherent way to avoid environmental pollution and also the water supply. It is in these efforts to remove these compounds from sewage that Germany and Switzerland have been working as well as other European countries where these technologies are still only at the level of discussion, such as the United Kingdom and the Czech Republic (Jones et al., 2007; Gilbert, 2012; Bieber et al., 2018; Hrkal et al., 2019). However, in Brazil, where a large part of the population still does not have access to basic sanitation, the modernization of WWTPs to remove micropollutants is not a feasible reality. Modernizing WWTPs will likely only be viable in the medium to long term when higher levels of sanitary coverage are achieved. However, the health risk of relevant concentrations of micropollutants in drinking water seems to be a good argument for the medium term to refine the capacity to treat DWTPs in urban regions with the greatest potential for innovation in sanitation management.

2. METHODOLOGY

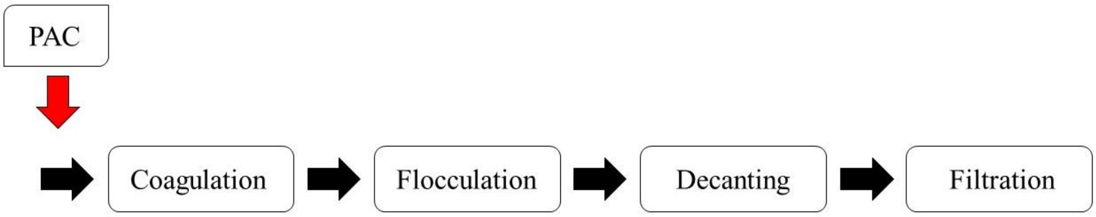
In the Curitiba region, the supply system is composed mainly of surface water from supply reservoirs in the metropolitan region. The system is integrated and the water produced by the DWTPs supplies Curitiba and some of the cities in the central urban core of the metropolitan region. The Integrated Supply System of Curitiba and the Metropolitan Region, according to estimates from the Supply Master Plan, supplied about 3.2 million inhabitants in 2020 (SANEPAR, 2013). However, four main DWTPs produce water for about 90% of this population. This study discussed the economic impacts of implementing complementary systems to remove pharmaceutical micropollutants in these four DWTPs. The current rated water production capacity of these four DWTPs is 3600 L/s, 3200 L/s, 2000 L/s and 900 L/s.

The complementary treatment system studied was a powder activated carbon (PAC) dosing system installed at the inlet of a conventional full-cycle DWTP (Figure 1). This system was chosen because its implementation costs were recently documented and operating costs could be estimated. Information on the costs of DWTPs and complementary treatment systems capable of reducing concentrations of pharmaceutical micropollutants in Brazil is scarce in the scientific literature. This system was designed to work seasonally and prevent that do not drink water from reaching the organoleptic potability standard due to the periodic formation of geosmin and 2-methylisoborneol (MIB). Its implementation costs were obtained from the public bidding of a PAC dosing system in a DWTP in the region of Curitiba. As this PAC dosing system is not yet in operation, operating costs were estimated from the predicted energy consumption, the estimated amount of activated carbon for the system and the expected costs for the final disposal of solid waste (sludge).

To estimate the cost of electricity, the tariff per kWh of December 2021 of this DWTP (Brazilian real 0.72 per kWh) without the tariff flag was considered. In Brazil, there is a tariff flag system that indicates whether electricity will cost more or less according to the conditions of electricity generation. It is noteworthy that in 2021, the Curitiba region was impacted by a great drought and the water reservoirs were greatly affected. The drought caused an increase in the price of electricity under the logic of the tariff flag. The electric energy cost estimate calculation was based on the total load foreseen in the project, available in the public bidding for the system. The estimate the amount of activated charcoal, a dosage of 25 mg/L was considered, which is an intermediate dosage used for water treatment and supply, according to Ferreira Filho (2021). Several investigations demonstrate that this PAC dosage is able to reduce concentrations of pharmaceutical micropollutants in water (e.g., Altmann et al., 2014; Bonvin et al., 2016; Kårelid et al., 2017). The PAC dosage chosen was validated using the Freundlich Isotherm model, for the priority compounds of Curitiba (Barcellos et al., 2020). Freundlich model parameters were taken from the scientific literature for each priority compound (e.g., Dickenson & Drews, 2010; Li et al., 2015; Kaur et al., 2018). The Freundlich Isotherm model calculates the amount of coal needed to reduce various concentrations of a pollutant in the water. The cost of the PAC considered was Brazilian real (BRL) 10.05 per kg (BRL 8.6 on 12/23/2020 corrected to BRL 10.05 by the National Cost Index of Construction) and was taken from a public bid the local sanitation concessionaire. All cost values used in this study were corrected using the National Cost Index of Construction (INCC) for 03/16/2022. The final disposal of waste (sludge) costs were estimated considering the total amount of coal expected to be used in the system and the price of BRL 150 per ton of sludge generated. This cost was transferred directly by the local sanitation concessionaire as the average value for the year 2022. It was considered that the amount of sludge generation related to the complementary PAC dosing system is the same amount of coal inserted in the system. In the case of this study, as the objective is pharmaceutical micropollutants, we estimated the operational cost of the system running continuously, 365 days a year. This complementary system's implementation and operation values were proportionally extrapolated to the four main DWTPs in Curitiba using the volume of water produced (nominal flow) as a reference.

In addition to the implementation and operation costs of the complementary system, the direct costs (without considering the water capture and distribution system) of implementation and operation of the DWTP in the region of Curitiba where this system is being installed were also obtained and estimated. Operating costs were passed directly by the sanitation concessionaire. These costs refer to the year 2021 and consist of four elements: 1) personnel, 2) electricity, 3) chemicals and waste disposal, and 4) several (Figure 2). In 2021, the entire population of Curitiba was subjected to rationing and water production in this DWTP was 20% lower than the annual average. Therefore, the average yearly costs in this DWTP of chemicals and waste disposal have been corrected to 20% higher values. Electricity values were not corrected as they are already about 20% more expensive due to the tariff flag. The implementation cost of each DWTP component and its assembly and construction was estimated proportionally by its nominal flow, considering the cost references of Mierzwa et al. (2008). Land costs were based on the minimum prices per m² of land in Curitiba in the region where the DWTP (BRL 233.81 on 03/16/2020 corrected to BRL 279.86 per m² by the INCC) is located and in its total area (about 73,604.4 m²). Minimum costs were calculated from the 2020 market research data provided by the Municipality of Curitiba. We chose to use the minimum cost because this value is closer to the m² reference cost of the Generic Plant of Values of the Municipality of Curitiba. To calculate the cost of the land only the area of the DWTP was considered.

Figure 1. Flowchart of treatment steps in investigated DWTPs.

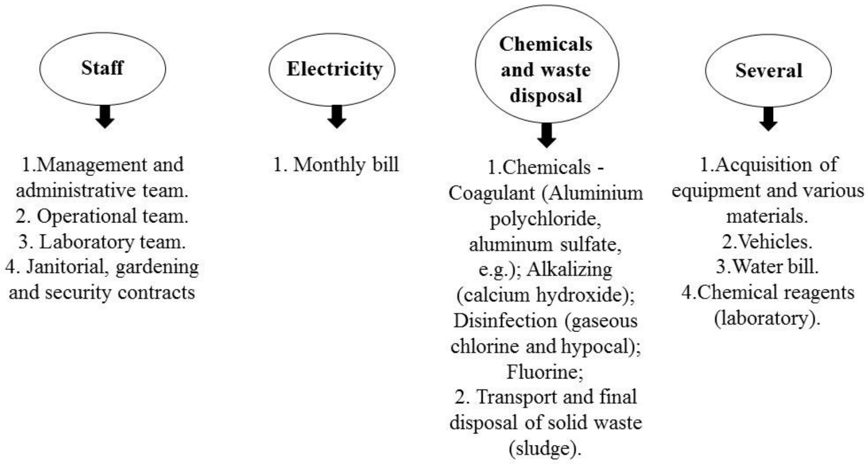


The cost analysis was performed considering the per capita cost of maintenance, operation and implementation of complementary systems and the payback period method for the value of the cubic meter of water produced. Eq. (1) (Hirschfeld, 2000) was used to compare the direct costs of the complementary systems (operation, maintenance and implantation) in relation to the total direct costs of a DWTP per m³ of water produced in a horizon of thirty years. The rate of return on investment considered was 11.75%, according to the 245th minute of the Monetary Policy Committee (Copom) of 03/16/2022 (https://www.bcb.gov.br/publicacoes/atascopom).

$$C = \frac{P\left[\frac{i(1+i)^{n}}{(1+i)^{n}-1}\right]+O}{V} \quad (1)$$

Where **C** is the cost per cubic meter of treated water; **P** is the present value of the investment, in this study the implementation cost; **O** is the annual cost of operating the system; **V** is annual volume of water produced (m^3); **i** is rate of return on investment (% /100); **n** is years to return on investment.

Figure 2. DWTP operating and maintenance costs.



3. RESULTS AND DISCUSSION

3.1 Direct costs of PAC complementary systems

Annual operating and maintenance costs of the reference DWTP and its complementary PAC system are listed in Table 1. These costs refer to this station's average annual water production, which is about 54,127,957.50 m^3 of produced water. In Table 2, the nominal flows, population served, total and per capita costs of maintenance, operation and implementation of the reference DWTP and the estimated values for the complementary PAC systems investigated are listed. Table 3 shows the treatment cost per m^3 of water produced for the reference DWTP compared to the investigated complementary systems and the sum of both. In the analysis of tables 2 and 3, only the nominal flows were considered for comparison purposes. Therefore, the operational costs of electricity, chemicals and waste disposal of the reference DWTP were proportionally corrected for an average flow of

2,000 L/s (about 63,072,000 m³ of water produced annually). Twenty percent of total electricity costs were subtracted due to the water scarcity tariff flag. The costs of water treatment per capita and per m³ of water produced were evaluated considering up to thirty years of payback time.

Table 1. Annual operational and maintenance costs of reference DWTP and complementary system.

Item	**Annual costs (BRL/year)**	**Annual costs (%)**
DWTP reference		
Chemicals	3,651,085.93	42.52
Staff	3,607,071.36	42.04
Electricity	782,965.20	9.13
Transport and final disposal of waste (sludge)	159,617.58	1.86
Several	378,802.68	4.42
Total	8,579,542.75	100
Complementary system reference		
PAC	15,846,840.00	97.49
Electricity	172,123.49	1.06
Transport and final disposal of waste (sludge)	236,520.00	1.46
Total	16,255,483.49	100

The operational costs of the investigated DWTP are similar to other studies on DWTPs and WWTPs in Brazil (Mierzwa et al., 2008; Trennepohl et al., 2017; Souza et al., 2021). Labor and chemicals account for most of the costs in large conventional DWTPs (Mierzwa et al., 2008; Trennepohl et al., 2017). In conventional biological treatment WWTPs (UASB reactors and activated sludge) labor also represents an important part of the operating costs, but the costs of chemical products are much lower (Souza et al., 2021). In activated sludge WWTPs, energy consumption is the second most significant cost after labor (Castellet & Molinos-Senante, 2016; Souza et al., 2021). Conventional sewage treatment in Brazil is predominantly biological, therefore, it requires few chemical products. While conventional water treatment in Brazil is basically physical-chemical and thus requires an essential amount of chemical products.

The operational costs of the complementary system with PAC are basically the costs of coal (Table 1). As the coal cannot be reused in this system, the operation of the system becomes expensive with the continuous dosing of the PAC. The total operating cost of the add-on system is nearly double that of a DWTP. The expenditure on electricity from the complementary system represents about 21.98% of the electricity expenditure of the entire station. As the reference DWTP basically works from the hydraulic load, the electricity consumption of the treatment step is really low. The electrical system of this DWTP is divided into two systems: 1) a system referring only to the water treatment stage (which was considered in this study); and 2) a water lift system that pumps the water to the city's supply system. The electric energy costs of the lift system are pretty high. However, as in this study, only the direct costs of the treatment stage were considered, and the electricity costs were not very representative. The cost of transport and final disposal of sludge from the complementary system were higher than the costs of the sludge generated by the entire DWTP.

The per capita costs of operation, maintenance and implementation of the reference DWTP and the complementary treatment systems were calculated by dividing the Integrated Supply System of Curitiba and the Metropolitan Region according to the population that each part of the system serves according to Supply Master Plan (SANEPAR, 2013). The per capita cost of maintenance and operation of complementary treatment systems are always higher than the costs of a DWTP (Table 2). The closest values of operation and maintenance of DWTP with the complementary systems are with the complementary system of DWTP 4. DWTP 4 has a work in progress to install 2000 L/s of nominal flow and will soon increase its production capacity and population served. Therefore, the complementary treatment system of this DWTP would also have an increase in costs, approaching the per capita cost of the other complementary systems. The per capita costs of implementing the complementary systems are much lower than those of a conventional DWTP, even considering a horizon of thirty years (Table 2). However, adding the per capita costs of maintenance, operation and implementation of the complementary systems and the reference DWTP in a horizon of thirty years, only the complementary system of the DWTP 4 is cheaper per inhabitant than the direct costs of treatment of a conventional DWTP (Table 2). The total costs per capita of the four complementary systems in thirty years are around BRL 26.27 per inhabitant/year, while a conventional DWTP costs BRL 20.70 per inhabitant/year. These values demonstrate that the economic impacts of implementing these complementary treatment systems would be greater per inhabitant than those of a DWTP, especially due to these systems' high annual operating costs.

Table 2. Nominal flow, total and per capita deployment costs, operation and maintenance of DWTP (reference) and complementary systems researched.

	DWTP 1 (reference)	Complementary systems				
		DWTP 1 (reference)	DWTP 2	DWTP 3	DWTP 4	Total
Nominal flow (L/s)	2,000	2,000	3,600	3,200	900	9,700
Population served (inha)	611,018.10	611,018.10	1,098,003.38	847,676.03	454,519.80	3,011,217.30
Operation and maintenance costs						
Annual costs (BRL/year)	9,523,611.20	16,255,483.49	29,259,870.28	26,008,773.58	7,314,967.57	78,839,094.92
Per capita annual costs (BRL/inha.year)	15.59	26.60	26.65	28.09	16.09	26.18
Deployment costs						
Costs (BRL)	93,766,552.98	1,591,431.76	2,864,577.17	2,546,290.82	716,144.29	7,718,444.04
Per capita costs (BRL/inha)	153.46	2.60	2.61	2.75	1.58	2.56
Total deployment per capita costs in 30 years (BRL/inha.year)	5.12	0.09	0.09	0.09	0.05	0.09
Total per capita costs year in 30 years (BRL/inha.year)	20.70	26.69	26.74	28.18	16.15	26.27

The direct costs of treatment (operation, maintenance and implementation) per m³ of water produced from the complementary system using PAC for treatment in the four main DWTPs in Curitiba are close to those of a conventional DWTP (Table 3) considering a return period of thirty years. As these costs are in relation to the m³ of water produced, they can be used both to evaluate the investment of one of these complementary systems and of the four, since the cost per m³ of water will be the same. The economic impacts of the complementary systems represent 78.52% of the direct costs of implementing and operating the water treatment of a conventional DWTP, considering a payback period of thirty years. Therefore, it is a representative investment in financial terms that, in a horizon of thirty years, produces the m³ of water only 21.48% (BRL 0.07134) cheaper than a DWTP. These costs indicate that these complementary systems represent a high investment for a water polishing system. As the cost of implementing these systems is low and their operating costs are high (Table 2), the cost impact on m³ of water produced is practically the same, considering a payback time of 1 or 30 years (Table 3). Therefore, the economic impacts of these complementary systems on the m³ of water produced are not amortized over time due to their high operating cost. Systems with low operating costs and high implementation costs, as is the case of a conventional DWTP, present an inverse behavior in the long term (thirty years) with their costs per m³ being amortized.

Table 3. Water treatment costs on the return period of thirty years.

Return period (years)	***Treatment cost (BRL/m³)**			**Complementary system cost percentage in relation to DWTP (%)**
	DWTP reference	**Complementary systems**	**DWTP reference with complementary systems**	
1	1.81234	0.28593	2.09826	15.78
5	0.56086	0.26469	0.82554	47.19
10	0.41142	0.26215	0.67357	63.72
15	0.36637	0.26138	0.62775	71.34
20	0.34692	0.26105	0.60797	75.25
25	0.33726	0.26089	0.59816	77.36
30	0.33214	0.26080	0.59295	78.52

*Calculated from Eq. (1).

3.2 Feasibility of implementing complementary systems to reduce pharmaceutical micropollutants

The health risk of pharmaceuticals in drinking water still needs to be better evaluated in the case of Brazil, especially in its main metropolises. There are still few studies on the presence of pharmaceutical micropollutants in the water supply. In Curitiba's water supply, the only monitoring campaigns identified average concentrations of 61 ng/L of caffeine (Machado et al., 2016). Even though caffeine is one of the priority compounds for the Curitiba region (Barcellos et al., 2020), further investigations are needed to understand this compound's variability and identify other pharmaceutical substances in the city’s supply waters for further risk assessments. If drug concentrations in supply waters actually represent a health risk, economic and political conditions had to be created to implement complementary systems to reduce concentrations of pharmaceutical micropollutants in supply waters. Technically the implementation of complementary systems in DWTPs does not seem to be a challenge in the context of Curitiba.

Implementing the complementary PAC dosing system at the entrance of DWTPs is technically feasible, so much so that it is being installed in a treatment plant in the region of Curitiba. However, if the implementation of this system has as emphasizes the reduction of pharmaceutical micropollutants, the system will need to work continuously. When the use of PAC exceeds 90-120 days a year, it is more economical to use granular activated carbon (GAC), in the form of a fixed bed (Ferreira Filho, 2021). In this case, the adsorber system can be downstream of the filtration system (post-filter systems) or be used in filtration (adsorber filter systems) with dual function, filtration and adsorption. Therefore, according to the scientific literature, this PAC dosing system is not the most economically suitable solution when the objective is the removal of pharmaceutical micropollutants in the water supply. The operation and maintenance costs of the GAC system are lower, due to the possibility of recycling coal and, consequently, less sludge generated. However, modeling through Eq. (1) with lower maintenance costs, the PAC dosing system, has little change in the cost of m³ of water produced. If this system operates only 90 days a year, the cost of water produced per m³ is BRL 0.27854, considering a payback period of thirty years. When the system operates 120 days a year, the cost of water produced per m³ is BRL 0.27265, considering a payback period of thirty years. In both contexts, 90 and 120 days, the values of m³ of produced water are a little more expensive than those presented in table 3, because the volume of produced water also decreases. Thus, it is demonstrated that the cost of m³ of produced water is little changed in this complementary PAC system, even using the system configurations recommended by the scientific literature.

If, on the one hand, the scientific literature indicates that the PAC is not the most economical solution, due to its operating costs (Ferreira Filho, 2021), economic studies using Eq. (1) point in the same direction. An investigation in a pilot DWTP, of 100 L/s, in Brazil demonstrated that the cost of the m³ of water produced by a GAC and ultrafiltration system are lower in a horizon of thirty years than the PAC system. The values found for a return period of thirty years are BRL 0.37 m³ for the conventional system with GAC and BRL 0.40 per m³ of water produced for the ultrafiltration system (Mierzwa et al., 2008), while for the PAC system we found a value of BRL 0.59 per m³ (table 3). However, some limitations were important in quantifying the costs of GAC and ultrafiltration systems and may have influenced the values of m³ of produced water. The costs of the GAC system and the DWTP of this investigation (Mierzwa et al., 2008) are theoretical, made through market research. The quantification of the costs of the ultrafiltration system is more reliable because it was based on a real system, but on a pilot scale. However, costs per m³ of water produced from pilot systems such as both can change significantly when the scale is real. However, these values demonstrate that complementary treatment systems with PAC (in real scale), GAC (theoretical values of pilot scale) and ultrafiltration (in pilot scale) anyway represent a high investment per m³ of water produced that needs to be very well justified economically and politically.

The modernization of water and sewage treatment systems should be widely discussed with society and stakeholders, both its technical aspects and the impacts of these works. This involvement of society was part of the Swiss and German process of readjusting the WWTPs to remove micropollutants (Bieber et al., 2018). In the developing world, this model of environmental governance that creates a political and discussion environment (Lee, 2006) is not yet a reality. However, the articulation of multisectoral networks of stakeholders in the pharmaceutical chain can change this context. In Curitiba, these networks for the management of pharmaceutical micropollutants have already begun to emerge (e.g., Barcellos et al., 2020). Economic investment in complementary treatment systems for the removal of pharmaceutical micropollutants would represent a significant allocation of resources (Tables 2 and 3) that could be directed to other sanitation sectors and, in the long term, would be paid for by society. Discussions about the origin of the resources allocated and who will pay for these investments to modernize water and sewage treatment systems to reduce concentrations of pharmaceutical micropollutants involve important aspects of social and environmental justice. It does not seem fair that consumers bear these costs, nor does it seem feasible that they compete with the allocation of resources from other priorities in the sanitation sector. In the case of most Brazilian cities, this would imply sharing the cost of this modernization with other cities in the state, even if only metropolis stations such as Curitiba undergo modernization. This is part of the cross-subsidy that guarantees the same water and sewage tariff for the entire state (Rezende & Heller, 2008). The works and operation of sanitation infrastructure in large cities are economically viable for sanitation concessionaires, as they generate profits, on the other hand, they are financially unfeasible in small cities and generate losses. Thus, the cross-subsidy makes it possible for metropolises to finance sanitation in smaller cities through the logic of tariff self-sustainability.

As demonstrated, the cost of these complementary systems for reducing pharmaceutical micropollutants is representative in economic terms and would imply an additional value in the water tariff. However, it seems fairer that the costs of pharmaceutical pollution in water are financed by its producers (pharmaceutical industry). The economic feasibility of this modernization of water and sewage treatment plants can emerge in developing countries when adequate social and environmental justice mechanisms are in place. The creation of a fund financed by the pharmaceutical industries is an alternative for solving this resource allocation and financing problem. These pharmaceutical corporations based in developed countries (e.g., USA, Germany, United Kingdom and Switzerland) generate millionaire revenues benefiting from large consumer markets (e.g., Brazil, India, China and Russia) and coincidentally, or not, they are located in the countries with the greatest advances in pharmaceutical micropollutants management (Barcellos et al., 2022).

4. CONCLUSION

This economic analysis demonstrates that despite being a technically viable alternative, complementary treatment systems in DWTPs using PAC to reduce pharmaceutical micropollutants are economically unfeasible. In addition, there seems to be no adequate political scenario for the implementation of these technologies in the context of the city of Curitiba. In terms of direct cost per capita in thirty years, these complementary systems cost BRL 5.57 a year higher than those of a DWTP. The direct costs of these systems per m^3 of water produced over a thirty-year horizon represent about 78.52% of the costs of a DWTP. Despite the costs per m^3 of water produced from complementary PAC systems being superior to systems with GAC (theoretical values of pilot scale) and ultrafiltration (values from a pilot plant), all these systems do not present real economic conditions to be implemented in the Brazilian context.

The modernization of DWTPs to reduce the concentration of drugs would be a representative allocation of resources in the sanitation sector, which still has the universalization of these services as a priority in Brazil. In addition, these costs would be transferred in the long term in full to consumers within the logic of tariff self-sustainability. This financing model does not seem adequate or socially and environmentally fair in the case of pharmaceutical micropollutants. The solution to this impasse, which may make it economically viable to modernize DWTPs and WWTPs to reduce pharmaceutical pollution in the developing world, is creating a fund financed by pharmaceutical companies. Multinational pharmaceutical production companies and the countries of origin of these companies that benefit from large consumer markets, such as Brazil, can play an essential role in enabling strategies of this type, transferring resources and technology to the developing world.

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CHAPTER 6: CONCLUSIONS AND MAIN FINDINGS

Proposing paths for the management of pharmaceutical micropollutants is a major political, technical and economic challenge, especially for developing countries such as Brazil. Politically, the disarticulation between different governmental spheres and sectors of organized civil society is a cultural problem. Without networking and synergy between other groups of stakeholders, complex environmental issues can hardly be overcome. At this point, the way forward is collective management approaches, as has already occurred in developed countries. Technically, the solutions exist and can even be economical, but they represent a paradigm shift. The new paradigm advocates new urban infrastructures as nature-based solutions and new mechanisms of transferring means (political, economic and technical) from rich countries and large drug producers to developing countries and major consumer markets (Brazil, Russia, India and China). Economically, it is necessary to indicate paths that respect the basic precepts of social and environmental justice. These paths cannot make sanitation services more expensive (leaving these costs to the population) or pressure sanitation companies without a scientific basis and feasible solutions.

In Chapter 2, management approaches were typified and although the prominence in management studies and practices is the technical approach, there are two cleavages of management approaches: the “hard” and the “soft”. The technical approach makes up the “hard” technologies, which often depend on a large allocation of financial resources and advanced technologies. While “soft” technologies, composed of governmental, organizational and community approaches, are less dependent on heavy investments in technological solutions and more dependent on technologies, initiatives and convergence of interests in networks formed by multiple stakeholders involved in the pharmaceutical chain. This division is theoretically important, but it is necessary to expand the range of initiatives and consider the two possibilities for advancement. This chapter indicates 15 opportunities for managing pharmaceutical micropollutants that are feasible for the developing world, which can be applied even in countries with low basic sanitation levels and limited budget availability. These 15 opportunities dispel the myth that the management of micropollutants necessarily depends on universal sanitation and high investments. However, the money route is crucial to understanding the problems and solutions in drug pollution management. It is precisely the nations that host the largest pharmaceutical industries that benefit most from the sale and consumption of pharmaceutical products (such as the USA, Germany, Switzerland and the UK) that present the greatest advances in management. It is often more important in environmental management to capture implicit intentions than advances apparent to create “smoke clouds” generated by governments or organizations to defend sectoral and corporate interests[6]. It is necessary to create mechanisms to expand the role and responsibility of corporations and countries that produce and spread these pollutants.

In Chapter 3, based on European experiences, a collective prioritization approach, unprecedented in Brazil, was developed. In this great effort with stakeholders, it was possible to establish priority pharmaceutical substances for water management in the region of Curitiba and also priority sectoral management strategies. Despite the explicit context of disarticulation between the different spheres of government and other sectoral groups of stakeholders, the advances in management were notable. The sectorial management strategies allowed pointing out the direction of management for the pharmaceutical sector, pharmaceutical industry, water industry and academics. The points of convergence between these sectoral strategies are interfaces between sectors that need to be taken advantage of in intersectoral actions. Unfortunately, the absence of the government sector when the discussion was about sectoral management strategies demonstrated the government's apathy toward the issue. This kind of approach is very important for the developing world. In addition to boosting articulation networks, which are so important in management, the process of these approaches produces results validated by a group and, therefore, capable of laying the foundations in the field of management. As collective prioritizations are constructed by a large group of stakeholders and agreed upon after much interaction and debate, the “Matthew effect[7]” has less influence, enabling innovations and significant advances in management. These real management spaces are promising and strategic for the

[6] These advances apparent in pharmaceutical micropollutants management may be being driven by the pharmaceutical industry to create “smoke clouds” for the effects of their products on the rest of the world. This discussion is dealt with in depth in chapter 2.

[7] This phenomenon consists of selecting already known and very selected options without significant innovations and advances. In chapter 3, a little of this phenomenon is discussed.

entire field of environmental management and need to be used more in Brazil and in other developing countries. Universities and research centers seem to play a leading role in these spaces.

Chapter 4 discusses a systemic solution for urban planning that is still little discussed and applied in Brazil. As challenging as it may seem, Blue-Green Infrastructure is a holistic solution for cities. In addition to increasing urban resilience to climate change, it can mitigate chronic problems in Brazilian cities, such as water pollution in general and even drug pollution. The use of filter gardens (wetlands) in urban riverbeds is an alternative to mitigate the effects of climate change and reduce pollution by micropollutants in rivers in Curitiba. Urban requalification projects in the city that bring these fundamentals begin to arise, but unfortunately, they have not yet gotten off the ground. A change in the urban planning paradigm is needed, something that can only be built gradually, as happened with the “Water Sensitive Urban Design – WSUD”, the Australian school of water-sensitive urban planning. This urban planning model can greatly improve the quality of life and reduce all water-related problems in cities (scarcity, pollution, floods, e.g.). Paradoxically, the short budgets of developing countries can drive public policies with this bias, mainly due to the relatively low costs of these alternatives and their high public acceptance. The Blue-Green Infrastructure is the future of urban planning, and its gradual construction in Brazil needs strong groups within the academy capable of taking its fundamentals to public policies. The application of these concepts needs to be part of the master plans. Legislation that encourages these infrastructures are essential tools to boost this new paradigm of planning. Urban requalification and revitalization projects are up-and-coming for applying these new urban design precepts. The use and development of tools to assess the impacts and feasibility of these projects, such as the Australian software MUSIC[8], is a fruitful field for future studies and necessary for disseminating these infrastructures in cities.

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[8] MUSIC (Model for Urban Stormwater Improvement Conceptualisation) software is Australia's leading tool for water-sensitive urban design. Across Australia, city managers, planners, government, and engineers use MUSIC to scale Blue-Green Infrastructure, to manage the impact of urban development and other changes in land use and rivers. Some local governments and states require MUSIC to project the effects of large-scale urban development. Although this tool is specific to the Australian context (the model's input parameters use information regarding the soil and climate of Australia), it has already been used successfully in New Zealand and Europe.

In Chapter 5, the sensitive economic aspect inherent to technologies to reduce concentrations of pharmaceutical micropollutants in the sanitation cycle is addressed. Through multisectoral dialogue and collaborative work with the local sanitation concessionaire, drinking water was defined as a priority matrix. The economic study of a complementary powdered activated carbon dosing system demonstrated the high order of magnitude of the costs required to modernize treatment systems. The direct price per capita of these complementary systems in thirty years is higher than that of a conventional Drinking Water Treatment Plant. The cost per m^3 of water produced, considering a return period of thirty years, represents 78.25% of the prices of a conventional Drinking Water Treatment Plant. These values are even higher, mainly due to operating costs, than granular activated carbon and ultrafiltration systems. Despite the economic unfeasibility, technically these complementary systems prove viable for the city of Curitiba. However, there is still a long way to go so that these technologies can be part of the reality of Curitiba and other metropolises in the developing world. The political scenario is very far from countries like Switzerland and Germany that are modernizing treatment systems. There is a lack of involvement of stakeholders and the population itself. However, the most significant challenge is economic. A new financing model seems necessary to modernize water and sewage treatment systems to reduce pharmaceutical micropollutants. The millionaire's revenues of pharmaceutical multinationals and the countries that host them should be shared with their consumer markets to mitigate the problems of pharmaceutical pollution. A fund financed by these large pharmaceutical corporations seems to be an alternative with the potential to make these technical interventions economically viable.

APPENDICES

APPENDIX A

SUPPLEMENTARY MATERIAL CHAPTER 2

Collaborative projects to pharmaceutical micropollutants management that integrated the 106 scientific documents.

Project	Countries involved	Goal
1-Poseidon	Germany, Austria, Poland, France, Switzerland, Finland and Spain	“Assessment of technologies for the removal of pharmaceuticals and personal care products in sewage and drinking water facilities to improve the indirect potable water reuse (Poseidon, 2004).”
2-Novaquatis	Switzerland and Germany	“Improving water pollution control by reducing inputs of nutrients and micropollutants, and closing nutrient cycles (Novaquatis, 2021).”
3-Reclaim Water	Germany, Italy, United Kingdom, France, Switzerland, Denmark, Slovenia, Spain, Netherlands, China, Belgium, Australia, Mexico, South Africa and Singapore.	“Develop hazard mitigation technologies for water reclamation providing safe and cost-effective routes for managed aquifer recharge (Reclaim Water, 2008).”
4-NORMAN	Spain, France, Italy, United Kingdom, Netherlands, Slovenia, Slovakia, Sweden, Norway and Germany.	“To create a network among European reference laboratories and related organisations in dealing with emerging environmental pollutants for which Europe-wide data are lacking (NORMAN, 2008).”
5-Start	Germany.	Start Project - Management Strategies for Pharmaceuticals in Drinking Water - is a transdisciplinary project that developed an integrative strategy for reducing the occurrence of pharmaceuticals in the water cycle and thus in drinking water for Germany (Titz & Döll, 2009).
6-Neptune	Switzerland, Sweden, Belgium, Germany, Norway, Italy, Denmark, Germany, Romania, United Kingdom, Austria, Bulgaria, Canada and Australia.	“Focusing on technology solutions allowing to meet present and future standards via upgrading of existing municipal infrastructure as well as via new techniques. By including pathogens and ecotoxicity aspects into life cycle assessment studies (LCA), the project is helping to improve the comparability of various technical options and propose a suitability ranking (Neptune, 2021).”

7-PILLS	Germany, France, United Kingdom, Switzerland, Luxembourg and Netherlands.	“The PILLS Project “Pharmaceutical Input and Elimination from Local Sources” encompasses the idea of investigating wastewater quality and researching and testing elimination methods to achieve better wastewater treatment at the source. (PILLS, 2011)”.
8-SAUBER+	Germany.	“Analyses the risks of pharmaceutical and chemical inputs into wastewater from retirement homes, nursing homes and hospices, and develops strategies for action (Souber, 2021)”.
9-NanoPharm	Germany	“The objective of the NanoPharm project was to develop and test novel technological approaches to the degradation of drug contaminants in different waters by use of photocatalysts (e.g. zinc or TiO2 nanoparticles) modified by means of different methods (NanoPharma, 2021).”
10-VUNA	Switzerland and South Africa.	“To recover nutrients from urine, by developing a dry sanitation system, which is affordable, produces a valuable fertiliser, promotes entrepreneurship and reduces pollution of water resources (VUNA, 2015)”.
11-ASKURIS	Germany.	“Characterization and assessment of risks induced by anthropogenic trace compounds and multi-resistant bacteria in the Berlin urban water cycle, by making use of innovative analytical techniques. Providing technological and natural barriers to reduce trace pollutants and bacteria. Developing a risk management guide for water supplyand wastewater treatment enterprises (ASKURIS, 2021)”.
12-PHARMAS	United Kingdom, France, Sweden, Germany, Netherlands and Denmark.	“A consortium of world-class scientists from both academia and industry has been assembled to assess the risks to wild animals and humans posed by environmental exposure to pharmaceuticals. Their expertise will be supplemented by an advisory group consisting of representatives of all stakeholders. This project will concentrate on two classes of human pharmaceuticals, namely antibiotics and anti-cancer drugs, because there are good reasons for thinking that these could be of particular concern (PHARMAS, 2021).”
13-TAPES	Netherlands, Belgium, Germany, United Kingdom and Switzerland.	“TAPES developed a new platform to share knowledge, to exploit and develop new knowledge and experience for water authorities, water companies, managers of wastewater treatment plants, national and local government, and interested public. TAPES included technological pilots, demonstration projects and the development of a decision support system for investments in the water cycle. (TAPES 2021).”
14-AQUARIUS	Norway and Czech Republic	“This interdisciplinary Aquarius project was focused on very complex analysis of water pollution by different pharmaceutics and social survey, concerning the willingness of consumers to economically

		participate in ensuring the quality of drinking water was performed in the Czech Republic and Norway. The results will be transferred to future practical utilization and are planned for updating the legislative documents. The overall project rating is very good (Aquarius, 2021)"
15-WEMSI	United Kingdom and Brazil.	"This cross-disciplinary project draws together environmental science; (waste) water engineering, eco-toxicological analysis; and stakeholder engagement to consider the increasingly recognised problems of water-quality standards. The aim to investigate the micropollutants potential negative impacts and identify technical and policy solutions (WEMSI, 2021)."
16-Solutions	Germany, Netherlands, Slovakia, Sweden, Belgium, Switzerland, Norway, Bulgaria, United Kingdom, France, Serbia, Austria, China, Czechia, Australia and Brazil.	"SOLUTIONS searches for new and improved tools, models, and methods to support decisions in environmental and water policies. Therefore, the overall goal of the project is to produce consistent solutions for the large number of legacy, present and future emerging chemicals posing a risk to European water bodies with respect to ecosystems and human health (SOLUTIONS, 2021)".
17-Values4Water	Netherlands.	"This project focuses on the question 'How to identify and use the relevant underlying values in developing water governance for change? We take a multidisciplinary approach to investigate multi-actor environments, where individual beneficial actions might lead to undesirable outcomes at the collective level (ValuesWater,2021)".
18-Innovec'EAU	Spain, Portugal and France	"The aim of this project is to carry out a study on waste water from homes of elderly people in south-west Europe, and thus to install technologies for the treatment and monitoring of drug residues (Innovec'EAU, 2021)."
19-MORPHEUS	Sweden, Germany, Poland and Lithuania.	"MORPHEUS will integrate information on pharmaceutical consumption, existing technologies, release rates and environmental occurrence in coastal regions in the South Baltic. This information will aid wastewater treatment plants and authorities in a future implementation of the most suitable advanced treatment technology (MORPHEUS, 2021)".
20-COMBACTE-CARE	United Kingdom, Netherlands, Switzerland, Spain, Germany, Israel, Greece, France, Kosovo, Belgium and	"This project unites the knowledge and capabilities of leading drug resistant bacterial infection experts in the field by bringing together prominent clinical and microbiology research groups in Europe to address the challenges of the observational and interventional clinical studies (COMBACTE-CARE, 2021)".

	Sweden	
21-Effect-Net Project	Germany.	“With a focus on two groups of emerging micropollutants in aquatic environments, food additives and pharmaceuticals, the project Effect-Net crosses the borders between (natural and socio-political) science and public interest by providing an analytical network which gives insight into the cross-linking of consumer behavior and ecological impact EffectNet (2021)”.

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APPENDIX B

SUPPLEMENTARY MATERIAL CHAPTER 3

1) Groups, institutions, total number of stakeholders invited and those who participated of the event.

Groups	Institutions	Invited		Participated			
				1º Part		2º Part	
Policy makers	SEMA (Secretary of Environment of Paraná)	3		1		0	
	SESA (Secretariy of Health of Paraná)	2		2		0	
	SMMA (Secretary of Environment of Curitiba)	1		1		0	
	SMS (Secretary of Health of Curitiba)	1	10	1	7	0	0
	IAP (Environmental Institute of Paraná)	1		1		0	
	AGUASPARANA (Waters Institute of Paraná)	2		1		0	
	Consortium Paraná Health	1		0		0	
Researchers	PUCPR (Pontifical Catholic University of Paraná)	4		3		3	
	UTFPR (Federal Technological University of Paraná)	1	15	0	7	0	4
	UFPR (Federal University of Paraná)	8		3		1	
	UP (Positivo University)	2		1		0	
Hospital and Pharmaceutical sector	CRF-PR (Regional Pharmacy Council of Paraná)	2		2		0	
	SINDIFAR (Syndicate of Pharmaceuticals of Paraná)	1		0		0	
	SINDIFARMA (Syndicate of Retail Trade Pharmaceutical Products of Paraná)	2	10	1	7	1	6
	ANFARMAG (National Association of Pharmaceuticals Magistrates)	2		1		2	
	Little Prince Hospital	3		3		3	
Pharmaceutical industry	Herbarium	1		0			
	VPHAR	1		1		1	
	TECPAR	4		4		4	
	Novartis	1	10	1	7	0	6
	Prati-Donaduzzi	1		0		0	
	Ervas Curam	1		0		0	
	Nunes Farma	1		1		1	
Water industry	Parana State Sanitation Company (SANEPAR)	10	10	6	6	6	6
Total		55		34		22	
		55		37			

2) Forty compounds selected, as a 'long list', presented to stakeholders for prioritization.

Product	Position on the ranking of sold on the pharmacies of Curitiba[i]	Position on the ranking of distributed on the MHUs of Curitiba[i]	Monitored in the waters of region	Detected in the waters of region	Excreted unchanged via urine (%)	LOEC - lowest observed effect concentration
Ibuprofen	13	3	Yes[i]	Yes[i]	1[a]	0,010 ug/L[h]
Paracetamol	2, 10 and 12	11	Yes[i]	Yes[i]	<5 [a]	>32 ug/L[h]
Omeprazole	9	4	No[i]	No[i]	<1 [a]	-[d]
Simvastatin	24	2	No[i]	No[i]	13 [a]	-[d]
Fluoxetine	25	8	No[i]	No[i]	<10 [a]	0,001 ug/L[h]
Atenolol	28	7	Yes[i]	Yes[i]	<90 [a]	3200 ug/L[h]
Amoxicillin	8 and 35	16, 56 and 75	No[i]	No[i]	60 [a]	1.56 ug/L[h]
Acetylsalicylic acid	22	10	Yes[i]	Yes[i]	2-30 [a]	10 ug/L[h]
Dipyrone	1, 5, 11 e 42	49	No[i]	No[i]	-[d]	-[d]
Ethinylestradiol	6, 16, 46 e 60	54	Yes[i]	Yes[i]	16[e]	0,0001 ug/L[h]
Metformin	14	5	Yes[i]	Yes[i]	100 [a]	-[d]
Hydrochlorothiazide	31	6	No[i]	No[i]	<61[g]	-[d]
Cephalexin	26	44	No[i]	No[i]	70-100[g]	
Ketoprofen	38	51	No[i]	No[i]	<1 [a]	1041,3 ug/L[h]
Levothyroxine	55	13	No[i]	No[i]	30-55 [a]	-[d]
Loratadina	34	20	No[i]	No[i]	40 [a]	-[d]
Enalapril	23	1	No[i]	No[i]	20 [a]	-[d]
Estradiol	-[b]	53	Yes[i]	Yes[i]	-[c]	0,00093 ug/L[h]
Diclofenac	7 and 12	- [b]	Yes[i]	Yes[i]	<1 [a]	0,3 ug/L[h]
Caffeine	1,11,12 and 42	- [b]	Yes[i]	Yes[i]	- [c]	-[d]
Levonorgestrel	6	54	No[i]	No[i]	-[d]	0,0008 ug/L[h]
Nimesulide	4	- [b]	No[i]	No[i]	<1[f]	-[d]
Losartan	3	- [b]	No[i]	No[i]	4 [a]	1560 ug/L[h]
Anlodipine	- [b]	9	No[i]	No[i]	<10 [a]	-[d]
Amitriptyline	- [b]	12	No[i]	No[i]	<2 [a]	-[d]
Carbamazepine	- [b]	14	Yes[j]	Yes[j]	2 [a]	1 ug/L[h]
Clonazepam	18	- [b]	No[i]	No[i]	<0,5 [a]	-[d]
Nafazoline	15	- [b]	No[i]	No[i]	-[d]	-[d]
Diazepam	- [b]	18	Yes[j]	Yes[j]	<1 [a]	-[d]
Estrone	- [b]	- [b]	Yes[i]	Yes[i]	- [c]	0,0318 ug/L[h]
Pantoprazole	21	- [b]	No[i]	No[i]	0 [a]	-[d]
Glibenclamide	- [b]	17	No[i]	No[i]	<5 [a]	-[d]
Furosemide	- [b]	19	No[i]	No[i]	80-90 [a]	10 ug/L[h]
Zolpiden	29	- [b]	No[i]	No[i]	0 [a]	-[d]
Sertraline	27	- [b]	No[i]	No[i]	0 [a]	15 ug/L[h]
Valproic acid	- [b]	15	No[i]	No[i]	<3 [a]	-[d]
Lithium carbonate	- [b]	21	No[i]	No[i]	95 [a]	-[d]
Glycazide	- [b]	22	No[i]	No[i]	<5 [a]	-[d]
Carvedilol	- [b]	24	No[i]	No[i]	<2 [a]	-[d]
Prednisone	- [b]	25	No[i]	No[i]	11-30 [a]	-[d]

Notes: a: according to Ashley & Currie (2009).

b: not found among the 60 pharmaceuticals more consumed or distributed.

c: it's excreted by human body in quantities, however its origin generally is not connected at use of medicines.
d: no information found.
e: according to Cunha (2014); Lucena (2013) and Johnson & Williams (2004).
f: according to Bernareggi (1998).
g: according to EMC (2017).
h: lower concentrations tested with effects, Wiki Pharma's database (2018).
I : according to Barcellos, Bollmann & Azevedo (2019, p. 78-101).
J: according to Böger et al. (2018).

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3) Main strategies for the management of pharmaceutical micropollutants indicated by the literature.

Who	Possible Activities
Pharmaceutical companies	Publication of data relevant for environmental assessment, publication of analytical methods and results, offering appropriate package sizes, integration of environmental aspects in the development of new pharmaceuticals and new therapies, dedication to green pharmacy, less over the counter products, establish drug take-back where not already in place, proper information of doctors, pharmacists and the general public
Patients	Improvement of compliance, intake of pharmaceuticals only if necessary and only after prescription by a medical doctor, expired medications not disposed of down the drain; instead returned to pharmacy if drug take-back system is established or into the household waste if appropriate (check with local authorities and pharmacies), no lifestyle pharmaceuticals
Pharmacists	Information of patients, participation in drug take-back
Hospitals	Integration of the delivering pharmacy/wholesaler into handling expired medications, informing doctors/ patients and applying medication classification systems according to environmental criteria
Medical doctors	Prescribing according to environmental criteria if alternatives are available
Health insurance providers	Maintaining necessary medical standards and demonstrating reduction potential and economic benefits, informing doctors and patients, applying pharmaceutical classification systems according to environmental criteria
Sanitation companies	Reduction of input through broken sewerage/piping, reduction of total water flow to be treated (separate transport of wastewater and rainwater) thereby increasing concentration of pharmaceuticals, applying affordable technologies, development of less water- and energy demanding treatment systems and technologies; extended monitoring, advanced treatment if necessary, information of the general public
Government	Initiation and back up of communication between all stakeholders, development of limits/thresholds for pharmaceuticals in different environmental compartments and drinking water, establishing classification systems for pharmaceuticals; inclusion of pharmaceuticals in environmental legislation, more restrictive connection between environmental properties and authorization of human pharmaceuticals, improvement of legislation for the management of expired medications, establishing incentives for the development of greener pharmaceuticals

Source: adapted (Kümmerer 2009).

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