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Prioritization of pharmaceuticals in urban rivers: the case of oral contraceptives in the Belém River basin, Curitiba / PR, Brazil

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ABSTRACT

Efforts to prioritize pharmaceutical products in urban rivers are still rare in Brazil. However, European and U.S. management experiences of pharmaceuticals in urban waters show that this has been one of the first steps necessary to reduce and control this type of pollution. The main objective of this research was to evaluate the presence of oral contraceptives in the catchment area of the Belém River in Curitiba based on the different criteria normally applied to prioritization. For this, in addition to a literature review, historical data on the concentrations of contraceptive hormones in the Belém River, data on pharmaceutical consumption in the basin (collected through interviews by random sampling in pharmacies and from the database of medicines provided by the City of Curitiba Health Units), and data from interviews conducted using intentional sampling with regional stakeholders. The results show that a consistent set of criteria supporting prioritization of ethinylestradiol and estradiol already exists, while the periodic monitoring of these two hormones has proved feasible and necessary in the waters of the region.

Keywords: female sex hormones, pharmaceutical management, prioritization of pharmaceuticals.

Priorização de fármacos nos rios urbanos: o caso dos contraceptivos orais na bacia do rio Belém, Curitiba/PR, Brasil

RESUMO

Esforços para priorizar produtos farmacêuticos em rios urbanos ainda são escassos no Brasil, mas as experiências europeia e norte-americana de gestão de produtos farmacêuticos em águas urbanas mostram que este foi um dos primeiros passos para reduzir e controlar este tipo de poluição. O objetivo principal desta pesquisa foi avaliar o caso de anticoncepcionais orais na área de abrangência do rio Belém, em Curitiba, sob a ótica das diferentes dimensões que têm sido consideradas no processo de priorização. Para isso, além da revisão da literatura, foram utilizados dados históricos sobre a concentração de hormônios contraceptivos nas águas do rio Belém, dados sobre o consumo de fármacos na área da bacia hidrográfica (coletados por meio de entrevistas realizadas por amostragem aleatória em farmácias e pelo banco de dados de medicamentos fornecido pela Prefeitura de Curitiba por meio das Unidades de Saúde) e os dados das entrevistas feitas por amostragem intencional com *stakeholders* locais. Os resultados mostram que, em relação ao etinilestradiol e ao estradiol, já existe um conjunto consistente de critérios que apoiam sua priorização, enquanto que a regulamentação do monitoramento periódico desses dois hormônios se mostrou viável e necessária nas águas da região.

Palavras-chave: gestão de produtos farmacêuticos, hormônios sexuais femininos, priorização de fármacos.

1. INTRODUCTION

Prioritization methodology for controlling and reducing micropollutants in general, and pharmaceuticals in particular, in urban rivers has been a major management challenge given the wide variety of compounds reported in the literature (Berninger *et al.*, 2016; Aubakirova *et al.*, 2017). As a result, the assessment of the environmental and health risks related to the presence of such residues, alone or in combination, is very difficult (Voogt *et al.*, 2009; Riva *et al.*, 2015). Nevertheless, studies globally have reported a variety of prioritization methods to control micropollutants in the waters based on different criteria (Daouk *et al.*, 2015; Riva *et al.*, 2015; Mansour *et al.*, 2016; Aubakirova *et al.*, 2017; Burns *et al.*, 2018). Overall, the most important criteria considered by these methodologies have been: presence of the substance (assessed by consumption and identification in the environment); risk to environment or human health (tested for a range of organisms on various trophic levels); persistence in the environment (natural biodegradation and removal in wastewater treatment systems); and feasible monitoring (existing monitoring methods and appropriate equipment) (Helwig *et al.*, 2013; Daouk *et al.*, 2015; Mansour *et al.*, 2016; Burns *et al.*, 2018).

Two important examples of prioritization are the Norman Network and the European Watch-List. The prioritization methodology elaborated by the Norman Network is about the prioritization of emerging compounds that is included pharmaceuticals. The Norman Network is a global network of stakeholders whose goal is the exchange of information on emerging environmental substances. This network seeks to promote and benefit synergies among research teams from different countries (Norman Network, 2018). In this same direction, European legislation has used a Watch-List mechanism to prioritize emerging contaminants. This mechanism was added in the 2013 update of the Water Directive with the goal of obtaining monitoring data for the establishment of future priorities. This list focuses on pollutants for which available data to assess their risks are still insufficient to allow conclusions on their effects. This Watch-List Directive included several pharmaceuticals in an effort towards prioritization (European Union, 2013).

Given that prioritizing pharmaceuticals in urban rivers that receive domestic effluents is directly related to medicine consumption (a region-specific variable), there is an intrinsic dependence on information related to regional usage of pharmaceuticals, which presents a challenge to prioritization in several regions (Al-Khazrajy and Boxall, 2016; Mansour *et al.*, 2016). Prioritization efforts have been reported in North America, Europe, Australia, and East Asia (Voogt *et al.*, 2009; Guo *et al.*, 2016). However, most of these efforts have been concentrated in Europe and the United States (Al-Khazrajy and Boxall, 2016; Burns *et al.*, 2018), where some pharmaceuticals already undergo systematic monitoring regulated by law and where more advanced proposals are being prepared to control their concentration in water.

Management of urban catchment areas is very challenging due to the large numbers of people and diversity of local stakeholder sectors involved. Knowing stakeholder priorities for water management and the treatment of pharmaceuticals is essential since it is the stakeholders that encourage, negotiate, and undertake these management initiatives.

Due to the lack of studies on pharmaceutical prioritization (Santos, 2015) and management in Brazil (Barcellos, 2018), this study sought to evaluate the different criteria that have been considered for prioritizing of pharmaceuticals, in case of oral contraceptive drugs in the Belém River basin, in Curitiba, State of Paraná, Brazil. The main active ingredients in these drugs, ethinylestradiol and estradiol, are already prioritized, and systematic monitoring is regulated by law in the United States and the European Union. Additionally, we sought to determine if enough evidence is already available to consider these hormones as priorities for water management in the study region.

2. METHODOLOGY

The study area was the Belém River catchment area (Figure 1), which is entirely located within the municipality of Curitiba, Paraná State and is completely urbanized. The river drainage area comprises 87.85 km², occupying 20% of the territory of the city and many of the main neighborhoods and architectural and landscape elements that represent Curitiba in a national and international context are located within the catchment area. According to data from the Brazilian Institute of Geography and Statistics (IBGE), the basin contained 475,606 of the 1,751,907 inhabitants of Curitiba in 2010, corresponding to 27% of the population. The institute (IBGE, 2017) estimates that the current population of Curitiba has reached 1,908,359 inhabitants, and the Belém River catchment area approximately 518,000 inhabitants. According to Lara (2014), approximately 43% of the properties in the catchment area are not properly connected to the sewage collection network, resulting in water containing high levels of domestic sewage pollution. In terms of the general quality of the Belém River water, there is ongoing degradation of the springs near the mouth due to habitual and diffuse sources of pollution, and approximately 90% of this pollution is derived from domestic sewage discharged through drainage networks (Bollmann and Edwiges, 2008).

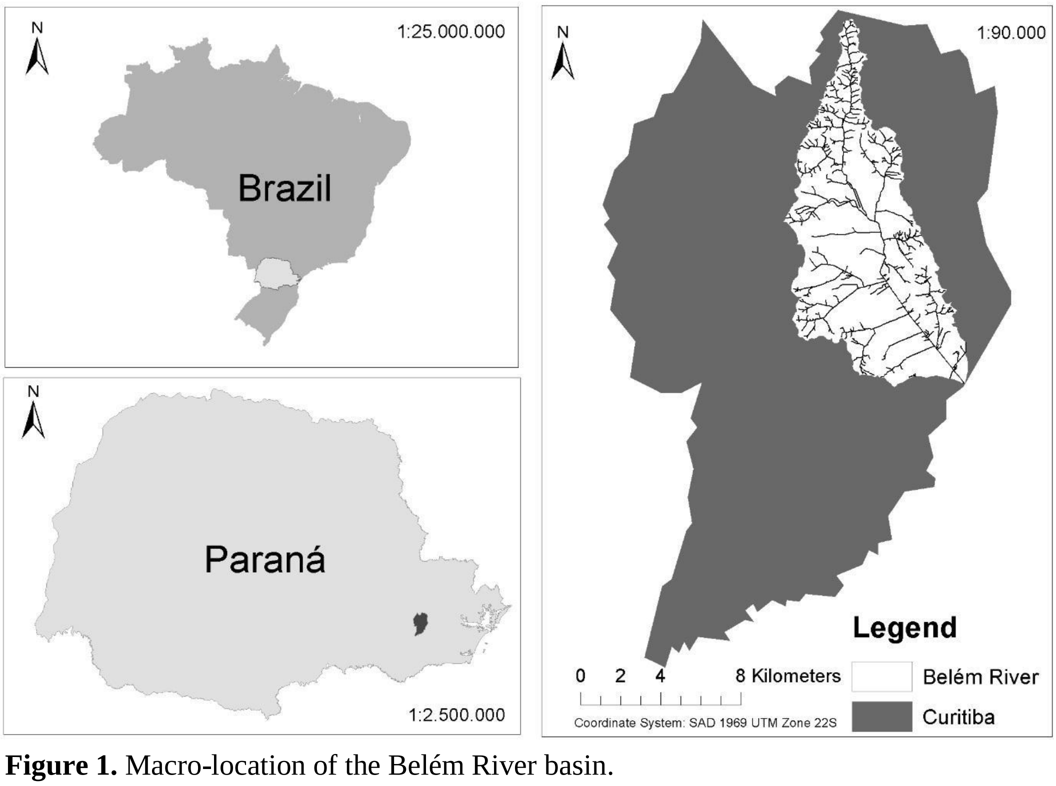

Figure 1. Macro-location of the Belém River basin.

Due to the complexity and variability of environmental characteristics and urban settlement of the Belém River catchment area, the region was divided into three parts: 1) Northern Belém, encompassing the region of the headwaters; 2) Central Belém, in the central region of the basin; and 3) Southern Belém, near the mouth of the basin (Figure 2).

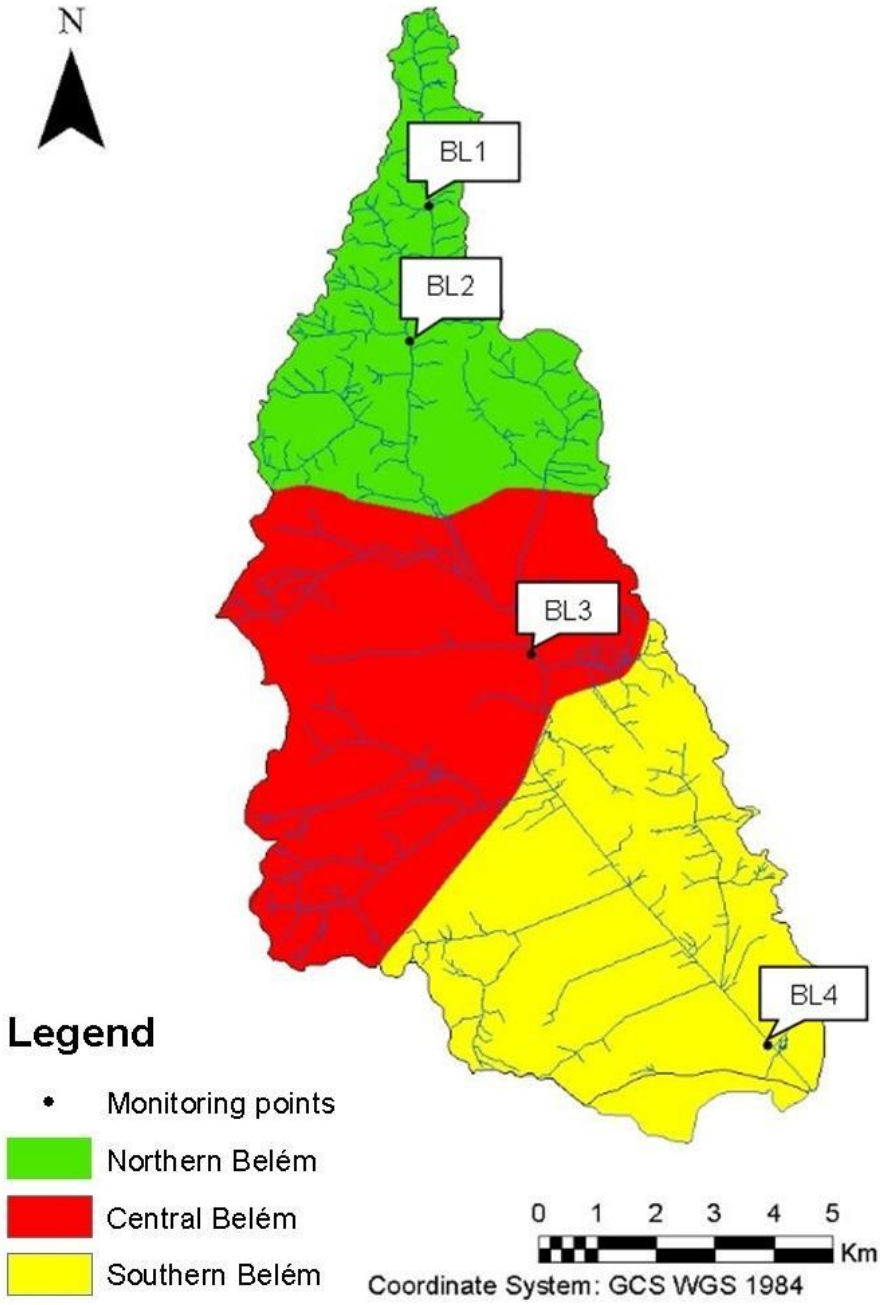

Figure 2. Demarcation of the regions: Northern Belém, Central Belém and Southern Belém, indicating the water quality monitoring points.

This division was based on the methodology proposed by Carvalho Junior (2007), and later also used by Knopki (2008), where the authors divided the catchment area into four major regions. However, in this study we combined Regions 1 and 2 reported by these authors, since they represent very small areas and, although they feature subtle distinctions, overall they present environmental and urban homogeneity. Notably, declivity, forest cover, water quality, and land use and occupation characteristics are similar in these regions.

The criteria considered for the prioritization of pharmaceuticals in this study were: the environmental and health risks of the compound; the presence and concentration of compounds in the water; consumption by the local population; and stakeholder priorities.

The following information was used for the evaluation of these dimensions: 1) pharmaceutical consumption in the Belém River catchment area, based on random interview data from 92 pharmacies between December, 2016 and June, 2017, as well as the distribution data for pharmaceuticals from the Municipal Health Units (UMSs) of the Municipal Health Department from June, 2015 to June, 2017; 2) data from interviews conducted with 32 local stakeholders, selected by intentional sampling, on their priorities for pharmaceutical management; 3) monitoring data on ethinylestradiol (EE2), estrone (E1), and estradiol (E2) from 2011 to 2017, available from the Laboratory of Advanced Studies in Environmental Chemistry (LEAQUA), from the Federal Technological University of Paraná (UTFPR); and 4) a literature review of micropollutant concentrations in the Belém River and information on the environmental effects of the studied compounds.

Hormone analysis was performed by high-performance liquid chromatography with diode array detector (HPLC-DAD). A 5L Van Dorn type bottle was used to collect water that was stored in 1L amber bottles. The extraction method for the hormones was developed using solid phase extraction (SPE). The sample was filtered through 0.45 µm cellulose acetate filters, after which the pH was adjusted to 3. 1 L of the filtered water sample was eluted through a preconditioned C18 SPE column (6 mL of hexane, 6 mL of ethyl acetate, 6 mL of methanol and 6 mL of ultrapure water) at a constant elution rate (10 mL min^{-1}). Then, the C18 SPE column was eluted with 12 mL of acetonitrile, the eluate was evaporated to dryness in a rotary evaporator and 1 mL of acetonitrile was added to re-dissolve the extract. Detailed analytical methodology and procedures are described elsewhere (Ide *et al.*, 2017; Machado *et al.*, 2017).

Purposive sampling was used to select the 32 interviewed stakeholders, considering their contributions to literature on micropollutants, involvement in initiatives for management of water pollution control applicable to pharmaceuticals, and referrals from institutional colleagues. The interviewees were not chosen randomly since the goal was not to generate information that could be generalized, but to know the points of view of a variety of stakeholders. This group included researchers from several universities (Positivo University, Pontifical Catholic University of Paraná, Federal University of Paraná, and Federal Technological University of Paraná), government sector staff (state and municipal departments of the environment, health and education, Environmental Institute of Paraná, and Water and Sanitation Company of Paraná State/SANEPAR), and representatives of the pharmaceutical industry (Pharmacy Council and unions), including the pharmaceutical manufacturing sector.

Interviews with stakeholders were conducted in person, by telephone, or by email (this was only in one case, because the selected person was studying abroad). Two questions were asked, an open question, which was the most important medicine for urban water management, and an objective question asking that classes of drugs (contraceptives, antibiotics, anti-inflammatories, analgesics, lipid and anti-hypertensive) were numbered in order of importance.

A shape file provided by the Department of Geoprocessing of the Institute of Research and Urban Planning of Curitiba (IPPUC) was used to select the sampled pharmacies in the Belém River basin; the file was compiled from permits issued by the Municipal Secretariat of Finance that contained the location of pharmacies. Using geoprocessing tools, 610 of the 1,352 pharmacies in Curitiba were found to be within the basin of the Belém River catchment area, representing the sampling universe. The Cochran formula (Cochran, 1977), Equation 1, was used to determine the sample size:

$$n = \frac{\frac{t^2PQ}{d^2}}{1+\frac{1}{N}\left(\frac{t^2PQ}{d^2}-1\right)} \quad (1)$$

Where:

n = sample size;

t = level of confidence chosen;

P = the percentage at which the phenomenon occurs;

Q = complementary percentage;

N = total number of pharmacies in the basin;

d = maximum error allowed.

For sample-size calculation, and taking N as 610, we set a confidence level of 90% (Student's *t*-value was 1.64), a maximum error of 8% (0.08), and the percentage at which the phenomenon occurs at 50% (0.5). The sample size for the catchment area studied was determined as 92 pharmacies, which were subsequently selected using a Random Number Generator. As pharmacies are not homogeneously distributed throughout the catchment area, the number of pharmacies in each of the 3 regions of the Belém River catchment area was recorded (Figure 2). Of the 610 pharmacies, 403 were found to be concentrated in Central Belém, which is in the central region of the city of Curitiba and has the most populated neighborhoods. Therefore, random selection of pharmacies was performed proportionally, per stratum (Northern, Central, and Southern Belém).

The interviews were carried out with the pharmacists or those responsible for the availability of medicines in pharmacies. The information requested in the interview was three selling rankings in ascending order: the ten best-selling drugs in the pharmacy (all classes of drugs including antibiotics and contraceptives), the best-selling antibiotics and the best-selling oral contraceptives.

3. RESULTS AND DISCUSSION

Estrone, estradiol, and ethinylestradiol are known to cause endocrine deregulation in marine animals and communities, with fish feminization observed even at very low concentrations (nanograms per liter). Table 1 shows the lowest observed effect concentration (LOEC) for which critical effects of estrone, estradiol and ethinylestradiol in water organisms have already been observed, according to WikiPharma, the Swedish digital database.

Although these three hormones can cause endocrine disruption, EE2 has a significantly higher individual endocrine disruption potency (Owen and Jobling, 2013), 10- to 50-fold higher than E2 and E1 (Nash *et al.*, 2004). According to Gilbert (2012), 5 – 6 ng L^{-1} of ethinylestradiol was enough to adversely affect aquatic populations and ecosystems, including collapsing fish communities, as shown in a study in an experimental lake in Canada (Kidd *et al.*, 2007); however, adverse effects were not observed in fish at concentrations below 0.2 – 0.1 ng L^{-1}. Nevertheless, the limit recommended by the European Commission is 0.035 ng L^{-1} in water, based on concentrations that European toxicologists consider safe for marine species (Gilbert, 2012).

The systematic monitoring of EE2, E2, and E1 hormones conducted by LEAQUA at UTFPR (Figure 3) showed that, although the concentrations of the three hormones in the Belém River are frequently below the detection limit (<48, <25 and <26 ng L^{-1}, respectively), concentration peaks of these pollutants can occur. The monitoring points in Central and Southern Belém (BL3 and BL4 in Figure 2) have been monitored since 2011, while monitoring of the points in Northern Belém (BL1 and BL2 in Figure 2) began in November, 2012.

Table 1. Lowest concentrations of female sex hormones tested with effects on aquatic organisms.

Compound	Animal	Critical effect	LOEC
EE2	Fish	Change in egg production	0.1 ng L^{-1}
	Fish	Change in sex/ increase of fertilization failure ratio	0.32 ng L^{-1}
	Fish	Feminization	0.96 ng L^{-1}
E2	Fish	Mortality	0.93 ng L^{-1}
	Fish	Increased body weight and length	2.86 ng L^{-1}
	Fish	Increase in the total length and vitellogenin/decreased fertility	8.66 ng L^{-1}
E1	Fish	Induction of plasma vitellogenin	31.8 ng L^{-1}
	Fish	Reduction in the gonadosomatic index	317.7 ng L^{-1}
	Fish	Induced intersex	100,000.00 ng L^{-1}

Source: WikiPharma (2017).

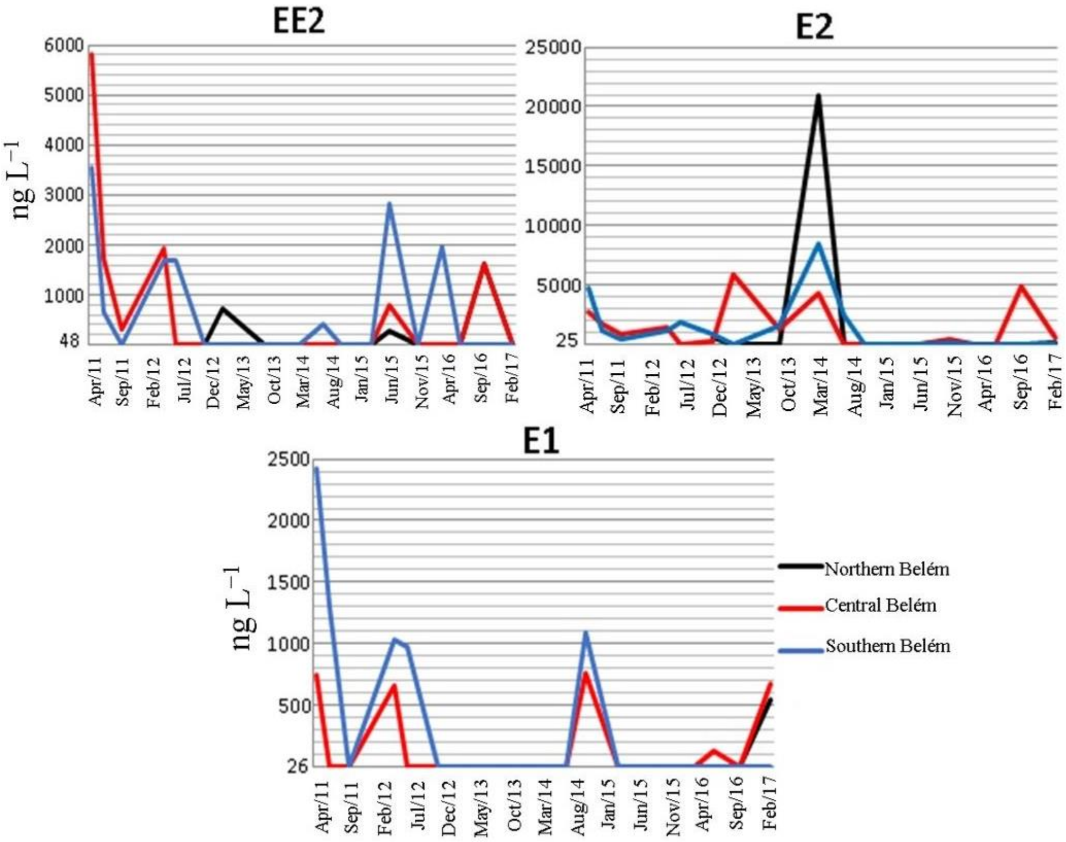

Figure 3. Temporal evolution of EE2, E2, and E1 concentrations in the waters of the Belém River.

The presence of oral contraceptive residues evidently pose an environmental risk given the significant concentrations confirmed in water, which additionally reflect the poor sanitation conditions in the urban area.

Although this catchment area is not a source of human water supply, this study on the concentration of female sex hormones in water is relevant since the Belém River flows directly into the Iguaçu River, which supplies municipalities downstream of the city of Curitiba. Given that the concentrations considered safe in natural waters are significantly lower than those found in the waters of the Belém River, this issue may be an important public health problem for the Curitiba region since the treatment systems employed to treat public water supply cannot remove them. Moreover, significant levels of female sex hormones have been found in the supply waters of the three most populous Brazilian cities (São Paulo, Rio de Janeiro and Belo

Horizonte), at concentrations that can have adverse effects on fish, as shown in the study by Dias (2014).

The analysis of pharmaceutical usage data indicated that oral contraceptives are accessed by the population mostly by purchase in pharmacies, since the amount distributed by UMS was approximately only 4.7% of the estimated amount consumed in Curitiba; this calculation took into account the relationship between a monthly average of 8,369 women who receive contraceptives in the UMSs and the expected monthly consumption in Curitiba, since estimates based on the IBGE census data of 2010 and information from the World Health Organization (Cunha, 2014) indicated that 179,564 (27% of the population) sexually active women (15–64 years) should consume these pharmaceuticals.

Contraceptives are the fourth most-sold class of pharmaceuticals in pharmacies in the region (Table 2), with injectable drugs being used significantly less than pills. The most-sold injectable drugs include Mesigyna (norethisterone enanthate + estradiol), ranked 76; Medroxyprogesterone acetate, ranked 77; and Perlutan (algestone + estradiol), ranked 91 in drug sales in pharmacies.

Table 2. Most sold therapeutic drug classes in pharmacies on the Belém River basin.

Sales Ranking	Therapeutic Classes
1	Analgesics
2	Anti-inflammatories
3	Antihypertensives
4	Contraceptives
5	Digestives
6	Antibiotics
7	Psychotropics
8	Antidiabetics
9	Nasal decongestants
10	Vitamins and supplements

The active ingredients in oral contraceptives with the highest relevance are ethinylestradiol, present in approximately 80% of the most sold contraceptives in pharmacies, and the compounds levonorgestrel, desogestrel, and drospiperone, present in 19% of the most sold contraceptives in pharmacies (Table 3). However, it should be stressed that if sales density is considered, the more relevant pharmaceuticals after ethinylestradiol are levonorgestrel (present in the morning-after pill), drospiperone, cyproterone, desogestrel, and estradiol (present in two of the three injectable contraceptives ranked among the most-sold pharmaceuticals in pharmacies).

Distribution of contraceptives by UMS strengthens the importance of levonorgestrel and estradiol, even though levels are substantially lower than acquisition from pharmacies. For example, the contraceptive most-distributed by UMS is an injectable drug containing estradiol as the active ingredient, ranking 68th among the most-distributed drugs, followed by a pill containing ethinylestradiol + levonorgestrel, ranking 70th among the drugs most-distributed by UMS.

Consequently, ethinylestradiol should be prioritized considering the strong evidence relating to the level of consumption. Although estradiol is consumed less than ethinylestradiol, and other active ingredients such as levonorgestrel, it should also be prioritized due to the high concentrations of these hormones in the Belém River and the proven associated environmental effects. However, E2 is also naturally excreted by the human body, partially explaining the high concentrations of E2 found in the environment.

Table 3. The most-sold oral contraceptives in pharmacies of the Belém River basin.

Formulation	Trade name	Intensity of sales[2]
0.15 mg levonorgestrel + 0.03 mg ethinylestradiol	Microvlar	2.80
0.15 mg levonorgestrel + 0.03 mg ethinylestradiol	Ciclo 21	2.90
3 mg drospirenone + 0.02 mg ethinylestradiol	Yaz	3.20
2 mg cyproterone acetate + 0.035 mg ethinylestradiol	Diane 35	3.51
3 mg drospirenone + 0.03 mg ethinylestradiol	Yasmin	3.57
0.075 mg desogestrel	Cerazette	3.92
3 or 2 or 1 mg estradiol + 2 or 3 mg dienogest	Qlaira	3.98
3 mg drospirenone + 0.03 mg ethinylestradiol	Elani ciclo	4.00
0.075 mg desogestrel	Desogestrel	4.01
3 mg drospirenone + 0.02 mg ethinylestradiol	Iumi	4.07
0.25 mg levonorgestrel + 0.05 mg ethinylestradiol	Neovlar	4.07
2.5 mg nomegestrol acetate + 1.5 mg estradiol	Stezza	4.12
2 mg cyproterone acetate + 0.035 mg ethinylestradiol	Selene	4.12
0.075 mg gestodene + 0.030 mg ethinylestradiol	Gynera	4.12
2 mg chlormadinone acetate + 0.03 mg ethinylestradiol	Belara	4.12
0.75 mg levonorgestrel	Diad[1]	4.13
0.1 mg levonorgestrel + 0.02 mg ethinylestradiol	Level	4.14
0.075 mg gestodene + 0.020 mg ethinylestradiol	Allestra 20	4.14
0.075 mg gestodene + 0.030 mg ethinylestradiol	Tamisa	4.14
0.75 mg levonorgestrel	Previdez[1]	4.14
0.15 mg desogestrel + 0.02 mg ethinylestradiol	Femina	4.15
0.06 gestodene + 0.015 ethinylestradiol	Sublima	4.15
1.5 mg levonorgestrel	Neodia[1]	4.15
0.15 mg desogestrel + 0.02 or 0.01 mg ethinylestradiol	Mercilon	4.16
0.15 mg desogestrel + 0.03 mg ethinylestradiol	Primera 30	4.16
2 mg cyproterone acetate + 0.035 mg ethinylestradiol	Diclin	4.16
0.15 mg levonorgestrel + 0.03 mg estradiol	Nordette	4.16
3 mg drospirenone + 0.02 mg ethinylestradiol	Drospirenone + ethinylestradiol	4.16
2 mg cyproterone acetate + 0.035 mg ethinylestradiol	Repopil	4.16

Note 1: abortifacients.
Note 2: average drug sales ranking among the 92 pharmacies.

Considering the level of consumption, the presence of levonorgestrel in the water should also be investigated, and the effect on aquatic communities should be monitored. Reports on the effects of levonorgestrel are scarce, according to the Swedish database Wiki Pharma. However, levonorgestrel levels are relevant from the point of view of consumption, particularly given the high dose present in contraceptive pills.

In addition to their importance in terms of consumption, contraceptives were also identified as important for the management of drugs by the 32 stakeholders interviewed, who further highlighted them as the most important therapeutic class of drugs (Table 4). Overall, therefore, oral contraceptives are considered a priority for drug management due to the high consumption, reported presence in the water, importance for the stakeholders involved in drug management, and the significant effects on aquatic communities.

Table 4. Prioritization of pharmaceutical products according to the 32 stakeholders interviewed.

Ranking of priorities	Therapeutic Class
1	Contraceptives
2	Antibiotics
3	Anti-inflammatories
4	Analgesics
5	Antihypertensives
6	Lipid Regulators
7	Others

4. CONCLUSIONS

With regard to ethinylestradiol and estradiol, a consistent set of criteria already exists that sustains prioritization for management strategies in the Curitiba region: the presence in the waters of the river at significant concentrations; consideration as priority pollutants among the therapeutic classes of drugs by stakeholders in the region; having a proven chronic deleterious environmental effect at concentrations found in the river; and, in terms of pharmaceutical consumption, forming part of a priority class of drugs, belonging to the fourth most-sold class in pharmacies.

As the analytical capacity to monitor these compounds already exists in the Curitiba region in terms of qualified personnel, equipment, and methodologies, systematic monitoring is feasible and necessary. However, given that only a few research centers are equipped to monitor compounds in Curitiba and the State of Paraná, systematic monitoring could at first be regulated from a health and environmental point of view in strategic hydrographic basins. Subsequently, as the technical capacity increases, systematic monitoring should encompass the whole region and standard methodology to determine concentrations using an adequate detection limit is required to set up official monitoring measures.

Once systematic monitoring is implemented with measures similar to those in the European Union and United States, safety levels can be established for these compounds in natural waters in Brazil, and the concentration limits in waters may subsequently be determined. However, prioritization studies on contraceptives and other medication must first be replicated in other regions in Brazil to meet this goal.

5. ACKNOWLEDGMENTS

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