Occurrence of pharmaceuticals and cocaine in the urban drainage channels located on the outskirts of the São Vicente Island (São Paulo, Brazil) and related ecological risk assessment

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Abstract

“Wealth by the sea and poverty away from the sea breeze” is a metaphor that mirrors what happens along the Brazilian coastal zone, namely in São Vicente Island, São Paulo, Brazil. Due to the high cost of the properties on this shore, the impoverished population started to migrate to the northern outskirts of the island (away from the tourist beaches), potentiating the emergence of poor housing conditions, namely stilt-house slums. Consequently, the urban drainage channels across these outskirts neighbourhoods are potentially contaminated by human wastes. In this context, the occurrence and preliminary ecological risk assessment of eleven pharmaceuticals of various therapeutic classes (including cocaine and its primary metabolite, benzoylecgonine) were investigated, for the first time, in five urban drainage channels whose diffuse loads flow continuously to the estuarine waters of São Vicente Island. The results showed the widespread presence of these environmental stressors in all urban channels analysed, namely losartan (7.3–2680.0 ng/L), caffeine (314.0–726.0 ng/L), acetaminophen (7.0–78.2 ng/L), atenolol (6.2–23.6 ng/L), benzoylecgonine (10.2–17.2 ng/L), furosemide (1.0–7.2 ng/L), cocaine (2.3–6.7 ng/L), carbamazepine (0.2–2.6 ng/L), diclofenac (1.1–2.5 ng/L), orphenadrine (0.2–1.1 ng/L) and chlortalidone (0.5–1.0 ng/L). The overall total estimated load of pharmaceuticals and personal care products flowing to the estuarine waters of São Vicente Island is on the order of 41.1 g/day. The ecological risk assessment revealed a great environmental concern for São Vicente Island, ranging between low (e.g. carbamazepine and cocaine) and moderate to high (e.g. caffeine, acetaminophen and losartan) threats for the aquatic biota. Therefore, initiatives promoting basic sanitation, land-use regularisation and population awareness are highly recommended.

Keywords Subtropical ecosystem · Nonpoint source pollution · Domestic sewage · Pharmaceuticals · Illicit drugs · Risk assessment · Pollution effects

Introduction

During the last decades, a wide range of pharmaceuticals and personal care products (PPCPs) have been repeatedly reported worldwide in the coastal aquatic environments (Biel-Maeso et al. 2018; Dafouz et al. 2018; Fernández-Rubio et al. 2019). These chemical compounds include antiepileptics, stimulants, analgesics/anti-inflammatory agents, antihypertensive and illicit drugs (including cocaine and its primary metabolite, benzoylecgonine) and many others, that are used on a daily basis (Wang et al. 2019; Valdez-Carrillo et al. 2020; Roveri et al. 2021). Due to their large use in human and veterinary medicine, PPCPs are continuously entering the aquatic ecosystems, mainly through waste-water treatment plants (WWTP), with inadequate removal efficiencies, combined sewer overflows (CSOs), misconnections to...
storm water drains and/or leachates from municipal solid wastes (MSW) (Biel-Maes et al. 2018; Dafouz et al. 2018; Fernández-Rubio et al. 2019). Consequently, PPCPs are a major environmental concern mainly due to their potential deleterious effects on aquatic organisms, even at trace concentrations (generally at the ng/L or µg/L levels), which may include immobilization, growth inhibition, endocrine disruption, genotoxicity, carcinogenicity and mortality (Capaldo et al. 2019; Miller et al. 2019; Valdez-Carrillo et al. 2020).

Although in some developed countries, notably in Central America, Europe and Asia (Li et al. 2016; Maasz et al. 2019; Wang et al. 2019), strict preventive and/or regulatory measures have been implemented, most countries in Latin America, including Brazil (the 7th largest pharmaceutical’s world producer), do not have regulations regarding pharmaceutical and illicit drug discharges into aquatic ecosystems (Quadra et al. 2019; Fontes et al. 2020; Roveri et al. 2021). In Brazil, approximately 50 million people live along its 8500 km of coastline. Only, São Paulo shoreline encompasses 16 municipalities, representing 10% of the Brazilian coast, and has 600 urban drainage channels along the 290 tourist beaches (Undesa, 2017; Blackburn et al. 2019; Ibge 2019). However, studies that have evaluated the occurrence of pharmaceuticals and illicit drugs in urban drainage channels, which carry out the diffuse loads (popularly known as black tongues: mixture of urban runoff and untreated domestic sewage) into the beaches, known areas of intense human recreation, were restricted to two municipalities (i.e. Guarujá and Santos) of São Paulo coast (Roveri et al. 2020a; 2021). Furthermore, these studies revealed that carbamazepine, caffeine, acetaminophen, diclofenac, losartan and valsartan presented potential risk to sensitive aquatic organisms at maximum measured concentrations (Roveri et al. 2020a; 2021).

Yet, no previous studies have assessed the occurrence and ecological risk of PPCPs in the urban drainage channels located in the outskirts of São Vicente Island. São Vicente is a typical subtropical coastal city, located in southeast Brazil, that has suffered for decades from numerous economic and socio-environmental conflicts, which still persist today (Jakob et al. 2006; Zundt 2006; SMA/CPLA 2018). Considered an important Brazilian tourist destination, its economy developed from 1980, and began to attract investors, mainly in the area of civil construction, culminating in the intense urbanization of the São Vicente coastal region (Zundt, 2006; SMA/CPLEA 2016; SMA/CPLA 2018). However, due to the high cost of the new properties on the shoreline, part of the impoverished population started to migrate to the outskirts located on the north of the island (away from the tourist beaches), promoting the emergence of poor housing conditions, namely stilt-house slums (Jakob et al., 2006; SMA/CPLEA 2016; SMA/CPLA 2018). Consequently, the urban drainage channels that cross these outskirts are potentially contaminated by human wastes that flow daily to the estuarine waters of São Vicente Island. Moreover, this estuary is home to unique flora and fauna, being used for human recreational and subsistence activities, such as fishing and nautical tourism, and represents one of the main waterways that travel across the city towards the South Atlantic Ocean (SMA/CPLEA 2016; SMA/CPLA 2018).

Taking into consideration the previous research gaps, the aim of the current study was to assess, for the first time, the occurrence and the ecological potential risk of eleven PPCPs of various therapeutic classes (including cocaine and its primary metabolite, benzoylecgonine) in five urban drainage channels located on the north of São Vicente Island, which daily receives diffuse loads from the northern stilt-house slums of São Vicente Island. In a regional scale, this research is complementary to previous works carried out by our team in this area (Roveri et al., 2020a; 2020b; 2021), and thus, the major findings from this study will help public authorities and environmental agencies to plan and perform better actions to improve the environmental quality along of the São Paulo coastline. Moreover, at a global scale, the acquired knowledge will reinforce the importance of implementing continuous environmental monitoring programmes for tracking pharmaceuticals and illicit drugs in the coastal areas, mainly in developing countries.

**Materials and methods**

**Study site description and sample collection**

This study was carried out in São Vicente city (23° 57′ 47″ S; 46° 23′ 30″ W), a micro-region of the Metropolitan Region of Baixada Santista (MRBS), located at the eastern edge of the Atlantic Ocean in Brazil (Ibge 2019). The municipality’s economy is mainly driven by commercial activities associated with tourism, developed mainly along of the seven beaches located on the southern portion of the island, namely Itaquitanduva and Paranauê beaches (both located around the protected environments of Xixová Japuí State Park), and other five beaches where the tourism is more intense representing a key part of the social, recreational and cultural life of the inhabitants: Gonzaguinha, Milionários, Ilha Porchat, Itararé and Divisa (SMA/CPLEA 2016; SMA/CPLA 2018) (Fig. 1). In São Vicente, the climate favours the use of these beaches throughout the year, where the mean annual precipitation and temperature are approximately 3000 mm and 22 °C, respectively (SMA/CPLEA 2016; SMA/CPLA 2018).

Although São Vicente has a drainage area of about 148 km², about 117 km² are made up of areas of environmental preservation located in the mainland area. This area also houses approximately 30% of the municipality’s inhabitants (SMA/CPLEA 2016; SMA/CPLA 2018; Ibge 2019).
Thus, currently about 252,000 inhabitants are concentrated in a small and urbanized area of the insular area (31 km²), which represents a demographic density of more than 2300 inhabitants per km² (Fig. 1) (SMA/CPLEA 2016; SMA/CPLA 2018; Ibge 2019). Consequently, São Vicente Island is suffering for decades from socioeconomic and environmental problems, including the collapse of the city urban infrastructure (Jakob et al. 2006; Zundt 2006; SMA/CPLA 2018). São Vicente presents a socioeconomic asymmetry in the distribution of the inhabitants in its territory, with a clear division of the city according to the people income classes. The middle- and high-income social classes live in areas near the beachfront. But, the low-income families are distributed in the outskirt areas, where the sanitation infrastructures are precarious and often non-existent (Jakob et al. 2006; Zundt 2006; Ibge 2019). For instance, more than 24,000 illegal and precarious constructions are located in environmental protected areas (e.g. mangroves, sandbanks and hills) (SMA/CPLEA 2016; SMA/CPLA 2018; Ibge 2019). Several stilt-house slums are located on the Jockey Club neighbourhood (on the north of the island; on the border with the municipality of Santos) (Fig. 1). Due to the lack of land regulations, these areas are not served by a sanitation network, and consequently, the urban drainage channels located in the Jockey Club neighbourhood are potentially contaminated with human wastes, whose diffuse loads flow daily to the estuarine waters of São Vicente Island. Moreover, during the high tide, floods are common both in the Jockey Club and in the adjacent neighbourhoods (Fig. 1) (SMA/CPLEA 2016; SMA/CPLA 2018).

Five sampling points (labelled as P), one in each channel whose diffuse loads flow through the three stilt-house slums, were selected: (i) P1, channel located in Eduardo Souto street (tributary to the channel of Piçarro Dike street); (ii) P2, channel located in Piçarro Dike street; (iii) P3, channel located in Cachetas Dike street; (iv) P4, channel located in Lourival Moreira do Amaral street; and (v) P5, channel located in Doctor Alcides de Araújo Avenue (P4 and P5 were located upstream of the Sambaiatuba stilt-house slum) (Fig. 1). Water samples (1 L) were collected during the dry season and at low tide. No rainfall was recorded 48 h prior to water collection. For all locations, sampling took place on Friday, 18th June 2021. Firstly, the flow of the five urban channels was measured in order to calculate the PPCP load.
in terms of g/day, using the equation \( \Sigma \text{PPCPs (ng/L)} \times Q_{\text{flow}} \) (m\(^3\)/s), where \( \Sigma \text{PPCPs} \) is the total concentration of PPCPs and \( Q_{\text{flow}} \) is the water flow. Specifically, \( Q_{\text{flow}} = v \times B \times H \), where “\( v \)” is the velocity of flow (measured with a portable flowmeter), “\( B \)” is the width of the urban channel and “\( H \)” is depth of the channel (Jiang et al. 2020). Thereafter, discrete water samples (1L) were collected manually (at 30 cm depth in the water column) from each site with a stainless-steel bucket which had been pre-cleaned with nitric acid, methanol and distilled water and then rinsed twice with water from the sampling site before collection. After collection, water samples were stored in amber bottles (Chen et al. 2021), also previously cleaned with nitric acid, methanol and distilled water. After collection, water samples were stored in amber bottles and methanol and rinsed with distilled water to eliminate any trace of possible contaminants. All samples were kept at 4 °C, and target PPCPs were extracted from water samples within 4 days of collection (USEPA 2007).

**Preparation and analysis of pharmaceutical compounds**

**Chemicals and analytical standards**

Chemicals and analytical reagents such as nitric acid and sulphuric acid were purchased from Merck (Darmstadt, Germany). High purity grade solvents, used in performance-liquid chromatography (HPLC) and liquid chromatography with tandem mass spectrometry (LC–MS–MS), such as acetonitrile, methanol and isopropanol, were acquired from Sigma-Aldrich (Massachusetts, USA). Mobile phase grade additives, such as formic acid and ammonium acetate, were purchased from Sigma-Aldrich and Merck, respectively. Analytical standards (with purity grade > 98%) of carbamazepine, caffeine, acetaminophen, diclofenac, orphenadrine, atenolol and losartan were acquired from Sigma-Aldrich (Massachusetts, USA). Chlortaldione and furosemide were acquired from Higroton® (Novartis, Swiss), and cocaine and benzoylecgonine were acquired from Cerillant (Texas, USA).

**Sample preparation**

The extraction technique used in the hereby study used a matrix-matched calibration curve to quantify the PPCPs according to Wille et al. (2010) and fully described by Roveri et al. (2020a; 2021). The linearity of the method was evaluated by constructing a curve using seven calibration standards. The calibration curves of the compounds showed satisfactory coefficients of determination (0.90 ≤ \( r^2 \) ≤ 1.00) (Wille et al. 2010). Prior to the extraction, the following procedures were adopted: (i) the pH of each sample (ranging from 6.5 to 6.7) was adjusted to 7.0 using a sodium hydroxide solution (1 M); (ii) samples were filtered through a cellulose filter paper (Whatman® GF/C Glass microfiber filters, diameter 47 mm, particle retention 1.2 μm; Merck, Darmstadt, Germany); (iii) the filters were washed with 2 mL of methanol (Sigma-Aldrich, St. Louis, USA); and (iv) at the end, the methanol extract collected was then combined to the filtered sample. The solid-phase extraction was performed using SPE Chromabond HR-X cartridges (200 mg, 3 mL; Marcherey-Nagel, Duren, Germany). The cartridges were preconditioned with methanol (5 mL) and ultrapure water (5 mL) (Milli-Q®-Merck, Darmstadt, Germany). Thereafter, there were loaded with 1L of the filtered sample combined with the methanol from filter washings. The cartridges were then dried under vacuum for 30 min, and the elution was performed twice using 5 mL of methanol and 5 mL of acetone. After the extraction, the samples were dried under a nitrogen flow (at 50 °C) and eluted with water/acetonitrile (95:5 v/v) prior to mass spectrometry analysis. In the laboratory, each water sample was analysed in triplicate using LC–MS–MS. A concentration factor (1/1000) was used to obtain the final concentrations, and individual average results were expressed in ng/L (Table 1).

**LC–MS–MS analysis**

The selection of the PPCPs took into account the reported annual consumption, expected toxicity, environmental persistence and other previous regional studies (Cmed 2019; Roveri et al. 2020a; 2021). LC–MS/MS analytical procedures were validated by Shihomatzu (2015) and fully described by Roveri et al. (2021) (for more details, see Tables S1a and S1b). Briefly, an aliquot of 10 μL of sample was analysed with HPLC (HPLC Agilent 1260, Agilent™, Germany) combined with a mass spectrometer hybrid triple quadrupole/LIT instrument (3200QTRAP®-linear ion trap) (ABSciex, Ontario, Canada). The samples were analysed using an Agilent Zorbax Eclipse XDB–C18 column (50 × 4.6 mm ID, 1.8 μm column at 25 °C). The eluent flow was 0.7 mL/min, and the mobile phase for positive mode analysis was 0.1% formic acid (Sigma-Aldrich; LC–MS Grade) in water (solvent A) and acetonitrile (solvent B) (J.T. Baker, Philipsburg, NJ, USA). A linear gradient of 0.7 mL/min was used, starting with a mixture of solvent A (95%) and solvent B (5%). The percentage of solvent A was decreased linearly from 95 to 5% over 5 min, and this condition was maintained for 1 min. This mixture was then returned to initial conditions over 2 min, and the analytes were detected and quantified using the electrospray ionisation (ESI) and multiple reaction monitoring (MRM), with the selection of a precursor ion and two ion products to quantify and qualify each compound. The data were recorded and processed using the Analyst 1.5.2 software (ABSciex). The LC–MS–MS quality control data, such as MRM parameters for positive and negative ion modes, limit
of detection (LOD), and limit of quantification (LOQ), is also shown in Table S1a.

**Ecological risk assessment**

The ecological risk assessment followed the works of Roveri et al. (2020a; 2021). The risk quotient (RQ) for three different aquatic organisms (algae, crustaceans and fishes) was calculated following the equation $RQ = \frac{MEC}{PNEC}$, in which MEC is the maximum measured environmental concentration and PNEC the predicted no-effect concentration, both expressed in ng/L. The PNEC values for the acute and chronic toxicity data were obtained from peer-reviewed publications by performing searches in the Ecotoxicology Database (ECOTOX) (USEPA 2019), as well as in other literature sources using the PubMed database (see Table 2). When ecotoxicity laboratory experimentally derived data were not available, PNEC was estimated using the Ecological Structure Activity Relationships Programme (ECOSAR, v 2.0) (USEPA 2017). An attempt was made to compile specifically PNEC data for marine coastal species, since in the hereby study urban surface runoff will flow to the shoreline. However, due to the strong land-sea interaction in this study area and the lack of marine toxicity data, the freshwater species were also taken into consideration in the present study (Roveri et al. 2020a, 2021). The PNEC values for the acute and chronic toxicity data were thereafter calculated by dividing each toxicological endpoint by an assessment factor (AF). For saltwater environments, an AF of 10,000 and 100 should be considered in short- and

| Urban drainage channels of São Vicente |
|--------------------------------------|
| **Compound** | **Channel (P1)** | **Channel (P2)** | **Channel (P3)** | **Channel (P4)** | **Channel (P5)** | **Detection (%)** |
| Antiepileptic | | | | | | |
| Carbamazepine | 2.5 | 2.4 | 0.2 | 1.9 | 2.6 | 100.0 |
| Stimulants | | | | | | |
| Caffeine | 586.0 | 314.0 | 492.0 | 726.0 | 712.0 | 100.0 |
| Cocaine | 3.3 | 3.1 | 3.0 | 6.7 | 2.3 | 100.0 |
| Benzoylcegonine | 10.2 | 12.0 | 10.8 | 17.2 | 11.1 | 100.0 |
| Analgesic/Anti-inflammatory | | | | | | |
| Acetaminophen | 18.2 | 22.3 | 7.0 | 78.2 | 37.8 | 100.0 |
| Diclofenac | 2.0 | 2.3 | 1.1 | 2.3 | 2.5 | 100.0 |
| Orphenadrine | 1.0 | 0.2 | 0.7 | 1.0 | 1.1 | 100.0 |
| Antihypertensive | | | | | | |
| Atenolol | 12.4 | 15.1 | 6.2 | 23.6 | 17.1 | 100.0 |
| Losartan | 18.4 | 20.2 | 7.3 | 23.2 | 2680.0 | 100.0 |
| Diuretic | | | | | | |
| Chlortalidone | 0.8 | 1.0 | 0.5 | 1.0 | 0.7 | 100.0 |
| Furosemide | 6.0 | 2.5 | 1.0 | 2.3 | 7.2 | 100.0 |

∑ PPCPs in urban drainage channels of the São Vicente (ng/L)
| Compound          | MEC (ng/L) | Trophic level | Organisms/species | Endpoint | Concentrations (ng/L) | AF | PNEC (ng/L) | Reference               | RQ  |
|-------------------|------------|---------------|-------------------|----------|-----------------------|----|-------------|--------------------------|-----|
| Carbamazepine     | 2.6        | Acute         | Algae             | Skeletonema marinae<sup>1</sup> | 72 h EC50 | 1.00E+08 | 1.00E+04 | Minguez et al. (2014)    | <0.01 |
|                   |            |               | Crustacea         | Artemia salina<sup>2</sup>     | 48 h EC50 | 1.00E+08 | 1.00E+04 | Minguez et al. (2014)    | <0.01 |
|                   |            |               | Fish              | Oryzias latipes<sup>1</sup>    | 48 h EC50 | 3.52E+07 | 3.52E+02 | Kim et al. (2009)        | <0.01 |
| Chronic           |            |               | Crustacea         | Lemma gibba<sup>1</sup>        | LOEC/2 | 5.00E+05 | 5.00E+03 | Brain et al. (2004)      | <0.01 |
|                   |            |               | Fish              | Ceriodaphnia dubia<sup>1</sup> | NOEC  | 2.50E+04 | 2.50E+02 | Ferrari et al. (2003)    | 0.01 |
|                   |            |               | Fish              | Danio rerio<sup>1</sup>        | NOEC  | 2.50E+07 | 2.50E+05 | Ferrari et al. (2003)    | <0.01 |
| Caffeine          | 726.0      | Acute         | Algae             | Pseudokirchneriella subcapitata<sup>1</sup> | 72 h LC50 | 3.39E+08 | 3.39E+05 | Blaise et al. (2006)     | 0.02 |
|                   |            |               | Crustacea         | Daphnia dubia<sup>1</sup>      | 48 h LC50 | 5.00E+07 | 5.00E+03 | Moore et al. (2008)      | 0.15 |
|                   |            |               | Fish              | Pimephales promelas<sup>1</sup> | 48 h LC50 | 8.00E+07 | 8.00E+03 | Moore et al. (2008)      | 0.09 |
| Chronic           |            |               | Crustacea         | Lemma gibba<sup>1</sup>        | LOEC/2 | 5.00E+05 | 5.00E+03 | Brain et al. (2004)      | 0.15 |
|                   |            |               | Crustacea         | Ceriodaphnia dubia<sup>1</sup> | NOEC  | 2.00E+07 | 2.00E+05 | Brain et al. (2004)      | <0.01 |
|                   |            |               | Crustacea         | Pimephales promelas<sup>1</sup> | NOEC  | 3.00E+07 | 3.00E+05 | Brain et al. (2004)      | <0.01 |
| Cocaine           | 6.7        | Acute         | Green algae       | Pseudokirchneriella subcapitata<sup>1</sup> | 96 h LC50 | 4.35E+06 | 4.35E+02 | ECOSAR                   | 0.02 |
|                   |            |               | Crustacea         | Daphnia dubia<sup>1</sup>      | 48 h LC50 | 5.48E+06 | 5.48E+02 | ECOSAR                   | 0.01 |
|                   |            |               | Fish              | Fish<sup>2</sup>               | 96 h LC50 | 4.86E+07 | 4.86E+03 | ECOSAR                   | <0.01 |
| Chronic           |            |               | Green algae       | Pseudokirchneriella subcapitata<sup>1</sup> | 10^*(log (LOEC \times NOEC))/2) | 1.46E+06 | 1.46E+04 | ECOSAR                   | <0.01 |
|                   |            |               | Crustacea         | Mytilus edulis<sup>1</sup>     | NOEC  | 2.29E+09 | 2.29E+07 | ECOSAR                   | <0.01 |
|                   |            |               | Fish              | Fish<sup>2</sup>               | NOEC  | 7.18E+06 | 7.18E+04 | ECOSAR                   | <0.01 |
| Acetaminophen     | 78.2       | Acute         | Algae             | Phaeodactylum tricornutum<sup>2</sup> | 72 h EC50 | 2.39E+08 | 2.39E+04 | Claessens et al. (2013)  | <0.01 |
|                   |            |               | Crustacea         | Artemia salina<sup>2</sup>     | 48 h EC50 | 1.00E+08 | 1.00E+04 | Minguez et al. (2014)    | 0.01 |
|                   |            |               | Fish              | Oryzias latipes<sup>1</sup>    | 48 h EC50 | 2.66E+08 | 2.66E+04 | Kim et al. (2009)        | <0.01 |
| Chronic           |            |               | Crustacea         | Phaeodactylum tricornutum<sup>2</sup> | 72 h EC10 | 7.21E+07 | 7.21E+05 | Claessens et al. (2013)  | <0.01 |
|                   |            |               | Fish              | Daphnia magna<sup>1</sup>      | NOEC  | 4.03E+05 | 4.03E+03 | Kim et al. (2009)        | 0.02 |
|                   |            |               | Fish              | Danio rerio<sup>1</sup>        | LOEC/2 | 5.00E+03 | 5.00E+01 | Galas et al. (2013)      | 1.56 |
| Losartan          | 2680.0     | Acute         | Algae             | Lemma minor<sup>1</sup>        | 96 h EC50 | 6.46E+07 | 6.46E+03 | Godoy et al. (2015)      | 0.41 |
|                   |            |               | Crustacea         | Daphnia magna<sup>1</sup>      | 48 h LC50 | 331,000.00 | 3.31E+01 | FDA (2012)               | 80.97 |
|                   |            |               | Fish              | Pimephales promelas<sup>1</sup> | 48 h LC50 | 1.00E+09 | 1.00E+06 | FDA (2012)               | 0.03 |
| Chronic           |            |               | Green algae       | Pseudokirchneriella subcapitata<sup>1</sup> | 10^*(log (LOEC \times NOEC))/2) | 1.64E+06 | 1.64E+04 | ECOSAR                   | 0.16 |
|                   |            |               | Crustacea         | Daphnia dubia<sup>1</sup>      | 5.55E+05 | 5.55E+03 | ECOSAR                   | 0.48 |
|                   |            |               | Fish              | Fish<sup>1</sup>               | 2.94E+05 | 2.94E+03 | ECOSAR                   | 0.91 |
Results and discussion

Occurrence profile of the PPCPs in urban drainage channels of São Vicente Island

To date, information regarding the occurrence and the ecological risk of PPCPs in São Vicente Island are non-existent. Thus, this study screened and detected, for the first time, the occurrence of common PPCPs of various therapeutic classes (including cocaine and its primary metabolite, benzoylecgonine) in five urban drainage channels located on the northern outskirts of the São Vicente Island, whose waters daily flow into the estuaries. The occurrence and frequencies of detection of these eleven environmental stressors are shown in Table 1. In São Vicente, these five urban drainage channels pass through Jokey Club, a poor neighbourhood in São Vicente, where public health units, pharmacies, and some commercial establishments, including bars and supermarkets, could be found. Moreover, these channels are located near the three stilt-house slums of São Vicente, namely Piçarro Dike (area of influence of points P1 and P2), Cachetas Dike (area of influence of point P3) and Sambaiatuba slum (area of influence of points P4 and P5) (Fig. 1) (SMA/CPLEA 2016; SMA/CPLA 2018). Consequently, the investigated PPCPs were detected in all channels (100.0% frequency), namely antiepileptics (carbamazepine), stimulants (caffeine, cocaine and benzoylecgonine), analgesics/anti-inflammatories (acetaminophen, diclofenac and orphenadrine), antihypertensives (atenolol and losartan) and diuretics (chlorotaldione and furosemide) drugs (Table 1). Moreover, the highest concentrations of these PPCPs were observed at sampling points P4 and P5. For example, the total concentration of the eleven PPCPs ($\sum$PPCPs) in the urban channels ranged from 395.1 to 3474.4 ng/L: $\sum$PPCPs in P2 (395.1 ng/L) < P3 (529.8 ng/L) < P1 (660.8 ng/L) < P4 (883.4 ng/L) < P5 (3474.4 ng/L) (Table 1). Furthermore, the individual concentrations of the hereby PPCPs ranged from 0.2 (orphenadrine, detected in P2) to 2680.0 ng/L (losartan, detected in P5) (Table 1). MEC values of these PPCPs were also predominantly higher at the sampling points P4 and P5 (with a total of 6 PPCPs) and P5 (with a total of 5 PPCPs), e.g. losartan ($MEC = 2680.0 \text{ ng/L}$; detected in P5) > caffeine ($MEC = 726.0 \text{ ng/L}$; P4) > acetaminophen ($MEC = 78.2 \text{ ng/L}$; P4) > atenolol (23.6 ng/L; P4) > benzoylecgonine (MEC: 17.2 ng/L; P4) > furosemide (MEC: 7.2 ng/L; P5) > cocaine (MEC: 6.7 ng/L; P4) > carbamazepine (MEC: 2.6 ng/L; P5) > diclofenac (MEC: 2.5 ng/L; P5) > orphenadrine (MEC: 1.1 ng/L; P5) > chlorotaldione (MEC: 1.0 ng/L; P4) (Table 1). The higher PPCP concentrations observed in P4 and P5, where the concentrations of losartan were surprisingly high compared to the literature data (for more details, see Fig. 2 and Table S2), can be explained by the fact that both channels are in the area of influence of Sambaiatuba slum, where a large amount of garbage was observed on the streets during the fieldwork, namely organic products, food packaging, personal care products and building materials. In addition, due to the proximity to Vila Gilda Dick slum, considered the largest stilt-house slum in Brazil, both channels may receive a greater input of emerging pollutants from this area (mainly during the high tides, when floods are common in the Jockey Club and in the adjacent neighbourhoods) (SMA/CPLEA 2016; SMA/CPLA 2018). In this context, these eleven PPCPs and illicit drugs can be excreted by humans in their parenteral, metabolised or conjugated forms through urine and faeces, plus the leachate from municipal solid waste irregularly discarded on the streets, which can explain the occurrence of these environmental stressors in the urban channels of São Vicente (Roveri et al. 2020a; 2021).

The overall total mass load of the eleven PPCPs flowing to the estuarine waters of São Vicente were estimated to be about 41.1 g/day, i.e. caffeine (19.561 g/day) > losartan (19.002 g/day) > acetaminophen (1.13 g/day) > atenolol (0.514 g/day) > benzoylecgonine (0.424 g/day) > furosemide (0.131 g/day) > cocaine (0.127 g/day) > diclofenac (0.071 g/day) > carbamazepine (0.066 g/day) > chlorotaldione (0.028 g/day) > orphenadrine (0.028 g/day). These results are negligible when compared to those detected in the River Lambro basin, one of the most urbanized and industrialized areas of Italy, where the total mass loads of PPCPs were roughly 1100.0 g/day (Castiglioni et al. 2018) but relatively similar to the amounts reported in a rural area of Taige channel basin, China, where it is estimated a PPCP load flow of the 58.0 g/day (Jiang et al. 2020).

Except for illicit drugs, the occurrence profile of these PPCPs, encompassing several therapeutic classes, in São Vicente, was already expected based on the pattern of PPCPs consumption in the State of São Paulo, where the pharmacies and drugstores are responsible for most of the sales of pharmaceuticals in the country (Cmed 2019; Quadra et al. 2019; De Andrade Aragão et al. 2020). A recent study ranked the 150 most sold pharmaceutical drugs at the Metropolitan Region of São Paulo (MRSP), which is the largest urban agglomeration in the South America with approximately 21.5 million inhabitants, having included caffeine, carbamazepine, diclofenac, orphenadrine, atenolol,
furosemide, losartan and acetaminophen. Only chlortalidone (the drug with the lowest MEC in this study) was not listed in this ranking (De Andrade Aragão et al. 2020). Presumably, acetaminophen is the second-best seller drug because is recommended for treatment against fever caused for COVID-19 in worldwide (including Brazil) (Lemaitre et al. 2020; Scavone et al. 2020). Brazil has the 2nd highest number of cases and deaths worldwide (22.5 million cases and 574 thousand deaths of August 21, 2021), and São Paulo State is the main hotspot now (4.2 million cases and 144,000 deaths of August 21, 2021) (Fiocruz 2021). Moreover, acetaminophen is a recommended treatment against the fever caused by other diseases, such as dengue, chikungunya and zika (illnesses highly endemic in Brazil) (Deen and Von Seidlein, 2019).

In the MRBS (region bordering and with a great socioeconomic interdependence of the MRSP; see Fig. 2), there are 9 coastal municipalities, including São Vicente, where pharmaceutical drugs consumption is significant (Cmed 2019; Roveri et al. 2021). According to the Brazilian Association of Pharmacy and Drugstore Chains, there are approximately 2.2 million inhabitants (that almost doubles during the high tourist season), and around 6500 pharmacies and drugstores in this region (Abrafarma, 2017; Ibge 2019). Moreover, both MRSP and MRBS pharmacies sell non-prescription drugs, which means that the consumption of caffeine (present in the formulation of several drugs), acetaminophen, diclofenac and orphenadrine is not controlled (Cmed 2019; Quadra et al. 2019). Therefore, in this context, it is reasonable to assume that the pharmaceuticals with the highest reported concentrations hereby (e.g. estuary of São Vicente Island), are coincident with the sale and consumption rates of PPCP in MRBS. Thus, at a regional scale, the quantification of eleven PPCPs (including the illicit drugs), demonstrates the widespread presence of these compounds in the aquatic ecosystems of MRBS. The values recorded hereby are within the reported concentrations of other studies that took place in this region, where several PPCPs have been quantified in the sewage discharges from Santos Bay (Pereira et al. 2016; Cortez et al. 2018; Fontes et al. 2019; 2020) and Enseada of Guarujá (Roveri et al. 2020b), and in the urban drainage channels of Guarujá (Roveri et al. 2020a), and Santos (Roveri et al. 2021) (Fig. 2). The MEC of seven compounds (namely caffeine, cocaine, benzoylecgonine, acetaminophen, diclofenac, atenolol and losartan) in São Vicente channels were similar, although higher than the concentrations detected in the urban runoff of Santos (Fig. 2) (Roveri et al. 2021). In this case, although both studies were conducted...
in similar conditions (during the dry season and unaffected by the tidal regime), the socio-economic conditions of the neighbourhoods are different. Unlike São Vicente, in Santos, the study was conducted in valued areas near the beachfront, with better basic sanitation levels, and where middle and high-income social classes live (Roveri et al. 2021). On the other hand, higher concentrations were detected in the urban drainage channels that flow to the beaches of Guarujá, presumably due the fact that these channels receive high discharges of untreated domestic sewage from Enseada and Perequê slums (Guarujá has one of the highest slum indexes in the state of São Paulo) (Roveri et al. 2020a). Moreover, given that concentrations of these seven compounds in diffuse loads of São Vicente, Santos and Guarujá channels (Roveri et al. 2020a; 2021), were of same order of magnitude as in the ocean sewage discharges of the Santos and Guarujá cities (with some exceptions, normally concentrations were below 1000.0 ng/L) (Pereira et al. 2016; Cortez et al. 2018; Fontes et al. 2019; 2020; Roveri et al. 2020b), these findings can reinforce the theory that these WWTPs (with only a treatment primary level) are inefficient in removing pharmaceuticals and illicit drugs. Therefore, these seven compounds could be considered environmental tracers of wastewater and, consequently, ubiquitous and pseudo-persistent pollutants in any aquatic ecosystem of MRBS that receive non-point source pollution and/or untreated domestic sewage. Moreover, with the exception of losartan, the MEC values reported in this study for caffeine, cocaine, benzoylecgonine, acetaminophen and atenolol are of the same order or even lower than those concentrations reported in worldwide surface waters (e.g., Europe, US, Asia, Oceania and South America) (Table S2). Although an effluent cannot be compared with surface water far from a WWTP outlet, deleterious effects on the non-target biota were expected to occur and will be discussed on the following sections.

**Occurrence and ecological risks of stimulants (caffeine, cocaine and benzoylecgonine)**

Specifically, caffeine was the predominant compound in São Vicente, being detected in high concentrations for all channels (314.0–726.0 ng/L) (Table 1). Caffeine is widely used in the formulation of different pharmaceuticals (such as acetaminophen, also detected in São Vicente) (Li et al. 2020; Quadra et al. 2019; korekar et al. 2020). After consumed, caffeine is rapidly metabolized by the liver; however, about 0.5 to 10% is excreted through human urine and faeces (Machado et al. 2016). Another significant source of caffeine to domestic wastewater is likely to be the disposal of unconsumed foods containing caffeine, and/or rinsing of coffee pots and cups, directly into household sinks, toilets and in urban trash (Dafouz et al. 2018; Quadra et al. 2019; korekar et al. 2020). Consequently, the concentration of caffeine residues in environmental samples is often found in places nearby densely populated areas and with insufficient sanitation network (Li et al. 2020; Roveri et al. 2020a), such as along São Vicente channels. Although the physicochemical properties of caffeine are not a cause of concern, e.g., it is highly soluble in water (> 10,000 mg/L) and shows low hydrophobicity (log Kow — 0.07) (USEPA 2017), the MEC of caffeine detected in São Vicente can indicate potential ecological risk to the aquatic biota. According to the European Medicines Agency (EMA), pharmaceutical compounds with MEC greater than 10.0 ng/L need ecological risk assessment (EMA 2006). In this context, considering a worst-case scenario (ECB 2003), a screening-level environmental risk assessment (RQ) was conducted using the MEC values obtained in São Vicente (726.0 ng/L). The results showed that the occurrence of caffeine raises environmental concern, because the RQ suggests moderate ecological risk for *Daphnia dubia* (acute) and algae *Leuca gibba* (chronic) (Table 2). Similar MEC data has already been reported in previous works regarding surface waters of Spain and also indicated a moderate ecological risk for the aquatic biota, e.g. in Henarese Jaramae — Tajo Rivers (*MEC* = 410.0 ng/L) (Ferdandéz et al. 2010) and Guadalquivir River (*MEC* = 230.0 ng/L) (Robles-Molina et al. 2014). In RMBS, the caffeine detected in urban channels of Santos and Guarujá indicated high risk (*MEC* = 6550.0 ng/L) and moderate risk (*MEC* = 516.0 ng/L) for different trophic levels, respectively (Roveri et al. 2020a; 2021). Another important issue is that caffeine plus other environmental stressors were found simultaneously in São Vicente channels in a complex mixture, which may lead to an increase of the ecological risk because of their combined effects (e.g., non-interactive, additive action, antagonism or synergism), and therefore, it deserves more attention and additional studies (Di Lorenzo et al. 2019; Quadra et al. 2019).

The abusive consumption of cocaine (COC) is a serious worldwide problem, especially in Brazil, that was classified as the second world largest consumer of this psychoactive stimulant (only behind the USA), where about 1.46 million of citizens consume this drug (UNODC 2020). After consumption, cocaine that was snorted (intranasally), injected (intravenously) or inhaled (smoked) is partially excreted in its parent or metabolized compounds, e.g. via urine (Fernández-Rubio et al. 2019; Maasz et al. 2019). Only a small portion of the administered dose of cocaine (about 9%) is excreted in urine as parent compound (Fernández-Rubio et al. 2019; Maasz et al. 2019). Normally, benzoylecgonine (BE) is the primary metabolite most excreted in human urine (around 45% of the consumed dose), and therefore, higher concentrations of
benzoyl pseudoephedrine and/or aquatic ecosystems, compared to those of cocaine (Fernández-Rubio et al. 2019; Maasz et al. 2019). In this context, the MEC results obtained in the urban channels of São Vicente (17.2 ng/L BE and 6.7 ng/L COC) are similar to those obtained by other studies performed in surface waters worldwide, where the concentrations of BE detected also were higher than those of COC, such as in Czech Republic (8.4 ng/L BE; 3.1 ng/L COC) (Fedorova et al. 2014). Spain (142.0 ng/L BE; 42.3 ng/L COC) (Fernández-Rubio et al. 2019), Hungary (2.3 ng/L BE; 1.2 ng/L COC) (Maasz et al. 2019), Brazil [Guarujá (278.0 ng/L BE; 30.3 ng/L COC); and Santos (4.8 ng/L BE; 1.7 ng/L COC)] (Roveri et al. 2020a; 2021) (for more examples, see Table S2). In short, this relationship between cocaine and benzoyl pseudoephedrine is a reliable marker for human wastewater contamination in the urban channels of MRBS (Fig. 2) (Roveri et al. 2020a; 2021). However, at present, there is a scarcity of data about the PNEC of cocaine and the benzoyl pseudoephedrine to marine organisms (especially to the tropical marine organisms) (Fontes et al. 2020). In São Vicente, the acute and chronic RQ of cocaine and benzoyl pseudoephedrine presented low and no toxicity (RQ ≤ 0.01), respectively (COC, Table 2; BE, Table S3). However, a cautious interpretation of these results is recommended, because of the following: (i) illicit drugs are bioactive compounds able to cause specific effects even at low concentrations (Capaldo et al. 2019; Miller et al. 2019; Fontes et al. 2020). Therefore, low toxicity can be explained by the high PNEC estimated by ECOSAR program (COC, Table 2; BE, Table S3) (Roveri et al. 2020a, 2021; USEPA 2017); (ii) in a real scenario, one cannot exclude a possible synergistic interaction between the illicit drugs and other environmental stressors present in the channels studied (EMA 2006; USEPA 2017); and (iii) unaltered cocaine have moderate hydrophobicity (log Kow > 2.3), and thus, can potentially bioaccumulate (Table S1) (EMA 2006; Pereira et al. 2016; USEPA 2017), such as demonstrated for European eel (Anguilla anguilla) (Capaldo et al. 2019) and for amphipod crustacean Gammarus pulex (Miller et al. 2019). Recently, a study accomplished in the mouth of São Vicente estuary (on the southern portion of the island, see more details in Fig. 1) shown a widespread contamination of seawater, marine sediments and Perna perna (an important Brazilian seafood) by cocaine and denoting even a certain concern about the human consumption of this mussel (Fontes et al. 2020). Additionally, the present study shows that the five urban channels located in north portion of the São Vicente Island are an important non-point pollution sources (containing a complex mixture of illicit drugs and nine pharmaceuticals) for the coastal ecosystem.

**Occurrence and ecological risks of analgesic/anti-inflammatory, antihypertensive and diuretics drugs**

Hypertension is currently one of the greatest public health-care problems worldwide, including in Brazil, where about 33% of the 213 million inhabitants are hypertensive (Ribeiro et al. 2016; Hanlon et al. 2017; McNally et al. 2019). In Brazil, although many effective drugs to hypertension are available, a polytherapy is also often prescribed for treating this disease, by combining several drugs (e.g. losartan + diclofenac; losartan + furosemide; atenolol + furosemide; atenolol + diclofenac; and diclofenac + furosemide (Dos Santos et al. 2012). However, if not managed correctly, the polytherapy may counteract the benefits of a single treatment and, in extreme cases, may cause serious health problems (Secoli et al. 2010; Hanlon et al. 2017; McNally et al. 2019). Specifically, the use of diclofenac decreases the therapeutic efficacy of antihypertensive drugs when used concomitantly, leading to failure to control blood pressure (Dos Santos et al. 2012; Hanlon et al. 2017; McNally et al. 2019). In this context, the use of the polytherapy for the treatment of hypertension can explain the significant occurrence of antihypertensives (mainly losartan), analgesic, anti-inflammatory and diuretic drugs in the five urban channels of São Vicente due to several reasons: (i) the elderly people of São Vicente (aged ≥ 60 years) is approximately 15.0% of the population; therefore, the hypertension could be a natural consequence of ageing (Ribeiro et al. 2016; Ibge 2019); (ii) it is estimated that the worldwide population over 65 years of age usually consumes 5–10 pills/patient/day (Lacorte et al. 2018); (iii) approximately, one-quarter of the elderly population living in MRSP could be taking two or more potentially interacting medicines (Secoli et al. 2010); (iv) diclofenac, atenolol and losartan, for instance, are pharmaceuticals drugs commonly taken by elderly people (Cmed 2019); and (v) self-medication is a common practice among the Brazilian population (Arrais et al. 2016).

Among of these PPCPs, losartan (MEC: 2680.0 ng/L: value 268 times higher than recommended by European Union countries) and acetaminophen (MEC: 78.2 ng/L, (EMA 2006) signal great environmental concern for São Vicente estuary, because the RQ suggest moderate to high ecological risk (for both acute and chronic exposures) for algae, crustacean and/or fishes (Table 2). Although information about the toxicity of losartan is still poorly documented, a recent study detected cytotoxic effects for mussel Perna perna exposed to environmental realistic concentrations of losartan (up to 3000 ng/L) and, thus, very close to the levels detected in São Vicente (Cortez et al. 2018). In the urban channels of Guarujá and Santos, the RQ obtained for losartan also suggested moderate to high ecological risk (for both acute and chronic exposures) for different trophic levels.
(Roveri et al. 2020a; 2021). Other studies have also reported toxic effects of losartan (but in “non-relevant” environmental concentrations, in the order of mg/L) to different trophic levels, e.g. fish (Pimephales promelas), crustacean (Daphnia magna) (FDA 2012) and algae (Lemma minor) (Godoy et al. 2015). In the case of acetaminophen, analgesic known for its environmental persistence, and significant toxicity to aquatic species (Roveri et al. 2020a; 2021), previous studies conducted in surface waters, also reported moderate risks to crustacean Daphnia magna, e.g. in Valencia, Spain (RQ: 0.3; Vazquez-Roig et al. 2012), in Lahore, Pakistan (RQ: 0.4; Ashfaq et al. 2019) and in Santos, Brazil (RQ: 0.3; Roveri et al. 2021). Moreover, similar to this study (RQ = 1.56), high chronic risk for the fish Danio rerio was also reported in urban channels of Guarujá, Brazil (RQ: 7.8; Roveri et al. 2020a).

Although the RQs of atenolol, carbamazepine, orphenadrine, diclofenac, chlortalidone and furosemide were equal or below 0.01 (low or no risk) (Table 2; Table S3), some key physicochemical properties and/or degradation behaviours of these PPCPs deserve attention: (i) hydrophobicity and pseudo-persistence: carbamazepine and furosemide (log Kow > 2.3) and orphenadrine and diclofenac (log Kow > 3.0) can persist in the aquatic environment, potentially bioaccumulate and, thus, can cause ecotoxicity (Table S1) (EMA 2006; EC 2015; USEPA 2017) and (ii) biodegradability: based on kinetic reaction rate (k biol), represented on grams of suspended solids days (L/gss day), carbamazepine and diclofenac are considered barely degradable (k biol < 0.5 L/gss day), and atenolol is considered moderately degradable (0.5 < k biol < 1.0 L/gss day) (EC 2015; Arola et al. 2017). In this context, in recent years, several studies have confirmed the potential risks of these PPCPs in the aquatic environment and have suggested their inclusion in a list of priority substances in monitoring studies. For instance, (i) Besse and Garric (2008), based on quantitative and qualitative data for more than 100 PPCPs (e.g. ecotoxicological, pharmacological (mechanism of action — MoA, enzyme modulation, and adverse effects) and physicochemical data (log Kow)), established a priority list to monitor 40 PPCPs in all surface waters of France. As result, acetaminophen and furosemide were classified as high risk, diclofenac and losartan were classified as potentially hazardous and carbamazepine showed suspected ecological risk existence; (ii) due to its high toxicity, the European Commission included diclofenac in a list of priority substances for the monitoring in European surface waters (EC 2015); and (iii) Mathon et al. (2016) and Biel-Maeso et al. (2018) showed that diclofenac, atenolol, carbamazepine and furosemide were considered as refractory to secondary treatment, because they are poorly biodegradable and poorly adsorbable.

In addition, to our knowledge, this study seems to be the first quantification of the furosemide in urban drainage channels in the Brazilian coastal zone, which raises special concern since this PPCP is known to be an active endocrine disruptor (Al-Odaini et al. 2015). Future research should also include wastewater-based epidemiology (WBE) studies to estimate the PPCPs consumption rate (mg/day/1000 inhabitants), namely for illegal drugs, since these kinds of studies are almost inexistent in Brazil (Maldaner et al. 2012).

**Conclusion**

This study reported, for the first time, the occurrence of eleven PPCPs of various therapeutic classes in five urban drainage channels located on the Jockey Club, a poor neighbourhood of the São Vicente Island, São Paulo, Brazil, where the sanitation infrastructures are precarious and often non-existent. The results showed the widespread presence of these environmental stressors, namely carbamazepine, caffeine, cocaine, benzoylcegonine, acetaminophen, diclofenac, orphenadrine, atenolol, losartan, chlortalidone and furosemide, in surface drainage channels that daily flow to the estuarine waters located on the north portion of the island (one of the most important aquatic ecosystems of the Metropolitan Region of Baixada Santista). The highest concentrations of these PPCPs were detected in the area of influence of the Sambaiatuba and of the Vila Gilda Dike slums (the last is considered the largest stilt-house slums in Brazil), where a large amount of garbage could be easily observed in situ. Consequently, the preliminary ecological risk assessment signalled great environmental concern for São Vicente estuary, because the results suggest moderate to high ecological risks for the caffeine, acetaminophen and losartan and low risk for the carbamazepine and cocaine for the aquatic biota. However, benzoylcegonine, diclofenac, orphenadrine, atenolol, chlortalidone and furosemide did not reveal any ecological risk (RQ < 0.1). Therefore, several public actions are urgently required, such as the following: (i) amelioration of the basic sanitation facilities, simultaneously with the land regularisation of the three stilt-house slums of São Vicente, namely Piçarro Dike, Cachetas Dike and Sambaia-tuba slum; (ii) supervision and control of the commercial and residential properties of the Jockey Club neighbourhood, requesting its connection to the sewage collection network already established; and (iii) promotion of public education programmes about the use and correct disposal of waste in the environment (including pharmaceutical drugs). The new knowledge obtained in this study may help decision-makers, namely public authorities and environmental agencies, to plan and perform actions to improve the environmental quality of the Brazilian coastal waters. These actions should involve the following: (i) the inclusion of PPCPs and illicit drugs in the Brazilian environmental legislation as priority pollutants and (ii) the implementation of continuous
environmental monitoring programmes for tracking pharmaceuticals and illicit drugs in the coastal areas.

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