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Contaminantes de preocupação emergente: aspectos do consumo, detecção e descarte em ecossistemas aquáticos

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Tese apesentada ao Programa de Pós-Graduação em Biodiversidade e Conservação da Natureza da Universidade Federal de Juiz de Fora, como parte dos requisitos necessários à obtenção do grau de Doutorado em Biodiversidade e Conservação da Natureza na área de concentração Comportamento, Ecologia e Sistemática.

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RESUMO

As atividades humanas estão acelerando os ciclos biogeoquímicos e causando a deterioração dos corpos hídricos mundialmente, nos quais a poluição aquática afeta a qualidade e a quantidade de água. Os contaminantes sintéticos são agentes de mudanças globais que apresentam potencial para causar alterações globais comparadas a emissão de gases de efeito estufa e input de nutrientes, porém, muitas vezes, esta problemática não recebe tanta atenção pelos pesquisadores e financiadores comparando aos outros agentes de mudanças globais. Os contaminantes de preocupação emergente têm sido detectados em diversos ecossistemas aquáticos ao redor do mundo. Apesar das quantificações, alguns pesquisadores ainda argumentam que as concentrações são baixas para causar qualquer desequilíbrio ecológico ou prejudicar a saúde humana. No entanto, outros trabalhos têm demonstrado efeitos adversos em baixas concentrações, assim como efeitos a longo prazo e de misturas. No presente trabalho foi demonstrado, por meio de quatro diferentes estudos, que os contaminantes de preocupação emergente devem entrar em acordos globais, assim como merecem uma atenção maior dos governos nacionais de países em desenvolvimento. Os estudos apresentados na presente tese comtemplam tópicos de consumo, ocorrência e descarte dos contaminantes de preocupação emergente em ecossistemas aquáticos, dando embasamento científico para a necessidade de maior preocupação global. Dessa forma, os estudos mostraram: (1) utilizando a cafeína como objeto de estudo, foi demonstrado que as concentrações ambientais podem aumentar com o passar do tempo, especialmente em países onde o consumo per capita de café vem aumentando e com baixo investimento em rede de esgoto e estações de tratamento de esgoto. A cafeína foi utilizada como modelo, porém, é esperado que para outros compostos a tendência seja a mesma, uma vez que o consumo de medicamentos também tem aumentando ao longo do tempo. Dessa forma, a poluição por estes contaminantes só vai se agravar. (2). Por meio de um estudo espacial e temporal das concentrações de contaminantes de preocupação emergente, foi observado que os medicamentos mais consumidos podem apresentar maiores concentrações no ambiente. Além disso, as concentrações ao longo do tempo não apresentaram diminuição no rio utilizado como modelo de estudo. Dessa forma, espera-se que, a longo prazo, visto maior consumo de medicamentos, estas concentrações podem vir a aumentar. (3). Devido ao aumento populacional, os ecossistemas aquáticos estão cada vez mais susceptíveis a contaminação por contaminantes de preocupação emergente. Os reservatórios são importantes ambientes

aquáticos utilizados pelos seres humanos para abastecimento público, irrigação e pesca ou criação de peixes. O estudo indica contaminação por contaminantes de preocupação emergente em reservatórios brasileiros utilizados para estes fins. Isto é mais um alerta para possíveis problemas de saúde pública, mesmo com pouco conhecimento sobre a bioacumulação dos fármacos e transferência de compartimentos (ambiente aquático para terrestre). (4). Ainda assim, por meio de um questionário online, foi observado que as pessoas ainda descartam medicamentos da maneira incorreta. Isso é uma resposta a falta de informação da sociedade, mas também dos setores da saúde. Além disso, faltam de políticas públicas que envolvam logística reversa dos medicamentos e pontos de coleta disponíveis. Com estes estudos, fica claro a necessidade de maior preocupação e controle do descarte e mitigação de contaminantes de preocupação emergente nos ambientes aquáticos, evitando, assim, perde de biodiversidade, serviços ecossistêmicos e questões de saúde pública.

Palavras-chave: avaliação de risco, ambientes aquáticos, fármacos, medicamentos, poluição aquática.

ABSTRACT

Human activities are accelerating biogeochemical cycles and causing the deterioration of water bodies worldwide, being water pollution a global environmental problem that affects the water quality and quantity. Synthetic contaminants are agents of global change that have the potential to cause changes compared to the greenhouse gases emission and nutrients input, however, this problem often does not receive as much attention by researchers and funders comparing with other agent of global change. Pharmaceuticals and personal care products (PPCPs) have been detected in several aquatic ecosystems worldwide. Despite the quantifications, many researchers still argue that the concentrations are too low to cause any ecological imbalance or harm human health. However, other studies have shown adverse effects on biota, such as long-term effects and mixtures. In the present work, four different studies were developed to argue that PPCPs should be considered in global agreements, as well as deserve greater attention from developing countries. The studies presented in the present thesis contemplate topics of consumption, occurrence and disposal of contaminants of emerging concern in aquatic ecosystems, providing scientific basis for the need for greater global concern. Thus, the studies showed: (1) using caffeine as case study, it has been shown that environmental concentrations may increase in the near future, especially in countries where per capita coffee consumption is increasing and with low investment in the sewage network and water treatment plants. Caffeine was used as a model, however, other compounds are expected to have the same trend, since the medicines consumption also have been increasing over the years. Thus, pollution by these contaminants will only be aggravated. (2) Through a spatial and temporal investigating of PPCPs concentrations in a river, it was found that the most consumed drugs can appear in greater concentrations in the environment. Furthermore, the concentrations still similar after one year of investigation in the river used as a study model. Thus, it is expected that, in the long-term, the concentrations will increase due to enhanced consumption. (3) Due to population growth, aquatic ecosystems are susceptible to drug contamination. Reservoirs are important aquatic environments used by humans for public supply, irrigation and fishing or fish farming. The study indicates contamination by drugs in Brazilian reservoirs used for these purposes. This is another warning for possible public health issues, although still little about drugs bioaccumulation and the transfer of compartments (aquatic to terrestrial environment) is known. (4) Through an online questionnaire it was observed that people still discarded

medicines incorrectly. This is a response to the lack of information in society, but also in the health sectors. In addition, there is a lack of public policies that involve the logistic reverse of medicines and availability of collection points. With these studies, it is clear the need for greater concern and control over the disposal and mitigation of pharmaceuticals and personal care products in the aquatic environments, avoiding loss of biodiversity, ecosystem services and public health issues.

Keywords: risk assessment, aquatic environment, pharmaceuticals, medicines, aquatic pollution.

LISTA DE SIGLAS

CDU – Reservatório de Chapéu d'Uvas

CUN – Reservatório de Curuá-Uma

FUN – Reservatório de Funil

SIM – Reservatório de Simplício

ETE – Estação de Tratamento de Esgoto

LQ – Limite de Quantificação

ND – Não Detectado

TR – Tempo de Retenção

MEC – Measured Environmental Concentration (Concentração Ambiental Medida)

PNEC – Predicted No-effect Concentration (Concentração Previsivelmente Sem Efeitos)

NOEC – No-effect Concentration (CEOC: Conceição de Efeito Não Observado)

DP – Desvio Padrão

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1 Contextualização Teórica

Modificações estruturais e funcionais de ecossistemas aquáticos foram aceleradas no Antropoceno quando comparadas aos fatos evolutivos naturais. As atividades humanas têm alterado os ecossistemas profundamente, de uma forma tão intensificada, no qual os seres humanos estão moldando esta nova época geológica (STEFFEN et al., 2011; STEFFEN; CRUTZEN; MCNEILL, 2007). O Antropoceno se inicia desde a Era Industrial, sem indicação de quando esta época terminará (STEFFEN; CRUTZEN; MCNEILL, 2007). As evidências que marcam esta nova época são muitas, como o crescimento populacional, desmatamento, aceleração dos ciclos biogeoquímicos, mudanças climáticas e ambientais, mudanças nos regimes hidrológicos, emissão de gases de efeito estufa, poluição ambiental, perda de biodiversidade, e muitos outros (QUADRA et al., 2019b; ROCKSTROM et al., 2009; STEFFEN et al., 2011; STEFFEN; CRUTZEN; MCNEILL, 2007).

Não há dúvidas que a humanidade depende dos serviços ecossistêmicos fornecidos pelos recursos hídricos, como a regulação do clima, irrigação, abastecimento de alimento e processos de depuração (SCHWARZENBACH et al., 2010), porém, a deterioração deste ambientes é evidente, resultando em perda de qualidade e quantidade de água (SCHWARZENBACH et al., 2010; SMITH; SCHINDLER, 2009). O crescimento industrial e a urbanização descontrolada resultam em produtos residuais que são descartados no ambiente, muitas vezes, sem qualquer tratamento, tornando assim, a poluição aquática um dos principais desafios da limnologia atualmente (QUADRA et al., 2019b; SCHWARZENBACH et al., 2010). Os ecossistemas aquáticos são impactados pelo descarte de efluentes ricos em poluentes inorgânicos, como os metais pesados, e poluentes orgânicos, como fármacos e produtos de cuidado pessoal, muitos pesticidas e os poluentes orgânicos persistentes (QUADRA et al., 2019b).

A problemática da poluição aquática é muito complexa, porém, um primeiro passo é reavaliar onde são descartados os resíduos produzidos pelas atividades humanas. A demanda por água, aumenta a cada dia, mas a produção de resíduos também continua aumentando (QUADRA et al., 2019b). Não é contraditório descartarmos estes resíduos não tratados nos rios que fornecem um recurso vital (QUADRA et al., 2019b; ver Figura 2 em Apêndice A)? O uso não sustentável dos recursos hídricos pode ter consequências irreversíveis (QUADRA et al., 2019b).

Os contaminantes sintéticos, de maneira geral, não são incluídos nas avaliações de mudanças globais. Porém, estudos demonstram que a produção e a variedade de contaminantes sintéticos podem causar efeitos globais maiores do que outros agentes de mudanças globais, como os gases de efeito estufa, poluição por nutrientes, perda de hábitats e biodiversidade (BERNHARDT; ROSI; GESSNER, 2017). No entanto, apesar de tamanha importância como agentes de mudanças globais, o financiamento para pesquisas na área não é prioridade em alguns países (BERNHARDT; ROSI; GESSNER, 2017).

A introdução de novas substâncias que podem alterar negativamente os ecossistemas já foi apresentada como preocupação, mas o nível de ameaça ainda é pouco conhecido, apesar de haver evidências dos possíveis impactos em escala global (MACLEOD et al., 2014; ROCKSTROM et al., 2009). Normalmente, as preocupações são maiores se estas novas substâncias apresentam persistência, mobilidade em grandes escalas e potencial para causar impactos as formas de vida (ROCKSTROM et al., 2009). No entanto, a cada dia, novas substâncias são produzidas e comercializadas, sendo descartadas no ambiente, muitas vezes, sem um conhecimento robusto sobre as possíveis consequências (SOBEK; UNDEMAN, 2019). Dessa forma, é crucial que comecemos a praticar o manejo de maneira integrada e não por substâncias isoladas (SOBEK; UNDEMAN, 2019).

Os fármacos são um grupo de químicos que apresentam potencial para causar distúrbios nos ecossistemas e que precisam ser manejados. Este grupo é considerado como contaminantes de preocupação emergente, o que significa que, apesar da humanidade utilizá-los há alguns anos, as preocupações ambientais relacionadas são relativamente recentes, especialmente devido ao avanço das tecnologias de detecção que permitiu encontrar esses contaminantes no ambiente (PETROVIC; BARCELÓ, 2006). Além disso, os contaminantes de preocupação emergente geralmente não apresentam regulação específica e não são monitorados no ambiente, apesar de seus potenciais riscos para a saúde humana e ambiental (PETROVIC; BARCELÓ, 2006; RIZZO et al., 2019).

A indústria farmacêutica produz milhares de diferentes compostos e a sua importância para a economia mundial e saúde humana é inquestionável. Existe uma tendência mundial de aumento do consumo de medicamentos, o que segue o crescimento populacional (SOUZA et al., submetido). Porém, também é possível observar um aumento per capita de consumo de medicamentos mundialmente (SOUZA et al., 2020, submetido), sendo que para o Brasil, a mesma tendência foi observada (QUADRA et al., 2017; ver Figura 1 e 2 em Apêndice B). Este

aumento do consumo de medicamentos, contínuo e acentuado ao longo dos anos, está relacionado a alguns agravantes, como a automedicação, bem como a inversão da pirâmide populacional etária, onde é possível observar um aumento do número de medicamentos consumidos especialmente destinados a doenças crônicas (AN; JEON, 2006; PETROVIĆ; BARCELÓ, 2007; QUADRA et al., 2017). Apesar da importância da indústria farmacêutica para a saúde humana, este aumento da produção e do consumo de medicamentos tem um custo ambiental.

A cafeína, por exemplo, é uma das substâncias psicoativas mais consumidas no mundo e o seu consumo se dá tanto por produtos alimentícios, mas também medicamentos e produtos de cuidado pessoal (BUERGE et al., 2003; DIOGO et al., 2013). A concentração de cafeína nos diferentes compostos varia significativamente, mas o café apresenta uma das maiores concentrações comparando com outros produtos, além de ser consumido mundialmente (INTERNATIONAL COFFEE ORGANIZATION, 2020; MITCHELL et al., 2014). Uma pequena fração da cafeína é excretada em sua forma original após o consumo (MONTAGNER et al., 2014; TANG-LIU; WILLIAMS; RIEGELMAN, 1983), porém, muitas vezes, pode ser descartada antes mesmo de ser consumida (TOKIMOTO et al., 2005). Assim como para os medicamentos, o consumo de café também tem aumentado ao longo do tempo, consequentemente, a entrada de cafeína para o meio ambiente muito provavelmente segue a mesma tendência (QUADRA et al., 2020; ver Figura 1 em Apêndice C). O grande consumo aliado a um descarte sem tratamento, portanto, resulta na detecção da cafeína em diversos ecossistemas aquáticos (BRUTON et al., 2010; MACHADO et al., 2016; MONTAGNER et al., 2014). Inclusive, a cafeína tem sido utilizada como marcador de esgoto doméstico nos ambientes aquáticos (BUERGE et al., 2003; CHEN et al., 2002; GONÇALVES et al. 2017). Deste modo, avaliar os padrões de consumo que podem estar relacionados as concentrações ambientais de cafeína é essencial.

Os fármacos apresentam um grande potencial de alcançar os ecossistemas por diversos caminhos, especialmente consumo humano, uso na medicina veterinária e produção industrial (QUADRA et al., 2017; ver Figura 3 em Apêndice B). Cerca de 80% do volume total de efluentes são descartados diretamente no ambiente sem qualquer tratamento (UNWATER, 2017). No Brasil, quase 50% dos brasileiros não apresenta rede de coleta de esgoto, sendo que destes, um valor abaixo de 50% é tratado (ITB, 2019). Portanto, uma possível via destes compostos para os ecossistemas aquáticos é pelo descarte de efluentes não tratados no ambiente.

Após a ingestão de um medicamento, parte dele é excretado na sua forma parental e, mesmo que haja a coleta e o esgoto passe por uma estação de tratamento, os fármacos não são completamente removidos nestas estações e, portanto, mesmo que tratados, os efluentes estarão contribuindo para as concentrações de fármacos no ambiente (MONTAGNER et al., 2014; PETROVIĆ; BARCELÓ, 2007; QUADRA et al., 2017). No caso da cafeína, ela pode ser removida em até 98% dependendo da tecnologia das estações de tratamento (BRUTON et al., 2010; CAMACHO-MUÑOZ et al., 2012), porém, o consumo dessa substância é tão alto, que mesmo assim, as suas concentrações ambientais podem ser maiores quando comparadas a de outros micropoluentes. Os resíduos farmacêuticos podem permanecer no lodo da estações de tratamento e serem dispersados quando utilizados na fertilização da agricultura (HÖRSING et al., 2011; IVANOVÁ et al., 2018). Quando nos solos, os fármacos podem infiltrar para as águas subterrâneas ou serem lixiviados para um curso hídrico mais próximo (CHEFETZ; MUALEM; BEN-ARI, 2008; MONTEIRO; BOXALL, 2009; OPPEL et al., 2004). Muitas áreas rurais utilizam das águas subterrâneas para o consumo sem passar por um tratamento, e, novamente, mesmo que passem, os resíduos farmacêuticos não são completamente removidos nas estações de tratamento de água com tratamento convencional (STACKELBERG et al., 2004; VIENO et al., 2007).

O descarte incorreto de medicamentos feito pela população é mais uma via, muitas vezes negligenciada, dos fármacos alcançarem o ambiente (QUADRA et al., 2017; ver Figura 3 em Apêndice B), especialmente em países com baixa infraestrutura de saneamento e ausência de políticas para descarte adequado pelo consumidor final (BOUND; VOULVOULIS, 2005; QUADRA et al., 2019a; TONG; PEAKE; BRAUND, 2011). Os aterros sanitários podem não apresentar manutenção adequada para evitar a infiltração de resíduos na água subterrânea, ou ainda, alguns países apresentam os antigos lixões, que não há qualquer estrutura para contenção de resíduos tóxicos. Portanto, entender os padrões de consumo e descarte de medicamentos pela população é um passo importante para auxiliar na criação de medidas que auxiliem na mitigação da poluição por fármacos. Ainda assim, levar informação para a população, gerando consciência ambiental é crucial. Muitas vezes, apresentar a inconsistência entre os atos dos seres humanos e a busca por um ambiente equilibrado auxilia na mudança de hábitos.

Uma vez que alcançam o ambiente, os fármacos podem causar efeitos adversos a biota, tanto terrestre quanto aquática, bem como auxiliar no desenvolvimento de genes de resistência bacteriana (BOXALL, 2004; BRODIN et al., 2014; PETROVIĆ; BARCELÓ, 2007). Os efeitos

mais notáveis não são a morte de organismos, e sim, efeitos subletais, como alterações comportamentais, enzimáticas e reprodução, que podem desbalancear uma comunidade e, a longo prazo, causar efeitos ecológicos severos (BOXALL, 2004; BRODIN et al., 2014; PETROVIĆ; BARCELÓ, 2007). Ainda assim, a contaminação dos alimentos bem como da água potável deixa os seres humanos diretamente expostos a estes compostos (PETROVIĆ; BARCELÓ, 2007; WORLD HEALTH ORGANIZATION, 2012). Portanto, a poluição por fármacos é uma questão de saúde ambiental e humana.

Com a descoberta destes efeitos adversos ao meio ambiente, a preocupação com os fármacos aumenta cada vez mais, porém, em muitos países, este grupo ainda não é prioridade para regulação (SOUZA et al., 2020, submetido). Ainda temos muito o que entender sobre os fármacos no ambiente, como os efeitos de seus metabólitos e a longo prazo, bem como efeitos de misturas, suas capacidades de bioacumulação e persistência (BOXALL et al., 2012; PETROVIĆ; BARCELÓ, 2007; ZENKER et al., 2014). Como ainda conhecemos pouco, controlá-los é essencial, antes de se tornarem mais um problema irreversível (Figura 1). No Brasil, a escassez de saneamento básico como mencionado anteriormente, é ainda atrelada a um baixo investimento na ciência, o que resulta em poucos estudos sobre a quantificação de fármacos no país (QUADRA et al., 2017).

Na Europa, atualmente está se discutindo o Pacto Ecológico Europeu, chamado de "*Green Deal*", o que é uma proposta para o desenvolvimento sustentável com economia limpa e circular, visando a restauração da biodiversidade e redução da poluição (COMISSÃO EUROPÉIA, 2019). Esta discussão reforça que existe uma preocupação ambiental por trás do atual modelo de economia, bem como existem maneiras sustentáveis para o desenvolvimento humano. Portanto, com a atual discussão europeia para a redução da poluição, é essencial demonstrar que os contaminantes de preocupação emergente precisam também de controle ambiental, especialmente nos países em desenvolvimento, como o Brasil. Dessa forma, no presente trabalho, foram desenvolvidos diferentes estudos para argumentar sobre a necessidade de inclusão dos contaminantes de preocupação emergente em acordos globais, bem como em legislação nacional, especialmente em países em desenvolvimento.

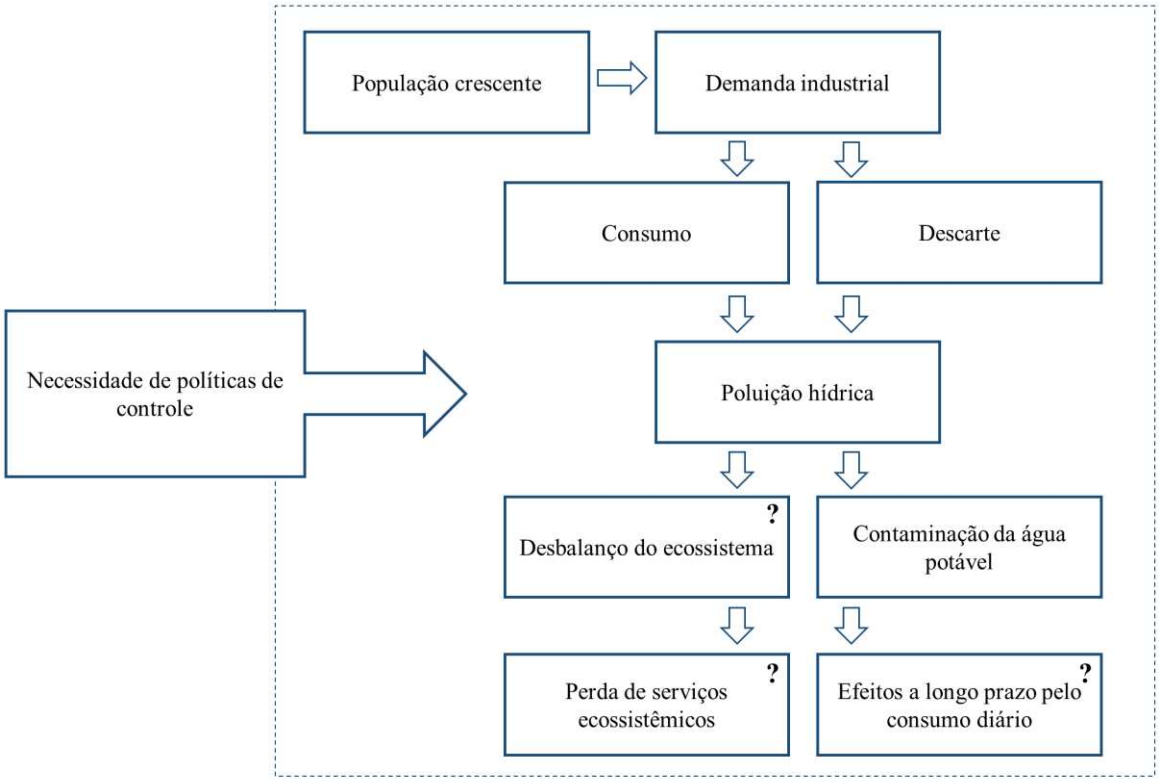

Figura 1. Esquema conceitual mostrando a problemática dos contaminantes de preocupação emergente no ambiente e como podem afetar a sociedade indiretamente (por perda de serviços ecossistêmicos) ou diretamente (consumo de água contaminada). As interrogações no esquema demonstram áreas de pouco conhecimento, evidenciando a necessidade de controle em todas as fases, desde a produção até o tratamento, antes que alcance níveis irreversíveis.

2 Objetivos

2.1 Objetivo geral

Demonstrar, por meio de quatro estudos, que os contaminantes de preocupação emergente devem ser considerados em acordos globais para regulação ambiental, assim como merecem uma atenção maior dos governos nacionais, especialmente de países em desenvolvimento.

2.2 Objetivos específicos

(1) Investigar os padrões globais de consumo de cafeína ao longo dos anos; suas relações com o índice de desenvolvimento humano e produto interno bruto; bem como detectar os possíveis *hotspots* de contaminação e seus impactos ambientais;

(2) Investigar a ocorrência e os riscos associados a presença de contaminantes de preocupação emergente no Rio Paraibuna, em uma abordagem temporal e espacial;

(3) Investigar a ocorrência de contaminantes de preocupação emergente em quatro reservatórios brasileiros integrando diferentes características;

(4) Investigar os padrões de consumo e descarte de medicamentos pela população brasileira, bem como fornecer informações sobre o descarte correto e consumo consciente para a população.

3 Metodologia

O diagrama abaixo traz o objetivo geral e objetivos específicos relacionados a presente tese, bem como a metodologia resumida para atender os objetivos (Figura 2).

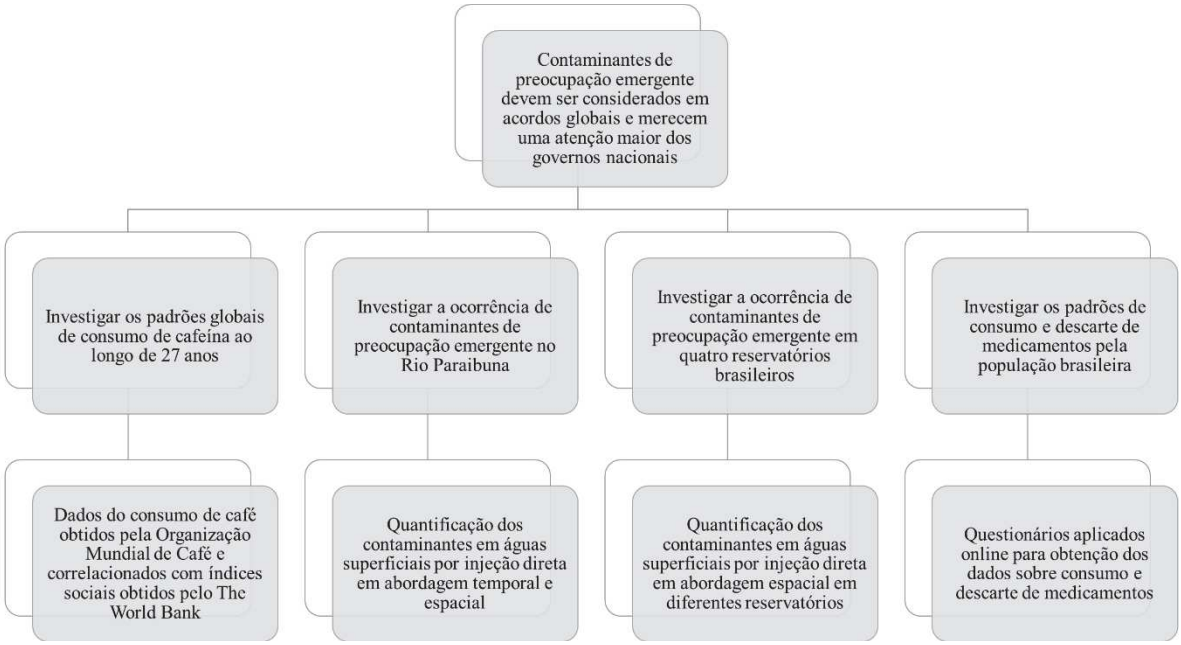

Figura 2. Diagrama contextualizando o objetivo geral do trabalho e objetivos específicos com as metodologias adotadas para atendê-los.

3.1 Consumo e concentrações de cafeína ao redor do mundo

Para explorar os padrões de consumo de cafeína ao redor do mundo e possíveis consequências ambientais, foi utilizado o consumo de café, monitorado globalmente pela Organização Internacional do Café, como representante do consumo de cafeína, visto que o café apresenta altas concentrações de cafeína comparando com outros produtos (MITCHELL et al., 2014). Dados de tamanho populacional, índice de desenvolvimento humano e produto interno bruto foram obtidos para 87 países (THE WORLD BANK, 2020) para verificar consumo per capita ao longo do tempo (1990 a 2016), bem como a influência dos índices no consumo. As correlações foram verificadas utilizando o método de Person ou Spearman quando as premissas não foram atendidas. O valor de significância adotado foi de 0,05. Todas as

estatísticas foram realizadas utilizando o software JMP (v.14.0.0). Os mapas foram criados utilizando o ArcGIS (ESRI, v10.3.1). A ferramenta meta-analítica de z-score foi utilizada para resumir o consumo do café ao longo dos anos por continentes, sendo que o gráfico foi criado pelo SigmaPlot (v.12.0). Todos os dados podem ser encontrados no Apêndice C correspondente a publicação deste estudo (QUADRA et al., 2020).

3.2 Concentrações de contaminantes de preocupação emergente no Rio Paraibuna

Para investigar a ocorrência e os riscos de contaminantes de preocupação emergente no Rio Paraibuna (Minas Gerais), em uma abordagem temporal e espacial, amostras de água superficial foram coletadas no rio a cada três meses com o objetivo de avaliar influência do ciclo hidrológico, de junho de 2017 a setembro de 2018, em quatro diferentes pontos amostrais localizados 40 km a jusante da cidade de Juiz de Fora (Figura 3). O reservatório de Chapéu d'Uvas (CDU), criado pelo barramento do Rio Paraibuna a montante da cidade de Juiz de Fora, foi também amostrado para fins referenciais.

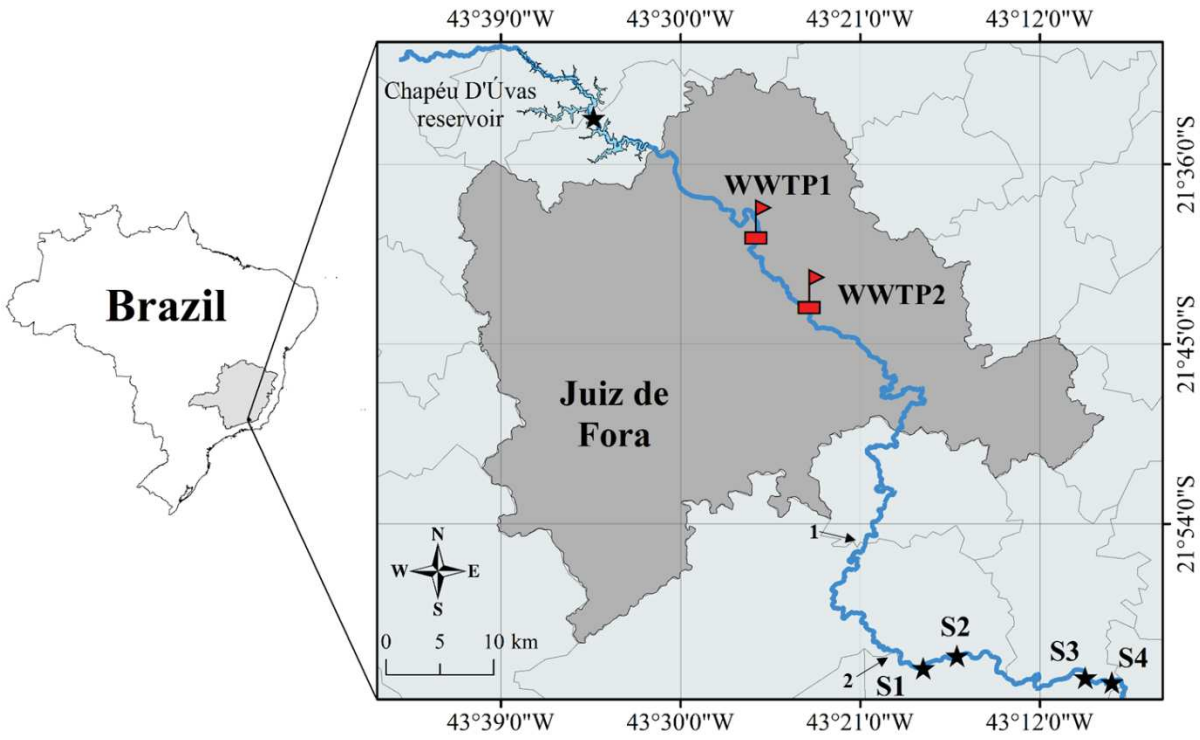

Figura 3. Mapa da área de estudo do Rio Paraibuna. As bandeiras indicam a localização das estações de tratamento de esgoto (ETEs – WWTP) em funcionamento durante a amostragem. O reservatório de Chapéu D'Uvas também está evidenciado como ponto de referência. As setas indicam a entrada do Rio Peixe (1) e Rio Preto (2).

Parâmetros físico-químicos (temperatura, pH, turbidez e condutividades) foram medidos *in situ* com uma sonda multiparâmetros (YSI 6600 V2) e dados pluviométricos foram adquiridos pelo Instituto Nacional Brasileiro de Meteorologia (INMET, 2018). Um total de 28 compostos foram quantificados nas amostras de água (Tabela 1) pelo método de injeção direta em cromatografia de alta performance acoplado a um espectrômetro de massas (UHPLC-Orbitrap-MS/MS, Thermo Fisher Scientific, San Jose, USA) no Departamento de Ciências Ambientais, Universidade de Estocolmo, Suécia. As amostras de água foram misturadas com a mistura dos padrões internos em uma concentração final 2,5 µg L^{-1}. Após homogeneização em vórtex por 10 segundos, as amostras foram filtradas (0,2 µm) e uma alíquota de 100 µL foi injetada no equipamento. O método de injeção direta otimiza tempo e recursos, sendo que a metodologia analítica foi previamente publicada (LI et al., 2018b; LI; MCLACHLAN, 2019). As análises foram processadas pelo software Xcalibur 3.1 (Thermo Scientific). Para as análises estatísticas, valores abaixo do limite de quantificação (LQ) foram considerados como metade do valor de LQ. Análises de variância foram realizadas para verificar diferenças espaciais e temporais das concentrações dos contaminantes de preocupação emergente. Correlações foram desenvolvidas pelo método de Spearman para verificar as relações entre as concentrações dos contaminantes de preocupação emergente e parâmetros físico-químicos. Os gráficos e análises estatísticas foram realizadas pelos softwares JMP (versão 14.1.0) e MetaboAnalystR 2.0 (CHONG; YAMAMOTO; XIA, 2019) (Chong et al. 2019).

Tabela 1. Lista dos padrões nativos investigados no estudo.

Contaminantes	CAS #	Classe terapêutica	Fórmula molecular	Peso molecular (g mol^{-1})	ESI modo	LQ (ng L^{-1})	IS correspondente
acesulfame	33665-90-6	Adoçante	$C_4H_5NO_4S$	163,15	-	10	acesulfame-d4
acetaminofeno	103-90-2	Analgésico	$C_8H_9NO_2$	151,17	+	25	acetaminofeno-d4
atenolol	29122-68-7	Beta bloqueador	$C_{14}H_{22}N_2O_3$	266,34	+	10	atenolol-d7
bezafibrato	41859-67-0	Regulador lipídico	$C_{19}H_{20}ClNO_4$	361,80	+	10	bezafibrato-d4
bicalutamida	90357-06-5	Anti-câncer	$C_{18}H_{14}F_4N_2O_4S$	430,37	+	10	bicalutamida-d4
cafeína	58-08-2	Estimulante	$C_8H_{10}N_4O_2$	194,19	+	10	cafeína-d9
carbamazepina	298-46-4	Antiepileptico	$C_{15}H_{12}N_2O$	236,27	+	10	carbamazepina-d8
carbamazepina-epoxide	36507-30-9	Metabólito	$C_{15}H_{12}N_2O_2$	252,27	+	10	venlafaxina-d6
ácido clofibrico	882-09-7	Metabólito	$C_{10}H_{11}ClO_3$	214,65	-	10	ácido clofibrico-d4
diclofenaco	15307-86-5	NSAID	$C_{14}H_{11}Cl_2NO_2$	296,15	+	10	diclofenaco-13C6
fluconazol	86386-73-4	Antifungico	$C_{13}H_{12}F_2N_6O$	306,27	+	100	fluconazol-d4
furosemida	54-31-9	Diuretico	$C_{12}H_{10}ClN_2O_5S$	329,73	+	10	furosemida-d5
gabapentina	60142-96-3	Antiepileptico	$C_9H_{17}NO_2$	171,24	+	10	gabapentina-d5
hidroclorotiazida	58-93-5	Diuretico	$C_7H_8ClN_3O_4S_2$	297,73	-	25	hidroclorotiazida-13C-d2
ketoprofeno	22071-15-4	NSAID	$C_{16}H_{14}O_3$	254,29	-	10	ketoprofeno-13c-d3
metformina	657-24-9	Antihiperglicêmico	$C_4H_{10}N_5$	128,16	+	50	metformina-d6
metotrexato	59-05-2	Anti-câncer	$C_{20}H_{22}N_8O_5$	454,45	+	10	metotrexato-d3
oxazepam	604-75-1	Hipnótico	$C_{15}H_{11}ClN_2O_2$	286,72	+	10	oxazepam-d5

Contaminantes	CAS #	Classe terapêutica	Fórmula molecular	Peso molecular (g mol^{-1})	ESI modo	LQ (ng L^{-1})	IS correspondente
pravastatina	81093-37-0	Regulador lipídico	$C_{23}H_{36}O_7$	424,53	-	25	pravastatina-d3
propranolol	525-66-6	Beta bloqueador	$C_{16}H_{21}NO_2$	259,35	+	10	propranolol-d7
sitagliptina	486460-32-6	Antidiabetico	$C_{16}H_{15}F_6N_5O$	407,32	+	10	sulfametoxazol-d4
sotalol	3930-20-9	Beta bloqueador	$C_{12}H_{20}N_2O_3S$	272,36	+	10	sotalol-d6
sulfametoxazol	723-46-6	Antibacteriano	$C_{10}H_{11}N_3O_3S$	253,28	+	25	sulfametoxazol-d4
tramadol	27203-92-5	Analgésico	$C_{16}H_{25}NO_2$	263,38	+	10	tramadol-d6
triclosan	3380-34-5	Antibacteriano	$C_{12}H_7Cl_3O_2$	289,54	-	25	triclosan-d3
valsartana	137862-53-4	Beta bloqueador	$C_{24}H_{29}N_5O_3$	435,53	-	25	valsartana-d3
valsartana acid	164265-78-5	Metabolito	$C_{14}H_{10}N_4O_2$	266,26	-	10	carboxy-ibuprofen-d3
venlafaxina	93413-69-5	Antidepressivo	$C_{17}H_{27}NO_2$	277,41	+	10	venlafaxina-d6

Análises não alvo também foram desenvolvidas utilizando o programa CompoundDiscoverer 3.0 (Thermo Scientific) (LI et al., 2018b). Os picos foram selecionados e integrados, com alinhamento de tempo de retenção, detecção de compostos desconhecidos e subtração do branco (água Milli-Q e metanol), além de pesquisa automática pela biblioteca online mzCloud. A área de pico de 5.000 foi definida como um limite de quantificação artificial e somente compostos com uma pontuação de combinação acima de 75 foram considerados.

Os dados foram comparados a base de dados globais UBA database atualizada em 2019 (AUS DER BEEK et al., 2016). O consumo de medicamentos (g por dia) pela população de Juiz de Fora foi estimado com base nos estoques de 58 Unidades Básicas de Saúde. A análise de risco foi desenvolvida considerando a medida ambiental (MEC) e concentrações preditas que não causam um efeito ecotoxicológicos (PNEC) (EUROPEAN COMMUNITIES, 2003; GINEBREDA et al., 2010; RIVERA-JAIMES et al., 2018). Dessa forma, a abordagem de pior cenário foi considerada, que envolve a divisão da maior medida MEC pelo teste mais sensível de PNEC para obtenção de um quociente de risco. Os valores que não causam efeito ecotoxicológicos (NOEC) são divididos por um fator de avaliação para obtenção dos valores de PNEC. Os valores do fator de avaliação levam em consideração o número de testes disponíveis com diferentes níveis tróficos, mais especificamente alga, Daphnia e peixe (EUROPEAN COMMUNITIES, 2003). Os valores do quociente de risco menores do 0,1 são considerados de baixo risco, entre 0,1 e 1 risco moderado e acima de 1 alto risco. O risco de mistura também foi obtido somando os riscos dos compostos encontrados no ambiente (DI LORENZO et al., 2019; RIVA et al., 2018; THOMAIDI et al., 2015).

3.3 Concentrações de contaminantes de preocupação emergente em reservatórios brasileiros

Para investigar a ocorrência de contaminantes de preocupação emergente nos reservatórios, a coleta de água superficial foi realizada em quatro reservatórios brasileiros (Chapéu D'Uvas em Minas Gerais, Curuá-Una no Pará, Funil e Simplício no Rio de Janeiro) (Tabela 2), onde os pontos amostrais foram distribuídos ao longo dos reservatórios (Figura 4). Foram realizadas uma coleta em cada reservatório e somente em camada superficial. Os contaminantes de preocupação emergente investigados e a metodologia analítica foi a mesma desenvolvida e apresentada para o método anterior (item 3.2). Análises de variância foram

desenvolvidas para verificar a variação das concentrações dos contaminantes de preocupação emergente espacialmente entre os reservatórios (Kruskal-Wallis test e Wilcoxon post-hoc).

Tabela 2. Características físicas dos reservatórios de Chapéu D'Uvas (CDU), Curuá-Una (CUN), Funil (FUN) e Simplício (SIM). O asterisco indica que o tamanho populacional é estimado.

Características	CDU	CUN	FUN	SIM
Ano de inundação	1994	1977	1969	2013
Área (km²)	12	72	40	15
Volume (m³)	146 x 10^6	472 x 10^6	6.2 x 10^9	114 x 10^6
Tempo de residência (dias)	> 100	40	44	4
Rio principal	Paraibuna	Curuá-Una	Paraíba do Sul	Paraíba do Sul
Vazão média (m³ s⁻¹)	180	190	1.120	1.120
População estimada (habitantes)	1.800	1.900	2.100.000	4.000.0000*

Fonte: LIMA et al., 2016; MACHADO, 2012; OLIVEIRA et al., 2003.

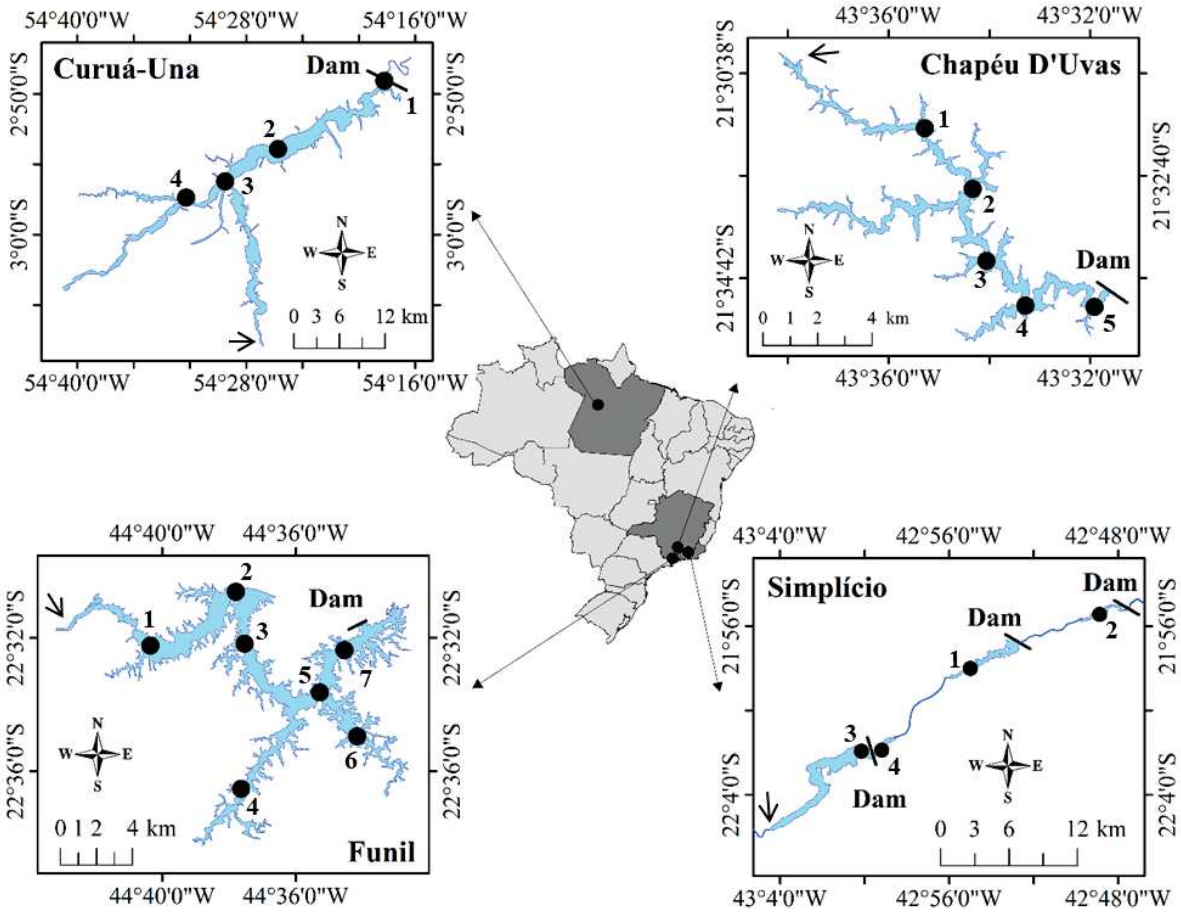

Figura 4. Mapa da área de estudo dos reservatórios investigados, onde os pontos indicam os pontos amostrais de cada reservatório. As setas indicam a entrada do rio principal e as barragens (dam) também estão identificadas.

3.4 Consumo de medicamentos pela população brasileira

Para investigar os hábitos de consumo e descarte de medicamentos pela população Brasileira, questionários online foram distribuídos via Google Forms. As questões foram elaboradas levando em consideração estudos prévios relacionados (BOUND; VOULVOULIS, 2005; SEEHUSEN; EDWARDS, 2006; VELLINGA et al., 2014). Os questionários seguiram o anonimato e não teve qualquer interferência direta com a população. As perguntas partiram desde questões mais gerais, como localização da residência, idade e nível de escolaridade, até questões mais específicas sobre automedicação, classes de medicamentos mais consumidas e forma de descarte dos medicamentos vencidos ou em desuso, conforme a Tabela 3. Todas as perguntas tinham a opção de preferência por não responder caso o participante se sentisse desconfortável.

Tabela 3. Intenção das perguntas do questionário e o tipo de resposta para cada uma delas.

Intenção das questões	**Tipo de resposta**
Localização da residência	Resposta curta
Idade	Múltipla escolha
Escolaridade	Múltipla escolha
Tomando algum medicamento atualmente	Sim ou Não
Número de medicamentos consumidos	Resposta curta
Automedicação	Sim ou Não
Classe de medicamentos mais consumida	Múltipla escolha
Efeitos adversos	Sim ou Não
Atitude ao sentir efeitos adversos	Múltipla escolha
Local de descarte dos medicamentos	Múltipla escolha
Conhecimento de coletores na cidade	Sim ou Não
Conhecimento sobre descarte de medicamentos	Sim ou Não
Conhecimento sobre os impactos ambientais do descarte incorreto	Sim ou Não

Foi utilizado uma ferramenta online (SURVEY MONKEY, 2020) para calcular o tamanho da amostra que seria representativa da população brasileira, conforme equação abaixo:

$$\text{Tamanho da amostra} = \frac{\frac{z^2 \times p\,(1-p)}{e^2}}{1 + \left(\frac{z^2 \times p\,(1-p)}{e^2 N}\right)}$$

Onde N é o tamanho populacional, e é a margem de erro (5%), e z é o escore z (confiabilidade de 95%).

A licença ética para realizar a pesquisa com seres humanos foi obtida pelo Comitê de Ética em Pesquisa da Universidade Federal de Juiz de Fora (CAAE: 88169518.6.0000.5147, aprovação: 2.761.846). Todos os dados podem ser encontrados no Apêndice D correspondente a publicação referente a este artigo (QUADRA et al., 2019a).

4 Resultados

4.1 Consumo e concentrações de cafeína ao redor do mundo

Os resultados demonstraram que 41 países (47%) apresentaram aumento significativo de consumo de café ao longo dos anos, ao passo que 31 países (36%) apresentaram redução significativa (Figura 5). É possível observar que os países importadores de café do continente Europeu foram os que apresentaram este aumento ao longo dos anos, enquanto países exportadores no continente Africano apresentaram um decréscimo no consumo interno (Figura 5). Quanto aos índices de desenvolvimento humano (IDH) e produto interno bruto (PIB), os padrões observados foram similares, ou seja, países importadores apresentaram uma maior correlação positiva do que os países exportadores (Figura 5).

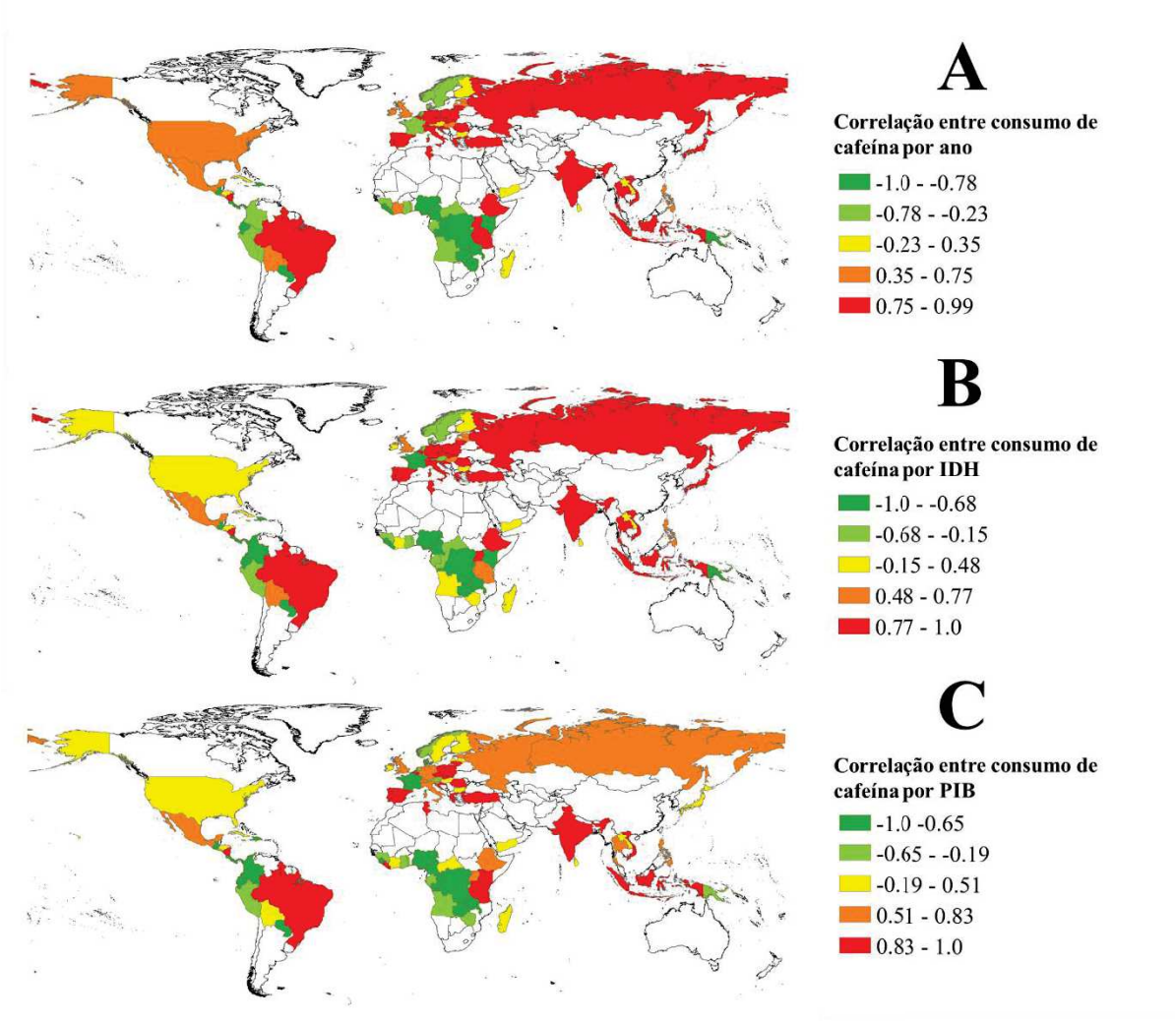

Figura 5. Correlações entre o consumo per capita de cafeína pelos (A) anos, (B) índice de desenvolvimento humano e (C) produto interno bruto entre os anos de 1990 e 2016. Os países representados em branco não apresentaram dados disponíveis.

Os dados de z-score suportam essas avaliações demonstrando que o continente Europeu chama a atenção pelo maior consumo de café per capita ao longo dos anos (Figura 6).

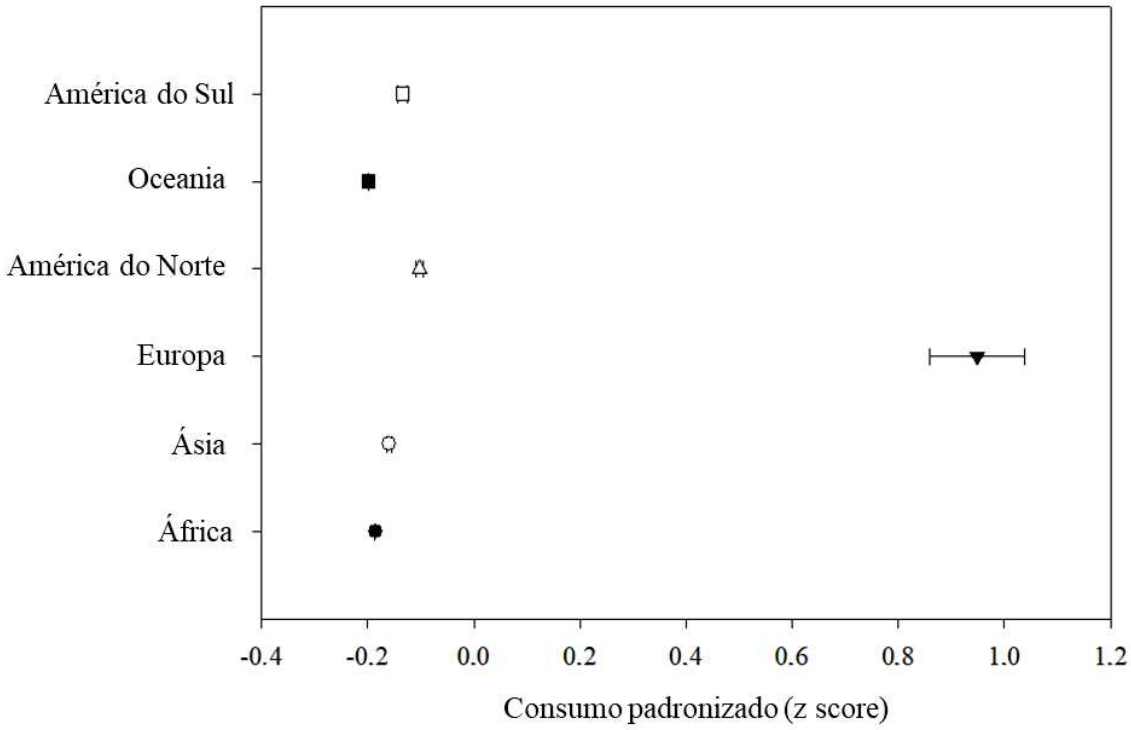

Figura 6. Consumo de cafeína pelos anos por continente. O eixo x demonstra os dados de consumo padronizados e o eixo y os continentes com seus intervalores de confiança. Os dados são entre 1990 e 2016.

Mais uma vez, o mapa de consumo médio também demonstra os maiores valores no continente Europeu (Figura 7). As correlações positivas mais fortes foram encontradas no Vietnã (1,00), Indonésia (0,99) e Brasil (0,98), enquanto as correlações negativas mais fortes foram encontradas no Malawi (-1,00), Zimbábue (-1,00) e Equador (-1,00).

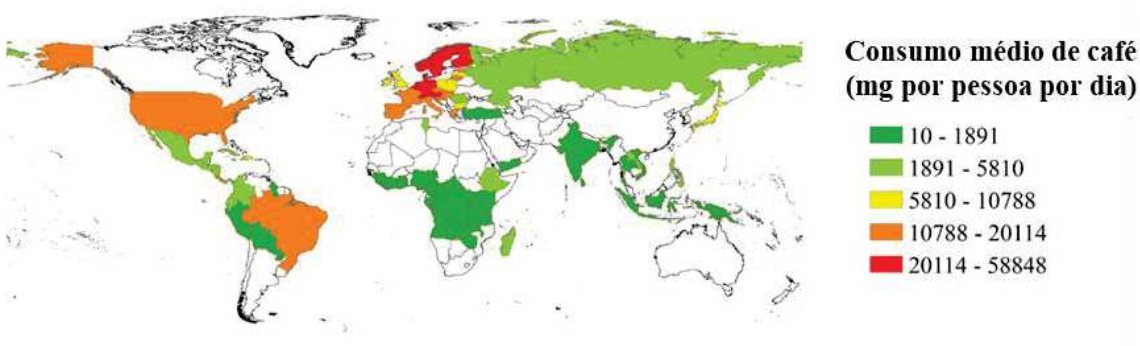

Figura 7. Consumo médio de cafeína (mg por pessoa por dia) entre 1990 e 2016 por países. Os países representados em branco não apresentaram dados disponíveis.

4.2 Concentrações de contaminantes de preocupação emergente no Rio Paraibuna

Dos 28 compostos que foram investigados no Rio Paraibuna, nove foram detectados em pelo menos uma amostra, variando em uma taxa de ocorrência de 17% para o ácido valsartana e 100% para o acesulfame, atenolol, cafeína, gabapentina, metformina e valsartana (Tabela 4, Tabela 5). A metformina apresentou a maior concentração dentre todos os compostos, chegando a 4.471 ng L^{-1}, seguido pela cafeína (1.763 ng L^{-1}), acesulfame (921 ng L^{-1}), valsartana (110 ng L^{-1}) e atenolol (106 ng L^{-1}) (Figura 8). Os compostos não foram encontrados no ambiente de referência (reservatório de Chapéu D'Uvas) acima da cidade de Juiz de Fora, somente a cafeína, mas em uma concentração máxima de 160 ng L^{-1}, ou seja, 11 vezes menor do que as concentrações após a cidade.

Tabela 4. Resumo dos resultados da ocorrência de contaminantes de preocupação emergente no Rio Paraibuna mostrando a frequência de detecção (%), valores mínimos e máximos, média e desvio padrão (DP), bem como a variação em um ano. ND = não detectado.

Contaminantes	Detecção (%)	Mín. (ng L^{-1})	Máx. (ng L^{-1})	Média (ng L^{-1})	DP (ng L^{-1})	Δ ano (ng L^{-1})
acesulfame	100	50	921	489	276	72
acetaminofeno	0	ND	ND	ND	ND	ND
atenolol	83	ND	106	52	29	5
bezafibrato	0	ND	ND	ND	ND	ND
bicalutamida	0	ND	ND	ND	ND	ND
cafeína	100	280	1763	672	304	366
carbamazepina	67	11	26	14	7	1
carbamazepina-epoxide	0	ND	ND	ND	ND	ND
ácido clofibrico	0	ND	ND	ND	ND	ND
diclofenaco	0	ND	ND	ND	ND	ND
fluconazol	0	ND	ND	ND	ND	ND
furosemida	0	ND	ND	ND	ND	ND
gabapentina	83	ND	46	25	13	8
hidroclorotiazida	58	32	79	29	23	22
ketoprofeno	0	ND	ND	ND	ND	ND
metformina	100	320	4471	2581	1235	381
metotrexato	0	ND	ND	ND	ND	ND
oxazepam	0	ND	ND	ND	ND	ND
pravastatina	0	ND	ND	ND	ND	ND
propranolol	0	ND	ND	ND	ND	ND
sitagliptina	0	ND	ND	ND	ND	ND
sotalol	0	ND	ND	ND	ND	ND
sulfametoxazol	0	ND	ND	ND	ND	ND
tramadol	0	ND	ND	ND	ND	ND
triclosan	0	ND	ND	ND	ND	ND

Contaminantes	Detecção (%)	Mín. (ng L^{-1})	Máx. (ng L^{-1})	Média (ng L^{-1})	DP (ng L^{-1})	Δ ano (ng L^{-1})
valsartana	83	ND	110	59	30	1
ácido valsartana	17	11	13	6	3	ND
venlafaxina	0	ND	ND	ND	ND	ND

Tabela 5. Resultados da quantificação de contaminantes de preocupação emergente (ng.L^{-1}) e parâmetros físico-químicos por ponto de junho de 2017 a setembro de 2018. ND = Não detectado. (Continua)

Campanhas	Junho 2017				Setembro 2017				Dezembro 2017			
Parâmetros	**P1**	**P2**	**P3**	**P4**	**P1**	**P2**	**P3**	**P4**	**P1**	**P2**	**P3**	**P4**
acesulfame	428	411	462	260	921	357	872	732	671	552	360	409
acetaminofeno	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
atenolol	53	49	53	47	94	44	83	62	49	40	31	35
bezafibrato	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
bicalutamida	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
cafeína	818	637	740	509	804	280	540	417	857	826	507	497
carbamazepina	17	14	15	ND	26	11	25	20	14	13	ND	ND
carbamazepina-epoxide	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
ácido clofibrico	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
diclofenaco	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
fluconazol	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
furosemida	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
gabapentina	23	22	22	23	46	21	37	35	22	19	15	19
hidroclorotiazida	37	32	42	ND	45	ND	34	ND	43	33	ND	ND
ketoprofeno	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
metformina	2917	2622	2766	2170	4072	1903	3577	2874	2939	2826	1899	2053
metotrexato	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Campanhas	Junho 2017				Setembro 2017				Dezembro 2017			
Parâmetros	**P1**	**P2**	**P3**	**P4**	**P1**	**P2**	**P3**	**P4**	**P1**	**P2**	**P3**	**P4**
oxazepam	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
pravastatina	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
propranolol	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
sitagliptina	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
sotalol	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
sulfametoxazol	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
tramadol	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
triclosan	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
valsartana	74	58	64	40	110	45	84	69	67	81	43	44
valsartana acid	11	ND	ND	ND	13	ND	12	13	ND	ND	ND	ND
venlafaxina	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
condutividade (µs cm^{-1})	44	50	58	56	88	82	82	81	48	50	54	54
pH	7,9	7,9	7,9	7,7	7,2	8,1	8,1	8,1	7,3	7,4	7,1	7,1
precipitação (mm)	28,5	28,5	28,5	28,5	19,0	19,0	19,0	19,0	145,6	145,6	145,6	145,6
temperatura (°C)	19,1	20,4	20,2	19,7	22,2	22,7	22,0	22,9	24,7	24,7	24,9	24,3
turbidez (NTU)	7,7	4,8	8,2	8,1	16,6	13,5	13,7	13,8	20,7	18,6	24,9	24,3

Tabela 5. (Continuação) Resultados da quantificação de contaminantes de preocupação emergente (ng.L^{-1}) e parâmetros físico-químicos por ponto de junho de 2017 a setembro de 2018. ND = Não detectado.

Campanhas	Março 2018				Junho 2018				Setembro 2018			
Parâmetros	**P1**	**P2**	**P3**	**P4**	**P1**	**P2**	**P3**	**P4**	**P1**	**P2**	**P3**	**P4**
acesulfame	69	61	50	57	680	153	522	492	851	864	742	767
acetaminofeno	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
atenolol	ND	ND	ND	ND	74	27	59	60	91	106	80	86
bezafibrato	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Campanhas	Março 2018				Junho 2018				Setembro 2018			
Parâmetros	**P1**	**P2**	**P3**	**P4**	**P1**	**P2**	**P3**	**P4**	**P1**	**P2**	**P3**	**P4**
bicalutamida	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
cafeína	547	391	346	396	1763	454	924	1029	776	915	517	635
carbamazepina	ND	ND	ND	ND	19	ND	16	14	23	24	23	23
carbamazepina-epoxide	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
ácido clofibrico	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
diclofenaco	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
fluconazol	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
furosemida	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
gabapentina	ND	ND	ND	ND	44	13	27	36	39	38	39	40
hidroclorotiazida	ND	ND	ND	ND	79	ND	45	52	56	61	51	47
ketoprofeno	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
metformina	458	421	320	378	4068	1465	3047	3420	4124	4471	3347	3810
metotrexato	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
oxazepam	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
pravastatina	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
propranolol	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
sitagliptina	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
sotalol	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
sulfametoxazol	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
tramadol	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
triclosan	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
valsartana	ND	ND	ND	ND	86	35	52	67	91	107	77	88
valsartana acid	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
venlafaxina	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
condutividade (µs cm^{-1})	38,0	29,0	34,0	34,0	48,0	48,0	48,0	45,0	63,0	65,0	63,0	64,0
pH	6,1	7,2	7,6	6,9	7,9	8,3	7,8	8,0	7,8	7,6	7,7	7,8
precipitação (mm)	279,0	279,0	279,0	279,0	19,0	19,0	19,0	19,0	76,0	76,0	76,0	76,0

Campanhas	Março 2018				Junho 2018				Setembro 2018			
Parâmetros	**P1**	**P2**	**P3**	**P4**	**P1**	**P2**	**P3**	**P4**	**P1**	**P2**	**P3**	**P4**
temperatura (°C)	23,6	24,1	24,9	25,3	19,3	23,9	19,7	23,4	21,6	21,9	21,3	21,7
turbidez (NTU)	164,0	195,9	137,2	113,9	13,7	10,7	24,4	12,0	12,5	10,0	11,7	9,7

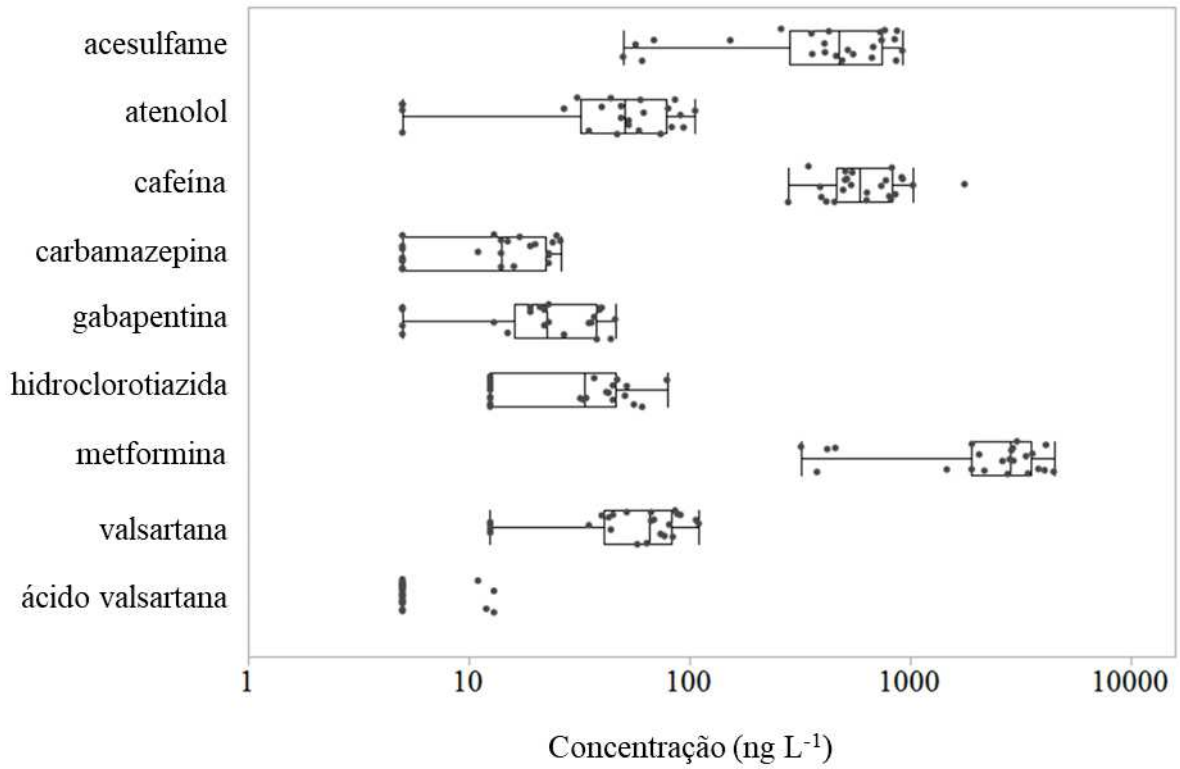

Figura 8. Concentração (ng L^{-1}) dos contaminantes de preocupação emergente detectados no Rio Paraibuna. As caixas definem os quartis enquanto as linhas o valor da mediana. As barras de erro representam os valores de mínimo e máximo.

A validade do fluxo de trabalho foi confirmada pela boa concordância geral entre a detecção dos contaminantes de preocupação emergente alvos nas análises alvo e não alvo. Todos os 9 analitos alvo detectados no rio foram identificados com sucesso na análise não alvo. A correlação entre as concentrações registradas a partir da análise alvo e as áreas dos picos da triagem não alvo foram bem correlacionadas, com R^2 de 0,78 para acessulfame e 0,97 para cafeína (Figura 9). Dois compostos-alvo não foram identificados na triagem não alvo (hidroclorotiazida e ácido valsartana), enquanto outros dois (paracetamol e sulfametoxazol) não ultrapassaram o limite de área de pico de 5.000. Esse limite relativamente alto foi selecionado para ser mais conservador, reduzindo o número de potenciais falsos positivos. A única discrepância foi encontrada para um dos fármacos alvo, o diclofenaco, que foi identificado na análise não alvo, mas não pode ser quantificado na análise alvo. Os cromatogramas foram então examinados visualmente e comparados com o padrão de referência. Como conclusão, essa identificação foi um falso positivo devido a um tempo de retenção incorreto. No entanto, o

fluxo de trabalho não alvo foi satisfatório e adequado para os objetivos, visto boa consistência geral entre os resultados da análise alvo e não alvo.

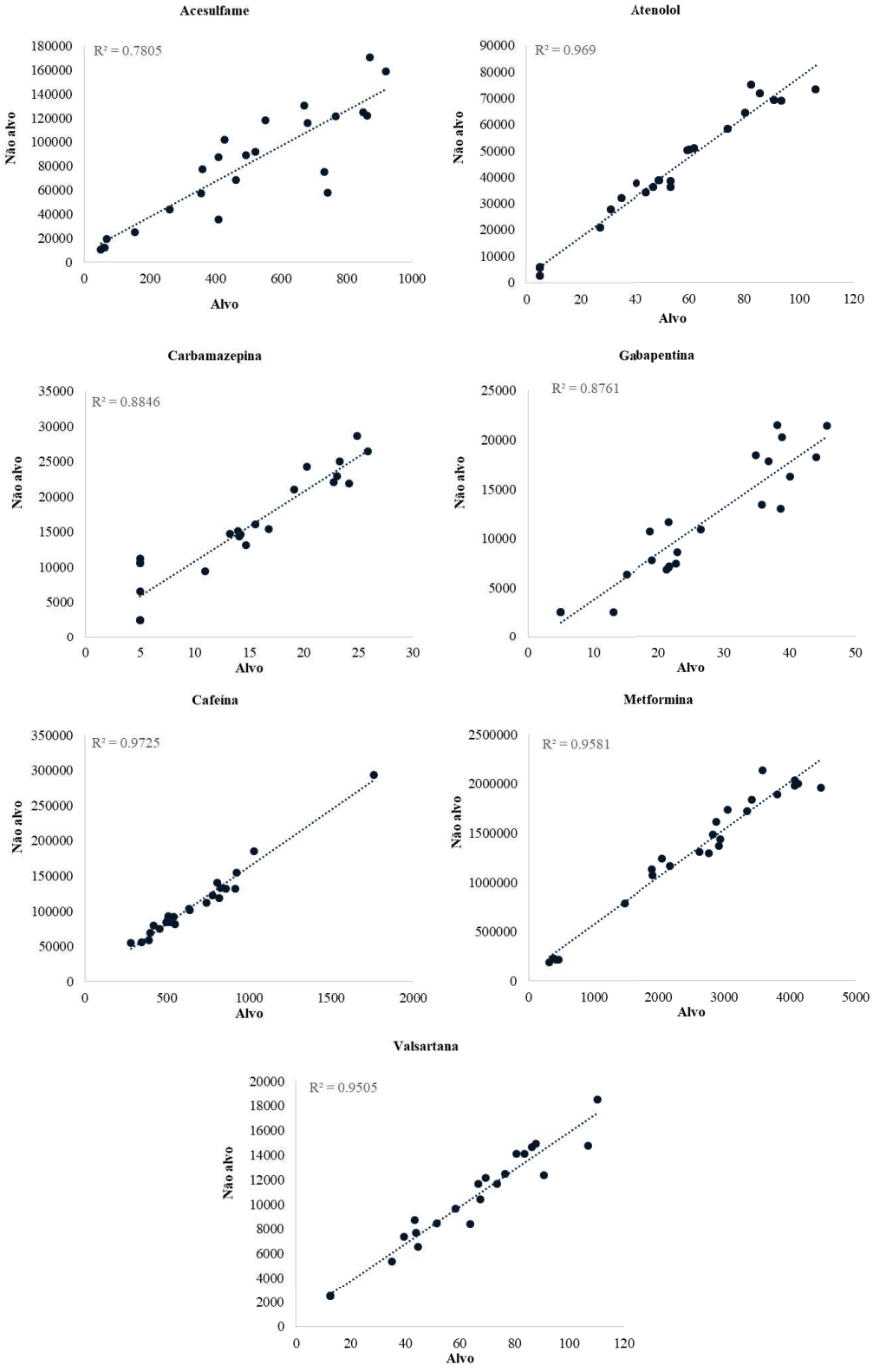

Figura 9. Correlação entre as análises alvo (ng L^{-1}) e não alvo (área dos picos) nas amostras do Rio Paraibuna.

Um total de 116 compostos químicos foram identificados pela análise não alvo em pelo menos uma das amostras de água (Tabela 6, Tabela 7). As amostras do ponto de referência identificaram 126 químicos, porém, 28 ficaram abaixo do LQ artificial, ao passo que nenhum químico apresentou essa característica para a lista de compostos do Rio Paraibuna. Além disso, a área de pico geral apresentou uma média cerca de duas vezes maior do que a média do ponto de referência em Chapéu D'Uvas. A maioria dos químicos identificados pela análise não alvo foram fármacos (22%) e esta lista pode ser útil para investigações futuras. Os produtos naturais e metabólitos humanos também foram representativos, bem como outras classes de compostos sintéticos, como os aditivos de alimento e produtos industriais.

Tabela 6. Lista de compostos identificados pela análise não alvo com respectivos tempos de retenção (TR) e pontuação de combinação na biblioteca online (mzCloud).

ESI modo	Nome como na mzCloud	Aplicação	Fórmula	Peso molecular	TR [min]	mzCloud pontuação
ESI-	1-(Carboxymethyl)cyclohexanecarboxylic acid	Fármacos: Produtos de transformação	$C_9 H_{14} O_4$	186	4	86
ESI+	1-Methylbenzotriazole	Industrial	$C_7 H_7 N_3$	133	3	98
ESI+	1,3-di-o-Tolylguanidine	Fármacos	$C_{15} H_{17} N_3$	239	4	95
ESI+	10,11-Dihydro-10,11-dihydroxycarbamazepine	Fármacos: Produtos de transformação	$C_{15} H_{14} N_2 O_3$	270	3	86
ESI+	12-Aminododecanoic acid	Produtos naturais / Metabólitos humanos	$C_{12} H_{25} N O_2$	215	5	84
ESI+	16,16-Dimethyl prostaglandin A2	Produtos naturais / Metabólitos humanos	$C_{22} H_{34} O_4$	384	1	78
ESI+	2-Methyl-4-isothiazolin-3-one	Industrial	$C_4 H_5 N O S$	115	1	86
ESI-	2-Naphthalenesulfonic acid	Industrial	$C_{10} H_8 O_3 S$	208	3	86
ESI+	2,2,6,6-Tetramethyl-4-piperidinol	Industrial	$C_9 H_{19} N O$	157	1	85
ESI+	2,3,4,9-Tetrahydro-1H-β-carboline-3-carboxylic acid	Produtos naturais / Metabólitos humanos	$C_{12} H_{12} N_2 O_2$	216	2	80
ESI+	2,4-Dimethylbenzaldehyde	Aditivos de alimento	$C_9 H_{10} O$	134	4	91
ESI+	2'-Deoxyadenosine	Produtos naturais / Metabólitos humanos	$C_{10} H_{13} N_5 O_3$	251	1	96
ESI+	3,4-Dihydroxyphenylpropionic acid	Produtos naturais / Metabólitos humanos	$C_9 H_{10} O_4$	164	1	88
ESI+	4-Aminophenol	Industrial	$C_6 H_7 N O$	109	2	78
ESI-	4-Dodecylbenzenesulfonic acid	Industrial	$C_{18} H_{30} O_3 S$	326	8	87
ESI+	4-Guanidinobutyric acid	Produtos naturais / Metabólitos humanos	$C_5 H_{11} N_3 O_2$	145	1	97
ESI-	4-Hydroxybenzaldehyde	Aditivos de alimento	$C_7 H_6 O_2$	122	4	78
ESI-	4-Hydroxybenzophenone	Fármacos	$C_{13} H_{10} O_2$	198	6	82
ESI-	4-Nitrophenol	Industrial	$C_6 H_5 N O_3$	139	4	84
ESI-	4-Oxoproline	Metabólitos humanos	$C_5 H_7 N O_3$	129	1	82

ESI modo	Nome como na mzCloud	Aplicação	Fórmula	Peso molecular	TR [min]	mzCloud pontuação
ESI+	6-Methylnicotinamide	Produtos naturais	$C_7 H_8 N_2 O$	114	1	81
ESI-	Acesulfame	Fármacos	$C_4 H_5 N O_4 S$	163	1	94
ESI+	Acetophenone	Industrial	$C_8 H_8 O$	120	4	83
ESI+	Acridine	Industrial	$C_{13} H_9 N$	179	3	76
ESI+	Adenine	Produtos naturais / Metabólitos humanos	$C_5 H_5 N_5$	135	1	76
ESI+	Adenosine	Produtos naturais / Metabólitos humanos	$C_{10} H_{13} N_5 O_4$	267	1	93
ESI-	Adipic acid	Industrial	$C_6 H_{10} O_4$	146	2	92
ESI+	Aniline	Industrial	$C_6 H_7 N$	93	1	93
ESI+	Asparagine	Produtos naturais / Metabólitos humanos	$C_4 H_8 N_2 O_3$	132	1	94
ESI+	Atenolol	Fármacos	$C_{14} H_{22} N_2 O_3$	266	2	97
ESI+	Atenolol acid	Fármacos: Produtos de transformação	$C_{14} H_{21} N O_4$	267	2	95
ESI-	Azelaic acid	Aditivos de alimento / Fármacos / Produtos naturais / Metabólitos humanos / Cosméticos	$C_9 H_{16} O_4$	188	4	84
ESI-	Benzoic acid	Agricultura / Aditivos de alimento / Fármacos / Cosméticos	$C_7 H_6 O_2$	122	3	78
ESI+	Benzotriazole	Fármacos / Cosméticos / Industrial	$C_6 H_5 N_3$	119	3	100
ESI+	Benzoylecgonine	Drogas de abuso	$C_{16} H_{19} N O_4$	289	3	93
ESI+	Betaine	Aditivos de alimento / Fármacos	$C_5 H_{11} N O_2$	117	1	92
ESI+	Bis(2-butoxyethyl) ether	Industrial	$C_{12} H_{26} O_3$	218	7	82
ESI+	Caffeine	Fármacos / Cosméticos / Aditivos de alimento / Produtos naturais	$C_8 H_{10} N_4 O_2$	194	3	97
ESI+	Caprolactam	Industrial / Aditivos de alimento	$C_6 H_{11} N O$	113	2	97
ESI+	Carbamazepine	Fármacos	$C_{15} H_{12} N_2 O$	236	5	97

ESI modo	Nome como na mzCloud	Aplicação	Fórmula	Peso molecular	TR [min]	mzCloud pontuação
ESI-	Citric acid	Fármacos / Cosméticos / Aditivos de alimento / Produtos naturais	$C_6 H_8 O_7$	192	1	79
ESI+	Clarithromycin	Fármacos	$C_{38} H_{69} N O_{13}$	747	6	98
ESI+	Creatine	Fármacos / Produtos naturais / Metabólitos humanos	$C_4 H_9 N_3 O_2$	131	1	75
ESI+	Crotonic acid	Aditivos de alimento / Cosméticos / Produtos naturais / Metabólitos humanos	$C_4 H_6 O_2$	86	5	96
ESI+	Cytosine	Produtos naturais / Metabólitos humanos	$C_4 H_5 N_3 O$	111	1	93
ESI+	D-(-)-Glutamine	Fármacos	$C_5 H_{10} N_2 O_3$	146	1	93
ESI+	D-(+)-Maltose	Cosméticos	$C_{12} H_{22} O_{11}$	364	1	95
ESI+	D-(+)-Proline	Fármacos / Cosméticos	$C_5 H_9 N O_2$	115	1	97
ESI+	D-Carnitine	Produtos naturais / Metabólitos humanos	$C_7 H_{15} N O_3$	161	1	94
ESI+	D-Panthenol	Fármacos / Cosméticos	$C_9 H_{19} N O_4$	205	4	98
ESI+	Decanamide	Produtos naturais / Metabólitos humanos	$C_{10} H_{21} N O$	171	7	90
ESI+	DEET	Agricultura	$C_{12} H_{17} N O$	191	6	98
ESI+	Diethanolamine	Industrial	$C_4 H_{11} N O_2$	105	1	94
ESI+	Diethyl phthalate	Industrial / Cosméticos	$C_{12} H_{14} O_4$	222	6	84
ESI-	Dinoterb	Agricultura	$C_{10} H_{12} N_2 O_5$	240	7	84
ESI+	DL-Arginine	Fármacos / Cosméticos	$C_6 H_{14} N_4 O_2$	174	1	97
ESI-	DL-Lactic Acid	Aditivos de alimento / Agricultura / Cosméticos	$C_3 H_6 O_3$	90	1	95
ESI+	DL-Lysine	Aditivos de alimento	$C_6 H_{14} N_2 O_2$	146	1	97
ESI+	DL-Tryptophan	Fármacos / Cosméticos	$C_{11} H_{12} N_2 O_2$	204	2	92
ESI-	Fumaric acid	Aditivos de alimento / Fármacos / Industrial	$C_4 H_4 O_4$	116	1	98

ESI modo	Nome como na mzCloud	Aplicação	Fórmula	Peso molecular	TR [min]	mzCloud pontuação
ESI+	Gabapentin	Fármacos	$C_9 H_{17} N O_2$	171	2	92
ESI+	Guanine	Produtos naturais / Metabólitos humanos	$C_5 H_5 N_5 O$	151	1	89
ESI+	Guanylurea	Fármacos: Produtos de transformação	$C_2 H_6 N_4 O$	102	1	87
ESI+	Hypoxanthine	Fármacos / Metabólitos humanos	$C_5 H_4 N_4 O$	136	1	97
ESI+	Indole-3-acrylic acid	Fármacos / Metabólitos humanos	$C_{11} H_9 N O_2$	187	2	95
ESI+	Isoamylamine	Aditivos de alimento	$C_5 H_{13} N$	87	2	96
ESI+	Isoleucine	Aditivos de alimento / Produtos naturaiss / Metabólitos humanos / Cosméticos	$C_6 H_{13} N O_2$	131	1	87
ESI-	Isorhamnetin	Produtos naturais / Metabólitos humanos	$C_{16} H_{12} O_7$	316	2	76
ESI+	L-(+)-Citrulline	Cosméticos / Fármacos / Produtos naturais / Metabólitos humanos	$C_6 H_{13} N_3 O_3$	175	1	95
ESI-	L-(+)-Lactic acid	Agricultura / Aditivos de alimento / Fármacos / Cosméticos	$C_3 H_6 O_3$	90	1	96
ESI-	L-(+)-Tartaric acid	Aditivos de alimento	$C_4 H_6 O_6$	150	1	89
ESI-	L-Aspartic acid	Aditivos de alimento / Fármacos / Cosméticos	$C_4 H_7 N O_4$	133	1	86
ESI+	L-Glutamic acid	Aditivos de alimento / Fármacos / Cosméticos	$C_5 H_9 N O_4$	147	1	95
ESI+	L-Histidine	Aditivos de alimento / Fármacos / Cosméticos	$C_6 H_9 N_3 O_2$	155	1	87
ESI+	L-Phenylalanine	Aditivos de alimento / Fármacos / Cosméticos	$C_9 H_{11} N O_2$	165	2	97
ESI+	L-Pyroglutamic acid	Cosméticos	$C_5 H_7 N O_3$	129	1	87
ESI+	L-Serine	Fármacos / Cosméticos	$C_3 H_7 N O_3$	105	1	93

ESI modo	Nome como na mzCloud	Aplicação	Fórmula	Peso molecular	TR [min]	mzCloud pontuação
ESI+	L-Threonine	Aditivos de alimento / Fármacos / Cosméticos	$C_4 H_9 N O_3$	119	1	95
ESI+	L-Tyrosine	Aditivos de alimento / Fármacos / Cosméticos	$C_9 H_{11} N O_3$	181	1	94
ESI+	Lactamide	Produtos naturais / Metabólitos humanos	$C_3 H_7 N O_2$	89	1	94
ESI+	Laurolactam	Cosméticos	$C_{12} H_{23} N O$	197	5	92
ESI-	Meclofenamic acid	Fármacos	$C_{14} H_{11} Cl_2 N O_2$	295	7	84
ESI+	Melamine	Agricultura	$C_3 H_6 N_6$	126	1	88
ESI+	Memantine	Fármacos	$C_{12} H_{21} N$	179	5	96
ESI+	Metamfepramone	Fármacos / Cosméticos	$C_{11} H_{15} N O$	177	5	79
ESI+	Metformin	Fármacos	$C_4 H_{11} N_5$	129	1	97
ESI+	Methionine sulfoxide	Produtos naturais / Metabólitos humanos	$C_5 H_{11} N O_3 S$	165	1	90
ESI-	Methylmalonic acid	Produtos naturais / Metabólitos humanos	$C_4 H_6 O_4$	118	1	87
ESI-	Monobutyl phthalate	Industrial	$C_{12} H_{14} O_4$	222	5	79
ESI+	Mycophenolic acid	Fármacos	$C_{17} H_{20} O_6$	298	4	82
ESI+	N-Acetyl-L-leucine	Fármacos	$C_8 H_{15} N O_3$	173	1	75
ESI+	N-Cyclohexylidene-2-carbamylcyclohex-1-enylamine	Produtos naturais / Metabólitos humanos	$C_{13} H_{20} N_2 O$	220	2	94
ESI+	N,N-Diethylethanolamine	Industrial	$C_6 H_{15} N O$	117	1	80
ESI+	Nicotinamide	Produtos naturais / Metabólitos humanos / Fármacos	$C_6 H_6 N_2 O$	122	1	85
ESI+	Ornithine	Cosméticos	$C_5 H_{12} N_2 O_2$	132	1	87
ESI+	Paracetamol	Fármacos	$C_8 H_9 N O_2$	151	2	95
ESI+	Phenethylamine	Aditivos de alimento	$C_8 H_{11} N$	121	2	87
ESI-	Pimelic acid	Produtos naturais / Metabólitos humanos	$C_7 H_{12} O_4$	160	2	85
ESI+	Propionylcarnitine	Fármacos	$C_{10} H_{19} N O_4$	217	1	86

ESI modo	Nome como na mzCloud	Aplicação	Fórmula	Peso molecular	TR [min]	mzCloud pontuação
ESI+	Pyridoxamine	Produtos naturais / Metabólitos humanos	$C_8 H_{12} N_2 O_2$	168	1	76
ESI-	Pyruvic acid	Produtos naturais / Metabólitos humanos	$C_3 H_4 O_3$	88	1	96
ESI+	Ranitidine	Fármacos	$C_{13} H_{22} N_4 O_3 S$	314	2	96
ESI+	Ricinine	Produtos naturais / Metabólitos humanos	$C_8 H_8 N_2 O_2$	164	2	87
ESI-	Suberic acid	Produtos naturais / Metabólitos humanos	$C_8 H_{14} O_4$	174	3	82
ESI+	Sulfamethoxazole	Fármacos	$C_{10} H_{11} N_3 O_3 S$	253	3	87
ESI+	Tertatolol	Fármacos	$C_{16} H_{25} N O_2 S$	295	1	80
ESI+	Tributyl phosphate	Industrial	$C_{12} H_{27} O_4 P$	266	8	81
ESI+	Triethanolamine	Industrial / Fármacos / Cosméticos	$C_6 H_{15} N O_3$	149	1	95
ESI+	Triisopropanolamine	Cosméticos	$C_9 H_{21} N O_3$	191	1	93
ESI+	Triisopropanolamine cyclic borate	Industrial	$C_9 H_{18} B N O_3$	199	2	92
ESI+	Tris(2-butoxyethyl) phosphate	Industrial	$C_{18} H_{39} O_7 P$	398	8	79
ESI-	Uric acid	Cosméticos / Produtos naturais / Metabólitos humanos	$C_5 H_4 N_4 O_3$	168	1	83
ESI+	Urocanic acid	Produtos naturais / Metabólitos humanos	$C_6 H_6 N_2 O_2$	138	1	96
ESI+	Valsartan	Fármacos	$C_{24} H_{29} N_5 O_3$	435	6	94
ESI-	Xanthine	Cosméticos / Produtos naturais / Metabólitos humanos / Fármacos	$C_5 H_4 N_4 O_2$	152	1	78
ESI-	β-D-Glucopyranuronic acid	Produtos naturais / Metabólitos humanos	$C_6 H_{10} O_7$	194	1	85

Tabela 7. Resultados da análise não alvo por ponto do Rio Paraibuna de junho de 2017 a setembro de 2018. (Continua)

Nome como na mzCloud	P1	P2	P3	P4	P1	P2	P3	P4	P1	P2	P3	P4
1-(Carboxymethyl)cyclohexanecarboxylic acid	52957	50995	57193	69753	47209	41955	46081	54734	100957	47459	47752	87117
1-Methylbenzotriazole	2053	3022	2052	8069	2333	20670	56798	42832	10609	10610	2056	2030
1,3-di-o-Tolylguanidine	43973	20678	6450	20082	7755	25933	80179	6708	20502	14832	81090	22495
10,11-Dihydro-10,11-dihydroxycarbamazepine	10201	7252	6869	5020	14714	5153	13880	14727	10783	9674	6510	6028
12-Aminododecanoic acid	45472	60247	45625	51676	29712	36546	33369	54820	68381	60779	94126	85712
16,16-Dimethyl prostaglandin A2	33156	27370	30845	32726	27901	27930	27973	30302	32571	29920	32153	30849
2-Methyl-4-isothiazolin-3-one	105261	36449	63936	37133	36227	53251	30285	33989	31533	54936	48520	21409
2-Naphthalenesulfonic acid	25333	32623	51999	43263	37245	22858	68246	32054	23503	21974	31682	21873
2,2,6,6-Tetramethyl-4-piperidinol	15614	18120	21376	47790	24306	18653	20990	20391	25098	27972	16805	22256
2,3,4,9-Tetrahydro-1H-β-carboline-3-carboxylic acid	4443	7379	10516	14251	4083	3648	13694	6602	7943	15111	9433	3972
2,4-Dimethylbenzaldehyde	17579	16910	22346	8435	6878	13084	13348	13027	21113	10646	16373	10673
2'-Deoxyadenosine	2373	2159	1915	2426	1392	1007	3337	5641	7715	6402	3431	4061
3,4-Dihydroxyphenylpropionic acid	30566	13614	10862	33073	15278	7282	23390	30488	37216	32525	26061	11555
4-Aminophenol	6907	7474	1383	6066	9048	10065	7880	1489	7618	7497	10746	6594
4-Dodecylbenzenesulfonic acid	146769	124382	96535	131247	96077	93151	94850	203116	181330	235141	123541	167139
4-Guanidinobutyric acid	112533	125311	111817	84359	83322	48520	82349	126824	107931	82576	63577	85066
4-Hydroxybenzaldehyde	28417	39840	30465	40684	29950	36876	22131	31910	28936	19445	23474	29226
4-Hydroxybenzophenone	72417	73112	69377	81881	78509	81053	81972	85724	67477	73577	76870	79177
4-Nitrophenol	21542	31552	22336	19555	68451	24435	52978	45673	69466	56245	60261	19478
4-Oxoproline	225580	90050	93682	382727	69736	71179	72281	77743	309463	236023	221276	95172
6-Methylnicotinamide	34542	28400	23163	32714	25353	28540	29027	24969	43042	35429	33364	32011
Acesulfame	102056	35536	68560	43941	158746	57012	170600	75311	130321	118383	77560	87284
Acetophenone	3936	6091	4263	6815	4196	5578	4728	5536	4582	4834	4260	5272
Acridine	2344	11038	8710	9684	9735	9208	2871	8415	3831	3464	7510	5945
Adenine	2594	2110	3167	2656	3374	1904	12343	2784	3298	1772	1764	1746

Nome como na mzCloud	P1	P2	P3	P4	P1	P2	P3	P4	P1	P2	P3	P4
Adenosine	6980	5221	4601	6826	4403	2979	8401	13363	11990	8255	6120	6215
Adipic acid	175152	58527	57368	99978	58300	50097	60354	59762	114943	102431	99769	129989
Aniline	6972	9978	6363	7249	6818	10577	9377	12704	6269	2665	3302	8195
Asparagine	4954	2082	963	3008	1181	3309	1513	1377	1531	2235	2673	4668
Atenolol	36260	38606	38406	36109	69068	34145	75007	51023	38580	37596	27800	32141
Atenolol acid	38941	39235	39307	29283	78645	34253	102979	73932	57813	55969	37666	41132
Azelaic acid	654539	458648	417941	548516	445380	407802	459616	480967	453179	425806	432627	529828
Benzoic acid	66589	56139	64647	86432	77497	53532	79491	83673	96772	69645	69232	55551
Benzotriazole	1706	10002	9951	7969	23778	8757	22851	23622	2386	1289	3395	2050
Benzoylecgonine	21981	35687	37440	27126	51002	16793	43505	26679	98878	94549	59124	53053
Betaine	92115	68015	53025	52584	21522	37654	25573	111752	67022	140525	36640	67639
Bis(2-butoxyethyl) ether	24204	29849	29402	28150	25455	28852	30910	30205	27965	27473	30053	24710
Caffeine	118644	101158	112448	93002	141011	54614	92540	79583	131711	133058	90158	84357
Caprolactam	7606829	9985195	7687204	7332801	6982770	8535750	9157864	9019571	6557228	6288244	9337814	5625232
Carbamazepine	15432	14341	13138	10584	26485	9401	28679	24288	14605	14723	10689	11263
Citric acid	54048	27850	22866	27621	25482	20117	38433	19524	68821	67686	36056	51807
Clarithromycin	1535	760	7345	7658	751	706	740	14448	8818	15030	1736	662
Creatine	48158	20801	167024	53279	30046	19535	23309	24997	32352	34314	27100	23602
Crotonic acid	206451	230065	227165	219551	193533	212497	223283	232220	197291	198923	221568	126074
Cytosine	982	2734	86511	1712	2148	1615	3451	54247	81560	73393	50320	68215
D-(-)-Glutamine	11181	1892	1047	8199	1148	8747	1084	2132	2982	2179	2525	1881
D-(+)-Maltose	22173	19665	17351	18140	18010	14367	22043	21264	25059	24400	24697	24535
D-(+)-Proline	75014	61011	35931	120749	37968	48770	55667	36812	91675	59010	82845	41314
D-Carnitine	111653	74153	123528	52504	50536	31467	61378	94966	51906	43457	92990	51802
D-Panthenol	2458	5271	2668	2978	4759	2606	5563	2628	2240	2914	2503	2804
Decanamide	441169	371038	526582	532269	340215	385489	808122	542068	488268	476658	1326944	432564
DEET	157606	243870	178291	221638	172475	123394	246926	269067	413140	272072	221510	184589

Nome como na mzCloud	P1	P2	P3	P4	P1	P2	P3	P4	P1	P2	P3	P4
Diethanolamine	150244	61176	72429	77904	146023	130469	79392	312309	137891	60520	63763	208494
Diethyl phthalate	228262	257407	220295	219962	228498	244784	321550	423544	348389	195529	201583	151630
Dinoterb	257680	275780	309627	246206	304630	286656	282226	239376	233903	193487	218094	180063
DL-Arginine	369763	139681	47089	156502	51062	4468	54015	134667	65100	39469	20591	35937
DL-Lactic Acid	122365	123098	207085	708603	84727	14889	141310	82314	407961	187686	114761	138758
DL-Lysine	23386	20741	18299	19132	18994	15153	23248	22427	26429	25734	26048	25877
DL-Tryptophan	64216	9775	3722	35839	10094	8998	9731	12652	32348	34563	19666	13761
Fumaric acid	72347	78720	81506	88071	68026	46011	55686	75437	138082	113810	87740	129753
Gabapentin	7351	7114	6928	8504	21367	6740	17732	18351	11583	10609	6324	7728
Guanine	22750	48256	14198	15006	19120	20891	17938	26428	29412	15800	15765	19500
Guanylurea	9849	8446	8019	7436	7798	7312	9017	9187	10109	9644	10369	10505
Hypoxanthine	27702	26169	30977	24486	32247	13982	29118	39638	39400	32860	28762	26423
Indole-3-acrylic acid	45781	7214	1804	23668	6833	4640	5190	7190	21282	22879	13852	9939
Isoamylamine	21439	17210	14459	17665	21438	9749	12398	10934	7930	12012	11732	9719
Isoleucine	727512	361022	477945	832172	521341	236120	561030	830692	987207	740103	548805	325178
Isorhamnetin	273696	362471	278341	207216	748380	246533	679993	399375	396364	398148	273850	263981
L-(+)-Citrulline	162434	27413	14429	77813	22109	24938	19924	24952	27978	17892	20579	20204
L-(+)-Lactic acid	697760	333232	688653	2043818	611326	257160	409115	520259	1369893	469259	522337	754305
L-(+)-Tartaric acid	3941	4820	4977	4441	5927	5516	5950	5718	6490	6594	4845	4593
L-Aspartic acid	35539	10907	9173	45745	7670	9722	8482	11158	20282	27974	26301	12556
L-Glutamic acid	34756	15840	15619	37545	11661	30379	8727	22038	22469	21477	17134	16944
L-Histidine	36392	15296	14613	15278	15168	13241	18565	17909	21105	18373	20801	19851
L-Phenylalanine	286285	151278	168705	310389	182293	82977	229803	317325	365710	303681	223950	119245
L-Pyroglutamic acid	162834	91835	74298	258532	90983	43883	92462	104411	233763	241173	203158	98703
L-Serine	62582	14714	13339	77724	9793	28683	10145	16989	39493	31067	33135	16740
L-Threonine	27111	9336	10340	36376	7543	16271	7950	14365	32364	18102	24447	11874
L-Tyrosine	176419	90432	87833	205561	112613	48149	127588	183405	230357	196990	150855	86689
Lactamide	62572	16758	22207	60220	10176	22474	11934	20072	47690	26884	37262	14937

Nome como na mzCloud	P1	P2	P3	P4	P1	P2	P3	P4	P1	P2	P3	P4
Laurolactam	19447	10685	7792	21956	11632	11248	13065	8881	17080	11207	8073	17154
Meclofenamic acid	16579	16606	15527	14626	14634	13801	14108	14221	15609	14827	13272	14355
Melamine	83240	73991	55029	105148	1793692	1339663	2241738	3104416	116381	107394	88871	93442
Memantine	7862	7007	5197	11939	5249	5844	5619	5887	8716	5335	4626	8282
Metamfepramone	770	8822	7888	823	712	743	8934	7602	701	9275	8223	8048
Metformin	1368727	1310917	1297848	1169338	2038270	1071578	2141148	1617938	1436087	1485301	1136405	1244096
Methionine sulfoxide	1683	812	950	4469	1011	3814	983	6777	1857	1539	1876	1426
Methylmalonic acid	8021	57528	136386	17447	47381	8464	22920	13158	62514	58711	8075	9233
Monobutyl phthalate	6899	7740	6413	9310	5638	4712	5697	7152	18036	14486	6678	14931
Mycophenolic acid	47404	52436	45700	31950	29529	39640	39422	41327	71156	49095	67103	57664
N-Acetyl-L-leucine	2904	4829	4301	2767	4707	2144	4357	4939	3226	6604	4108	4705
N-Cyclohexylidene-2-carbamylcyclohex-1-enylamine	19901	16733	21939	25016	14600	17047	44200	31370	25842	24477	85246	19713
N,N-Diethylethanolamine	7327	7515	3191	81937	3377	6293	4568	4966	5269	5582	7060	2168
Nicotinamide	19055	10498	6923	8043	5687	11419	5255	6668	6018	8823	3776	12195
Ornithine	47423	32344	28537	29836	29621	23630	36255	34974	41215	40132	40620	40354
Paracetamol	11216	2689	2576	2771	2642	8657	9748	10207	2574	3485	9841	2823
Phenethylamine	11855	61823	63107	12228	19616	14376	8327	59294	6201	9006	5403	9858
Pimelic acid	53966	29417	20768	30588	24495	14618	32702	26031	58863	36566	52417	80415
Propionylcarnitine	13172	13671	10724	10607	10429	10899	12059	12895	34357	33453	16061	15409
Pyridoxamine	1834	1487	1465	1587	1436	1381	1521	1527	1769	1486	5716	1306
Pyruvic acid	3729	4560	5092	4202	5839	5219	6192	5715	6141	7256	4585	4346
Ranitidine	11645	14191	9069	9014	7659	6253	6270	5873	4241	4539	4100	5384
Ricinine	8392	7658	8447	5269	30160	9748	29428	24078	85285	63830	56213	66571
Suberic acid	262133	148729	169760	216645	210612	141158	168947	165578	206358	182039	182776	183871
Sulfamethoxazole	3967	3728	3991	3673	3119	10625	3215	4606	3258	3662	3513	3650
Tertatolol	33805	35325	46435	25680	50589	27288	53747	50317	47623	55966	36503	36122
Tributyl phosphate	33274	26656	51465	41666	34236	29935	36170	19829	102057	41171	35343	103317

Nome como na mzCloud	P1	P2	P3	P4	P1	P2	P3	P4	P1	P2	P3	P4
Triethanolamine	322756	284699	285932	189872	781232	45853	162323	190778	1044245	215489	137241	131205
Triisopropanolamine	84415	85616	70429	233635	61474	216965	122403	354918	103062	105892	80696	236704
Triisopropanolamine cyclic borate	13068	24037	20343	65430	16709	59194	22878	77619	25269	30676	12318	42188
Tris(2-butoxyethyl) phosphate	150270	139745	118179	133159	132211	110442	128296	158623	130915	204367	111015	91520
Uric acid	19354	7258	507	5078	1253	970	39300	626	1606	1616	2052	7703
Urocanic acid	1418414	634639	797545	1805020	969809	336683	1188648	891177	2681258	1620880	1151874	535441
Valsartan	11671	9646	8426	7392	18524	6551	14109	12154	10419	14131	8730	7677
Xanthine	8406	7177	5355	8176	9586	4078	8421	8858	6492	9332	7387	4116
β-D-Glucopyranuronic acid	9025	10861	12570	10574	12349	11194	11631	11714	13544	14539	13630	12494

Tabela 7. (Continuação) Resultados da análise não alvo por ponto do Rio Paraibuna de junho de 2017 a setembro de 2018.

Nome como na mzCloud	P1	P2	P3	P4	P1	P2	P3	P4	P1	P2	P3	P4
1-(Carboxymethyl)cyclohexanecarboxylic acid	57458	87969	40697	48333	48592	63640	53407	60983	42079	131123	54811	51295
1-Methylbenzotriazole	1912	2064	2059	24052	15380	1873	15374	1976	23876	1880	2177	2029
1,3-di-o-Tolylguanidine	33833	5189	9429	80768	14108	24345	49132	10218	4973	51121	8917	4556
10,11-Dihydro-10,11-dihydroxycarbamazepine	2940	2896	3050	3097	11285	3405	7833	8151	11615	9557	11518	11618
12-Aminododecanoic acid	187147	474306	163806	79332	83043	94412	94058	47876	38216	64905	58724	50246
16,16-Dimethyl prostaglandin A2	29802	29535	30731	28971	24018	22846	24693	27117	23675	21632	26109	25542
2-Methyl-4-isothiazolin-3-one	35882	41787	39940	72820	28418	62168	92573	13466	9426	22942	13050	10938
2-Naphthalenesulfonic acid	20893	14687	57147	15158	30180	15940	29010	24242	17270	26909	23697	17336
2,2,6,6-Tetramethyl-4-piperidinol	22420	21404	30326	30321	29953	17965	31855	25072	26257	22700	6580	29522
2,3,4,9-Tetrahydro-1H-β-carboline-3-carboxylic acid	10229	5750	3925	11417	8740	6845	10685	5176	2411	18659	2119	4893
2,4-Dimethylbenzaldehyde	20954	1302	13324	36384	1314	34514	12058	9491	19078	13400	12541	6726
2'-Deoxyadenosine	67719	7486	69959	42421	5204	2798	962	910	1433	3369	12598	6889

Nome como na mzCloud	P1	P2	P3	P4	P1	P2	P3	P4	P1	P2	P3	P4
3,4-Dihydroxyphenylpropionic acid	45002	24375	19215	38693	25187	13708	34692	22678	13952	22919	9801	19288
4-Aminophenol	5983	2707	4157	4822	5254	1254	1363	9207	6505	2005	9352	2966
4-Dodecylbenzenesulfonic acid	304359	302034	163220	145748	165841	227452	140898	116099	128909	104901	195881	114046
4-Guanidinobutyric acid	104378	113570	108256	103351	85954	65936	62273	67082	93613	88374	90609	160772
4-Hydroxybenzaldehyde	32881	43778	23370	23894	22811	32014	31056	25536	24080	41677	24726	25893
4-Hydroxybenzophenone	68368	71020	83350	76414	74952	82573	82911	80980	75700	66101	71394	73390
4-Nitrophenol	40972	36914	31555	27173	64560	21845	33986	23562	85522	50094	46222	63248
4-Oxoproline	322217	129767	127058	400583	110997	202833	191841	126060	48899	140599	4315	81908
6-Methylnicotinamide	52626	30648	31888	45742	24922	23707	32592	28139	24566	26412	27092	26504
Acesulfame	19505	11966	10149	12281	115869	24917	91740	89242	125117	121802	57947	121540
Acetophenone	6482	7849	5128	5307	4376	4259	3024	5485	3310	4766	5103	3936
Acridine	2630	4395	6458	6120	3548	1075	8379	7128	8702	3711	6521	2546
Adenine	1542	1648	2132	1561	2546	24994	1702	1816	1910	1499	2168	1735
Adenosine	45114	5239	51772	58897	10292	7815	5542	5885	6906	12857	22620	12249
Adipic acid	103397	121295	72298	104286	73646	115110	119630	59140	82719	184961	76925	132905
Aniline	7182	10364	3717	3441	5023	7460	5363	6157	6440	5353	4728	3728
Asparagine	5513	2641	5960	7067	3562	17237	4939	3334	6135	3270	7330	7340
Atenolol	5968	5567	4317	5721	58321	20802	50202	50299	69352	73280	64420	71887
Atenolol acid	12308	12356	9329	10586	53506	17756	42818	43781	60253	63037	66712	61449
Azelaic acid	508428	410992	415871	479367	520165	510325	713344	514621	407168	511247	747843	530899
Benzoic acid	106237	6801	71001	85326	79400	46960	87992	63314	59557	75605	55595	64936
Benzotriazole	1471	1914	1721	5359	2625	1275	3538	3220	5881	3842	2828	6255
Benzoylecgonine	5594	5088	2858	5446	55894	12759	44340	35891	57468	55521	40661	53679
Betaine	128390	214029	45594	68814	46553	176923	223899	32000	145346	28962	887074	132286
Bis(2-butoxyethyl) ether	33190	24084	26868	25169	29685	26253	21056	25813	22968	24223	21735	19647
Caffeine	81601	58780	55559	69430	293623	75325	154621	185723	122131	132003	84439	103099
Caprolactam	6532492	5934358	5992007	7430153	8837896	7768957	7054295	7465248	7882551	6643654	8464995	7337752
Carbamazepine	4454	4886	3859	4156	21014	6519	16055	15108	25008	21861	22936	22073

Nome como na mzCloud	P1	P2	P3	P4	P1	P2	P3	P4	P1	P2	P3	P4
Citric acid	52095	42182	27413	24868	37525	23717	38349	40495	48118	101732	30238	44113
Clarithromycin	13383	16373	3765	747	2840	7312	738	669	676	674	14949	8013
Creatine	728317	32992	34101	45658	28315	32490	49416	53677	16300	27541	37942	17009
Crotonic acid	224547	192404	204979	132446	227382	222697	207309	197717	200990	197405	217451	212646
Cytosine	160399	4221	215529	4732	3407	1864	3459	1711	3052	69943	95564	79951
D-(-)-Glutamine	21187	23714	17333	13881	1715	44034	1443	1469	1649	2765	1382	1392
D-(+)-Maltose	25503	21498	21439	19721	18585	14127	21396	17928	19447	16609	19721	19839
D-(+)-Proline	85680	131254	97396	176288	36822	206317	65382	46768	11163	86194	9872	21261
D-Carnitine	195910	95515	42750	62655	35778	48237	132050	76169	102908	60843	115766	70355
D-Panthenol	2315	2292	2690	2786	3087	2629	2529	2590	3081	7046	2284	2684
Decanamide	514967	392756	563517	338189	448841	409002	340093	544280	511881	497060	502496	490602
DEET	5159721	10584437	39391770	1042498	379216	199040	3942984	479746	614770	769685	186740 7	6227866
Diethanolamine	170490	51864	48126	41082	162229	65485	219008	437349	312330	81136	574703	1645238
Diethyl phthalate	298824	288613	300269	305778	212320	191979	193889	185097	211545	182395	247106	196424
Dinoterb	213795	271525	120272	269898	243173	225028	278923	201256	211009	221391	102513	175234
DL-Arginine	9998	1644	21719	51314	124404	83946	76700	92303	64702	182549	56226	40664
DL-Lactic Acid	127703	91308	122068	238578	57499	85383	249818	39069	87783	179258	55104	58850
DL-Lysine	26898	22980	23035	20799	19602	16412	22566	18908	20511	17518	20799	20923
DL-Tryptophan	53959	29442	22819	42759	13038	16421	16941	23411	14741	18152	12312	22098
Fumaric acid	139590	151329	62187	72167	68513	65990	94654	65341	63795	135621	64189	88681
Gabapentin	3434	3939	3085	2789	18166	3722	10797	13352	20189	21443	12917	16203
Guanine	86656	66650	89535	65102	26387	49889	15715	12483	23560	28297	37543	48909
Guanylurea	9665	11032	10158	8892	7768	8417	13516	15676	21432	26544	28518	34054
Hypoxanthine	144423	123437	128552	93686	33532	40125	28978	21915	31647	31986	48715	39198
Indole-3-acrylic acid	36012	19037	15409	28608	7692	11284	8809	14951	9796	12694	7925	14015
Isoamylamine	27489	27275	22933	13344	10385	7614	6862	10549	22717	12270	18584	13963
Isoleucine	1091127	757864	734803	880668	606014	410329	732334	489769	366920	532689	332639	519518

Nome como na mzCloud	P1	P2	P3	P4	P1	P2	P3	P4	P1	P2	P3	P4
Isorhamnetin	70463	61879	62809	85031	421839	125603	357647	247285	496283	328289	306188	284569
L-(+)-Citrulline	33035	42968	34309	41652	19859	34224	19050	29065	11900	27091	12744	28268
L-(+)-Lactic acid	686894	499147	460016	661191	452974	423031	801496	348536	472264	787511	336062	650103
L-(+)-Tartaric acid	9888	4615	4355	6512	7513	4399	6967	5680	7313	7459	11291	7101
L-Aspartic acid	11391	5624	19380	56142	17512	28630	16537	6920	10009	15841	11787	8158
L-Glutamic acid	64660	45905	92433	110252	16676	170101	13872	12615	8821	16582	11888	11932
L-Histidine	18491	18351	18395	20965	15110	18485	15662	15099	14958	13026	14772	15034
L-Phenylalanine	417186	283335	270117	375101	265449	151590	298698	214877	138583	210823	119489	208676
L-Pyroglutamic acid	330477	101846	104824	287649	155090	115421	256502	146171	89979	194466	80015	145107
L-Serine	82065	50181	54855	99111	16495	147455	25578	18777	11837	16477	13448	14060
L-Threonine	42368	37492	48552	68121	10922	83583	11884	10891	5840	8141	7184	6946
L-Tyrosine	260244	164130	131503	233137	162756	97344	191268	151200	88762	157225	78921	140545
Lactamide	85844	58506	55749	71554	17782	64437	29642	14979	13942	18623	13096	13117
Laurolactam	13714	30900	11196	13981	26364	18538	25964	14212	11617	23508	13114	24232
Meclofenamic acid	14868	12870	12054	13248	14749	13471	14139	14706	13854	15762	13780	14767
Melamine	68235	91205	51129	60650	86735	47770	130618	85012	182879	138462	171287	217005
Memantine	5325	8579	6556	5053	14716	9034	13715	7107	4720	13597	6508	13440
Metamfepramone	7829	22631	52278	9739	7743	9049	5609	8212	832	8525	1484	6981
Metformin	215821	216170	188852	225794	1981776	784759	1736757	1838514	2001768	1959430	1724899	1892533
Methionine sulfoxide	36531	41973	40702	35235	940	38658	1026	915	1251	1059	1254	1462
Methylmalonic acid	2253	3673	3947	2741	65164	2088	65805	78621	29161	83715	20194	52480
Monobutyl phthalate	13551	106733	6137	6371	8282	7202	7298	6428	7423	18561	5204	7502
Mycophenolic acid	82525	16250	57312	16854	12705	10795	40120	37185	57479	43967	41962	22156
N-Acetyl-L-leucine	12768	6686	4517	7002	4861	2049	3507	4471	10339	5896	5155	4322
N-Cyclohexylidene-2-carbamylcyclohex-1-enylamine	18366	17046	31443	15138	23074	17688	16365	32719	29651	34314	25850	27720
N,N-Diethylethanolamine	1491	3149	3974	3597	36995	5749	15698	10130	8053	7550	89262	6176
Nicotinamide	9125	5880	2597	4164	12135	6201	11783	12761	11135	11061	25286	18273

Nome como na mzCloud	P1	P2	P3	P4	P1	P2	P3	P4	P1	P2	P3	P4
Ornithine	41945	35678	35261	32436	30568	24815	35191	29486	31985	27318	32436	32629
Paracetamol	5014	4614	2669	3436	3666	3094	3532	4551	10013	2460	2977	8209
Phenethylamine	32638	17219	15290	24057	15884	14301	60964	62052	23086	12435	20098	25584
Pimelic acid	62807	66800	28511	19257	33310	31395	54620	17482	30911	76281	37411	67633
Propionylcarnitine	14886	14753	15350	14471	10868	12121	11619	13545	11158	10368	13041	12758
Pyridoxamine	16902	6628	10917	11243	9997	1329	1531	3075	27600	24425	1290	1402
Pyruvic acid	9356	8959	6581	6161	7109	4162	6592	5374	6920	8151	10684	6719
Ranitidine	7810	7178	6099	5594	6427	3732	7200	6198	5985	5615	5971	5907
Ricinine	140750	127827	110570	117979	19666	5639	17176	15114	27652	23491	19201	21627
Suberic acid	190417	156638	170760	180360	203758	191744	227103	155571	190411	220784	217512	232496
Sulfamethoxazole	3296	3568	3533	3821	3311	4336	4358	3526	3678	3805	3788	3670
Tertatolol	10723	9772	14920	10424	101086	29273	79252	69050	123909	84703	86361	107793
Tributyl phosphate	42708	118099	25257	35112	16972	23200	22942	15192	21933	75703	18577	33591
Triethanolamine	291839	199936	104774	111052	279620	77104	357426	205534	263250	199686	243900	8052867
Triisopropanolamine	232601	83355	65093	107795	101899	96789	117920	116424	219896	68489	85039	89641
Triisopropanolamine cyclic borate	40736	28929	9363	27994	25395	22058	29501	28352	48841	19692	17128	15715
Tris(2-butoxyethyl) phosphate	109828	109175	93124	102455	115618	151020	101364	156263	137292	102980	130838	121725
Uric acid	1667	41662	2322	3784	2395	2138	6811	36694	2708	7162	1597	2175
Urocanic acid	2228107	888066	554168	276926	146492	664127	1565668	1074943	99434	1453611	60488	166876
Valsartan	4477	4125	4028	3781	14681	5378	8450	11685	12374	14772	12481	14921
Xanthine	13033	21805	15962	13013	7982	10903	6875	3512	5704	7882	4587	12988
β-D-Glucopyranuronic acid	24026	12470	12832	13550	14647	11007	14346	13398	15860	16356	16725	15856

O fármaco mais consumido durante o período de amostragem pela população de Juiz de Fora foi a metformina (média anual de 8.000 g dia^{-1}), seguido pela hidroclorotiazida (500 g dia^{-1}), atenolol (400 g dia^{-1}), furosemida (300 g dia^{-1}) e propranolol (300 g dia^{-1}) (Figura 10).

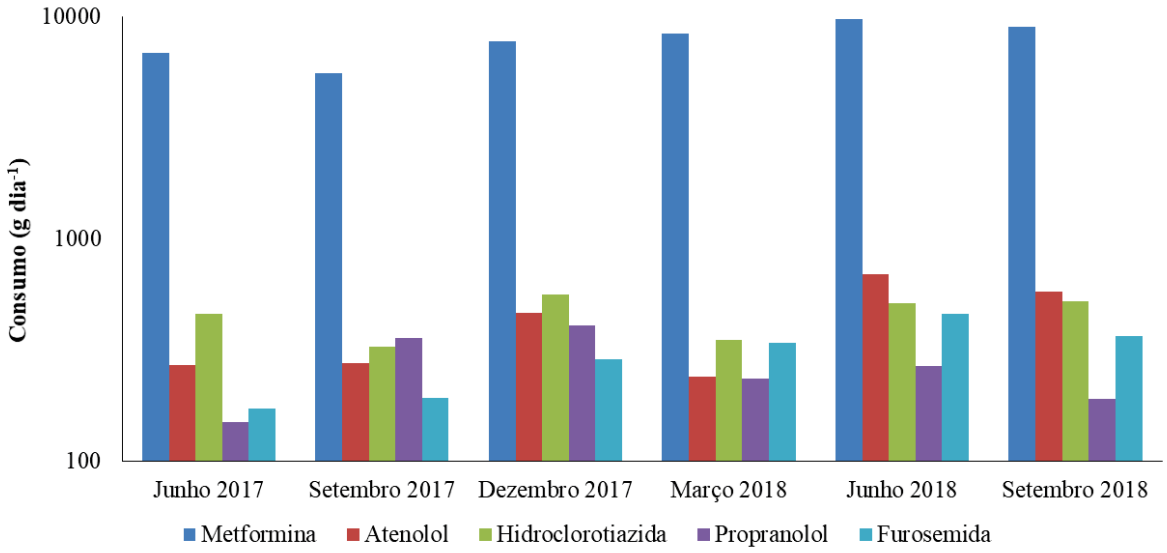

Figura 10. Consumo estimado dos fármacos (g dia^{-1}) pela população de Juiz de Fora durante o período de amostragem.

Os compostos não apresentaram uma variação espacial significante ($p > 0,05$) (Figura 11, Tabela 8), sendo possível usar a média das concentrações para cada composto considerando todos os quatro pontos amostrais para avaliar de maneira mais detalhada a variação temporal. A variação temporal, por sua vez, foi observada ($p < 0,05$) (Figura 11, Tabela 8), sendo que os menores valores foram observados em março de 2018, quando os registros de chuva foram mais elevados (Figura 12).

Tabela 8. Resultados estatísticos da variação espacial (entre os pontos) e temporal (entre as campanhas). Os valores em negrito demonstram significância estatística.

Contaminantes	Espacial		Temporal	
	F	*p*	F	*p*
acesulfame	0,5296	0,6671	11,4879	**<0,0001**
atenolol	0,2791	0,8398	18,8408	**<0,0001**
cafeína	2,0523	0,1389	1,5107	0,0685
carbamazepina	0,648	0,5934	8,2247	**0,0003**
gabapentina	0,6034	0,6204	12,4801	**<0,0001**
hidroclorotiazida	1,3554	0,285	3,8696	**0,0148**
metformina	0,4409	0,7263	12,5003	**<0,0001**
valsartana	0,5711	0,6406	8,6421	**0,0003**
ácido valsartana	0,6794	0,5749	5,3289	**0,0035**

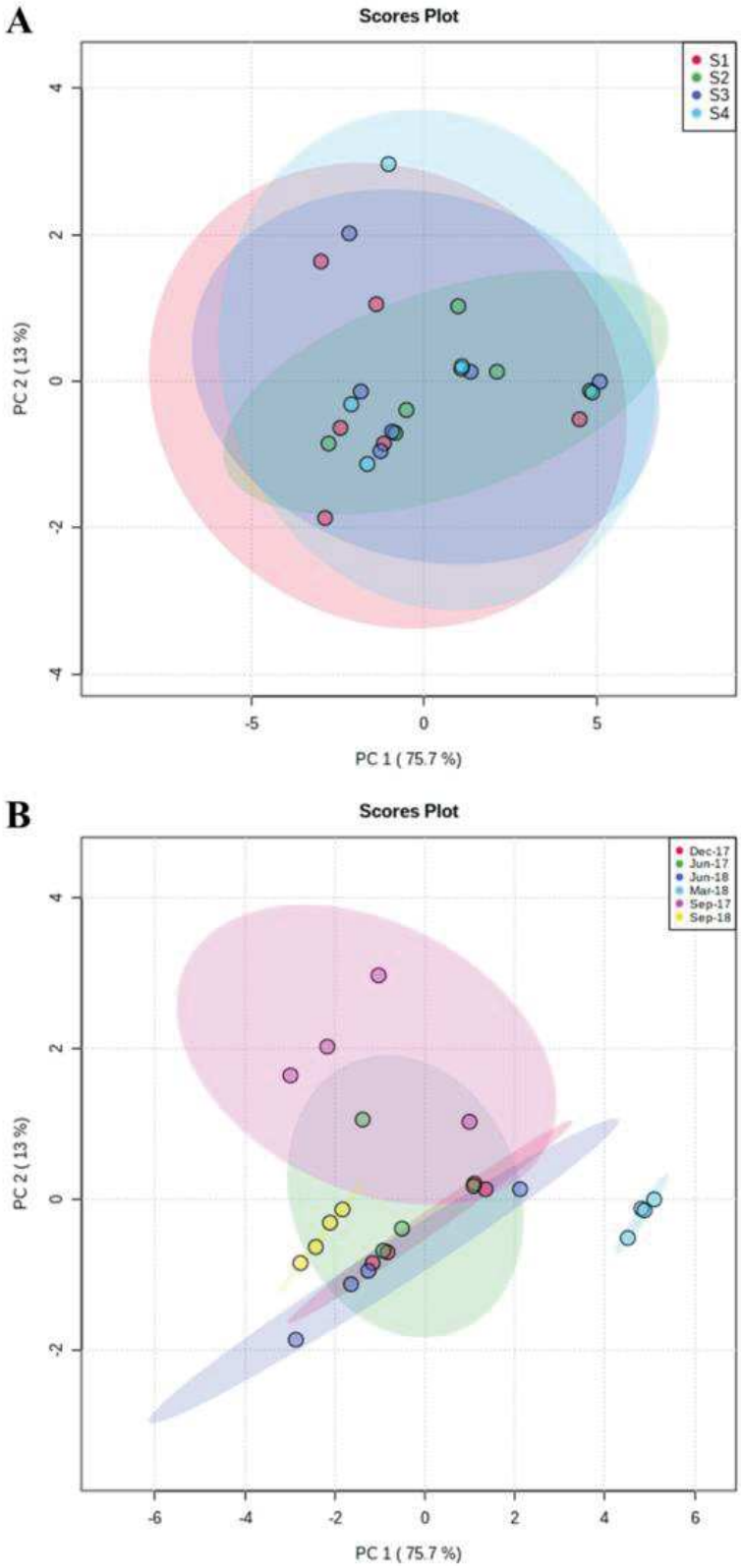

Figura 11. Análise de componentes principais mostrando variabilidade (A) espacial e (B) temporal dos contaminantes de preocupação emergente detectados no Rio Paraibuna.

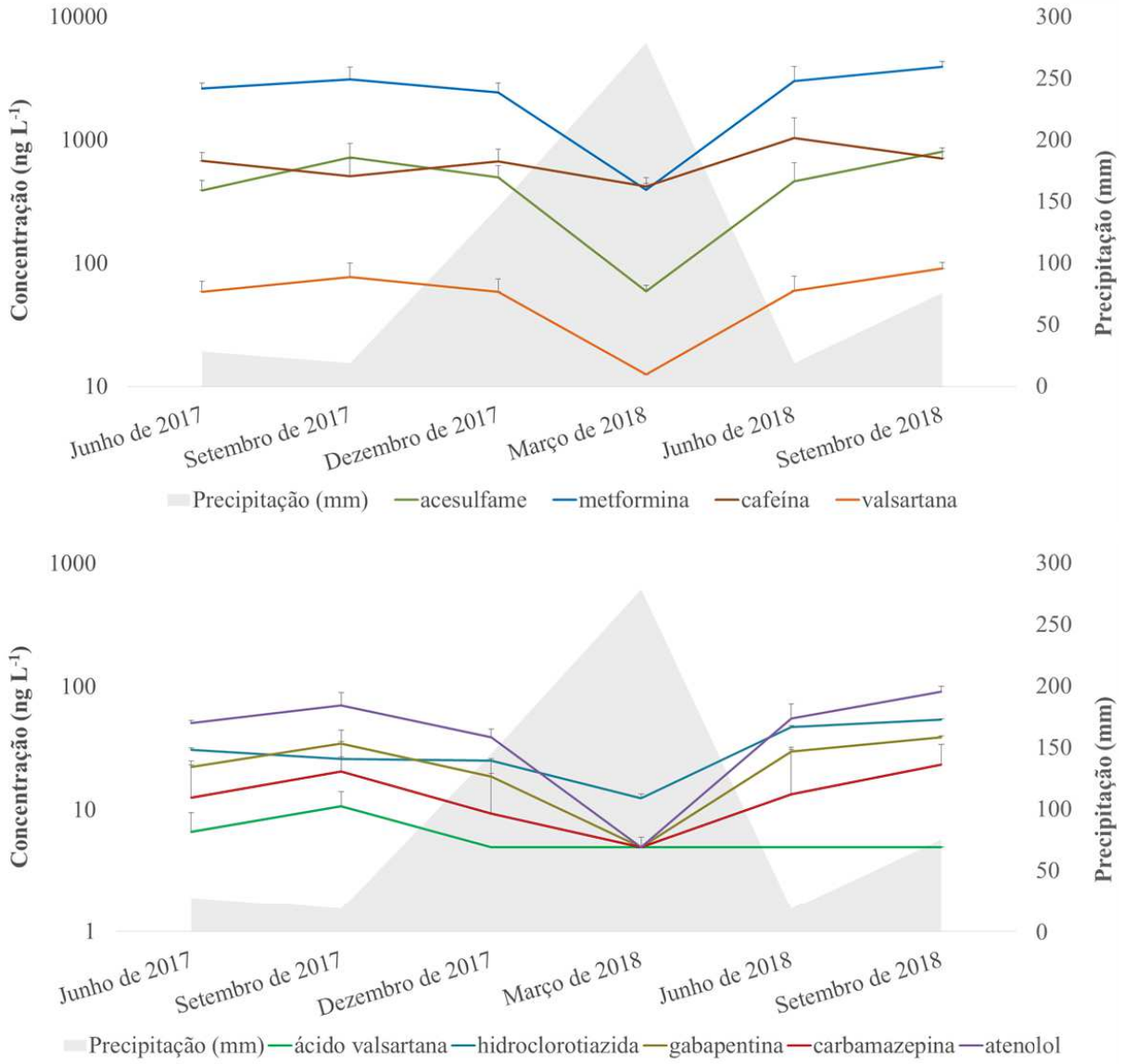

Figura 12. Média entre os pontos amostrais das concentrações dos contaminantes de preocupação emergente (ng L^{-1}) no Rio Paraibuna ao longo do tempo. O eixo y secundário demonstra a precipitação (mm) ao longo das campanhas.

Os outros parâmetros físico-químicos de condutividade, pH, temperatura e turbidez também apresentam variação temporal (Figura 13), sendo que a temperatura e a turbidez normalmente são correlacionadas positivamente com a precipitação.

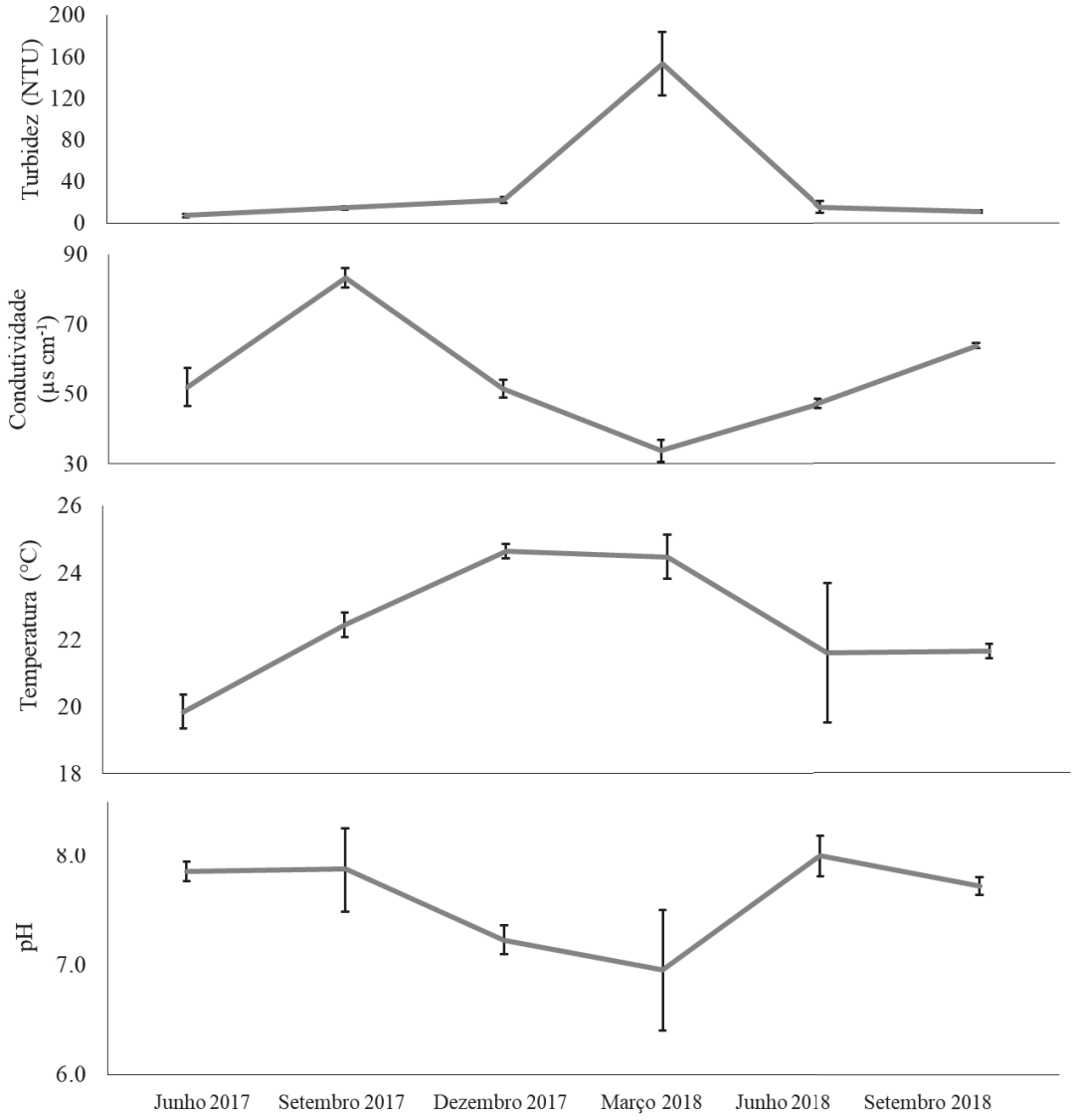

Figura 13. Temperatura (ºC), pH, condutividade (C µs cm^{-1}) e turbidez (NTU) apresentados como media e desvio padrão dos quatro pontos amostrais medidos no Rio Paraibuna de junho de 2017 a setembro de 2018.

Um baixo risco ambiental foi encontrado para 23 compostos (Figura 14). O risco moderado foi encontrado para metformina, oxazepam, triclosan e tramadol. Nenhum composto apresentou alto risco para o ambiente, somente quando uma avaliação de risco que leva em consideração um efeito comportamental foi considerada (Figura 14). Como os compostos não são encontrados isolados no ambiente, somando os riscos, a mistura dos contaminantes de preocupação emergente encontrados no Rio Paraibuna apresentaria um risco moderado (Figura 14).

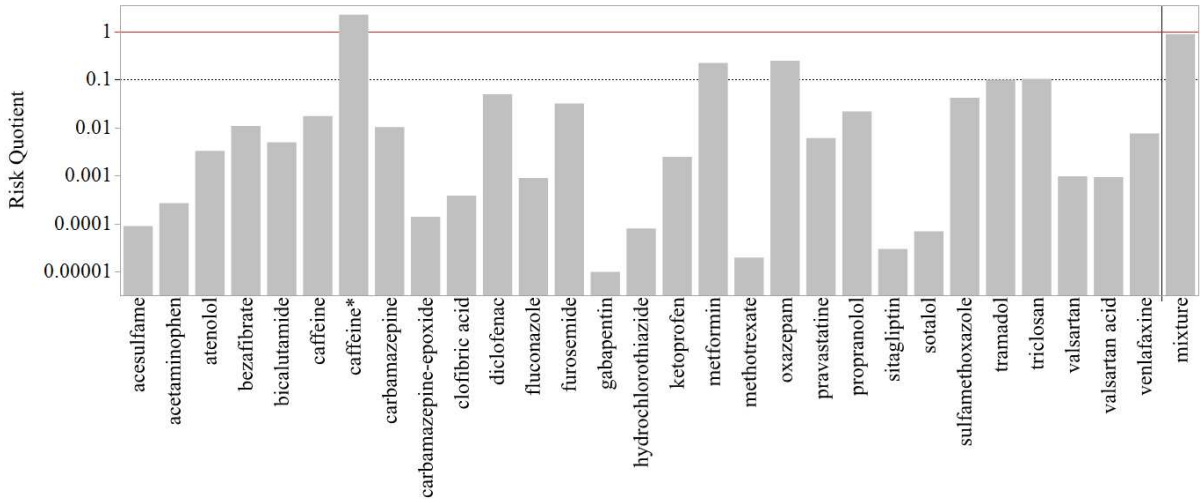

Figura 14. Resultados da avaliação de risco. Valores acima ou igual a linha pontilhada representam um risco moderado (0,1), enquanto valores iguais ou acima da linha vermelha (1) representam um alto risco para o ecossistema aquático. O asterisco representa uma avaliação de risco calculada com base em um PNEC considerando efeitos comportamentais.

4.3 Concentrações de contaminantes de preocupação emergente em reservatórios brasileiros

Dos 28 compostos investigados, oito foram encontrados em pelo menos uma amostra dos reservatórios, sendo que as medidas variaram de 62–576 ng L^{-1} para acesulfame, 16–32 ng L^{-1} para atenolol, 23–463 ng L^{-1} para cafeína, 10–22 ng L^{-1} para carbamazepina, 10–26 ng L^{-1} para gabapentina, 325–2.192 ng L^{-1} para metformina, 27–63 ng L^{-1} para valsartana e 12–33 ng L^{-1} para o ácido valsartana (Tabela 9, Tabela 10).

Tabela 9. Resumo dos resultados da quantificação de contaminantes de preocupação emergente dos reservatórios de Chapéu D'Uvas (CDU), Curuá-Una (CUN), Funil (FUN) e Simplício (SIM). ND = Não detectado.

Ingrediente ativo	Detecção (%)				Máx. (ng L^{-1})			
	CDU	CUN	FUN	SIM	CDU	CUN	FUN	SIM
acesulfame	0	0	100	100	ND	ND	576	362
acetaminofeno	0	0	0	0	ND	ND	ND	ND
atenolol	0	0	14	100	ND	ND	32	31
bezafibrato	0	0	0	0	ND	ND	ND	ND
bicalutamida	0	0	0	0	ND	ND	ND	ND
cafeína	100	100	100	100	160	136	463	113
carbamazepina	0	0	71	100	ND	ND	22	18
carbamazepina-epoxide	0	0	0	0	ND	ND	ND	ND
ácido clofibrico	0	0	0	0	ND	ND	ND	ND
diclofenaco	0	0	0	0	ND	ND	ND	ND
fluconazol	0	0	0	0	ND	ND	ND	ND
furosemida	0	0	0	0	ND	ND	ND	ND
gabapentina	0	0	71	100	ND	ND	20	26
hidroclorotiazida	0	0	0	0	ND	ND	ND	ND
ketoprofeno	0	0	0	0	ND	ND	ND	ND
metformina	0	0	100	100	ND	ND	2192	1724
metotrexato	0	0	0	0	ND	ND	ND	ND
oxazepam	0	0	0	0	ND	ND	ND	ND
pravastatina	0	0	0	0	ND	ND	ND	ND
propranolol	0	0	0	0	ND	ND	ND	ND
sitagliptina	0	0	0	0	ND	ND	ND	ND
sotalol	0	0	0	0	ND	ND	ND	ND
sulfametoxazol	0	0	0	0	ND	ND	ND	ND
tramadol	0	0	0	0	ND	ND	ND	ND
triclosan	0	0	0	0	ND	ND	ND	ND
valsartana	0	0	14	100	ND	ND	63	43
ácido valsartana	0	0	100	100	ND	ND	33	22
venlafaxina	0	0	0	0	ND	ND	ND	ND

Tabela 10. Resultados das concentrações de contaminantes de preocupação emergente (ng L^{-1}) e parâmetros físico-químicos nos reservatórios investigados. ND = Não detectado. (Continua)

Reservatórios	**Chapéu D'Uvas**					**Curuá-Una**			
Contaminantes	**CDU1**	**CDU2**	**CDU3**	**CDU4**	**CDU5**	**CUN1**	**CUN2**	**CUN3**	**CUN4**
acesulfame	ND	ND	ND	ND	ND	ND	ND	ND	ND
acetaminofeno	ND	ND	ND	ND	ND	ND	ND	ND	ND
atenolol	ND	ND	ND	ND	ND	ND	ND	ND	ND
bezafibrato	ND	ND	ND	ND	ND	ND	ND	ND	ND
bicalutamida	ND	ND	ND	ND	ND	ND	ND	ND	ND
cafeína	60	53	77	160	61	136	50	35	48
carbamazepina	ND	ND	ND	ND	ND	ND	ND	ND	ND
carbamazepina-epoxide	ND	ND	ND	ND	ND	ND	ND	ND	ND
ácido clofibrico	ND	ND	ND	ND	ND	ND	ND	ND	ND
diclofenaco	ND	ND	ND	ND	ND	ND	ND	ND	ND
fluconazol	ND	ND	ND	ND	ND	ND	ND	ND	ND
furosemida	ND	ND	ND	ND	ND	ND	ND	ND	ND
gabapentina	ND	ND	ND	ND	ND	ND	ND	ND	ND
hidroclorotiazida	ND	ND	ND	ND	ND	ND	ND	ND	ND
ketoprofeno	ND	ND	ND	ND	ND	ND	ND	ND	ND
metformina	ND	ND	ND	ND	ND	ND	ND	ND	ND
metotrexato	ND	ND	ND	ND	ND	ND	ND	ND	ND
oxazepam	ND	ND	ND	ND	ND	ND	ND	ND	ND
pravastatina	ND	ND	ND	ND	ND	ND	ND	ND	ND
propranolol	ND	ND	ND	ND	ND	ND	ND	ND	ND
sitagliptina	ND	ND	ND	ND	ND	ND	ND	ND	ND
sotalol	ND	ND	ND	ND	ND	ND	ND	ND	ND
sulfametoxazol	ND	ND	ND	ND	ND	ND	ND	ND	ND
tramadol	ND	ND	ND	ND	ND	ND	ND	ND	ND
triclosan	ND	ND	ND	ND	ND	ND	ND	ND	ND

Reservatórios	Chapéu D'Uvas					Curuá-Una			
Contaminantes	**CDU1**	**CDU2**	**CDU3**	**CDU4**	**CDU5**	**CUN1**	**CUN2**	**CUN3**	**CUN4**
valsartana	ND	ND	ND	ND	ND	ND	ND	ND	ND
ácido valsartana	ND	ND	ND	ND	ND	ND	ND	ND	ND
venlafaxina	ND	ND	ND	ND	ND	ND	ND	ND	ND
condutividade (µs cm^{-1})	13,0	13,0	12,0	12,0	13,0	12,0	17,0	6,0	6,0
pH	8,4	8,2	8,0	8,0	8,0	6,7	6,7	5,3	5,5
temperatura (°C)	24,3	25,3	25,8	25,1	25,2	31,4	21,2	32,4	30,1
turbidez (NTU)	9,7	1,7	0,3	0,2	2,8	7,1	17,3	70,7	6,5
profundidade (m)	11,7	17,0	21,0	21,7	27,5	10,0	7,2	12,7	7,9

Tabela 10. (Continuação) Resultados das concentrações de contaminantes de preocupação emergente (ng L^{-1}) e parâmetros físico-químicos nos reservatórios investigados. ND = Não detectado.

Reservatórios	Funil							Simplício			
Contaminantes	**FUN1**	**FUN2**	**FUN3**	**FUN4**	**FUN5**	**FUN6**	**FUN7**	**SIM1**	**SIM2**	**SIM3**	**SIM4**
acesulfame	576	125	147	62	137	71	95	297	253	191	362
acetaminofeno	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
atenolol	32	ND	ND	ND	ND	ND	ND	31	29	16	29
bezafibrato	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
bicalutamida	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
cafeína	463	39	23	50	36	117	47	50	32	113	88
carbamazepina	22	10	15	ND	14	ND	11	17	18	10	17
carbamazepina-epoxide	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
ácido clofíbrico	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
diclofenaco	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
fluconazol	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
furosemida	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Reservatórios	Funil							Simplício			
Contaminantes	**FUN1**	**FUN2**	**FUN3**	**FUN4**	**FUN5**	**FUN6**	**FUN7**	**SIM1**	**SIM2**	**SIM3**	**SIM4**
gabapentina	20	ND	12	ND	14	13	10	26	20	18	23
hidroclorotiazida	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
ketoprofeno	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
metformina	2192	325	741	367	661	389	444	1593	1318	1210	1724
metotrexato	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
oxazepam	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
pravastatina	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
propranolol	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
sitagliptina	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
sotalol	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
sulfametoxazol	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
tramadol	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
triclosan	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
valsartana	63	ND	ND	ND	ND	ND	ND	35	27	32	43
ácido valsartana	15	23	33	12	27	17	22	20	22	14	22
venlafaxina	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
condutividade (µs cm^{-1})	89,0	99,0	113,0	102,0	110,0	106,0	113,0	93,0	91,0	90,0	88,0
pH	7,5	8,4	8,2	8,8	8,9	8,5	8,4	9,0	8,9	8,5	8,5
temperatura (°C)	20,0	23,2	23,9	24,3	24,1	23,3	23,7	19,2	22,4	23,1	23,0
turbidez (NTU)	13,7	4,3	6,8	2,1	0,0	4,8	5,1	2,2	1,1	3,3	3,8
profundidade (m)	6,8	29,4	41,7	12,6	51,8	23,9	42,7	60,5	22,0	11,8	1,5

A maioria dos compostos apresentou as maiores concentrações no reservatório de Simplício, no estado do Rio de Janeiro, somente as concentrações de cafeína e ácido valsartana foram maiores no reservatório de Funil, que é localizado antes do reservatório de Simplício no mesmo estado (Figura 15). As maiores concentrações encontradas foram da metformina em Funil (2.192 ng L^{-1}) e Simplício (1.724 ng L^{-1}), sendo que nos reservatórios com menor influência humana, Chapéu D'Uvas e Curuá-Una, somente a cafeína foi detectada, com o máximo de 160 ng L^{-1} em CDU e 136 ng L^{-1} em CUN (Tabela 10). Dessa forma, FUN e SIM apresentaram oito compostos detectados em suas águas, enquanto CDU e CUN somente a cafeína.

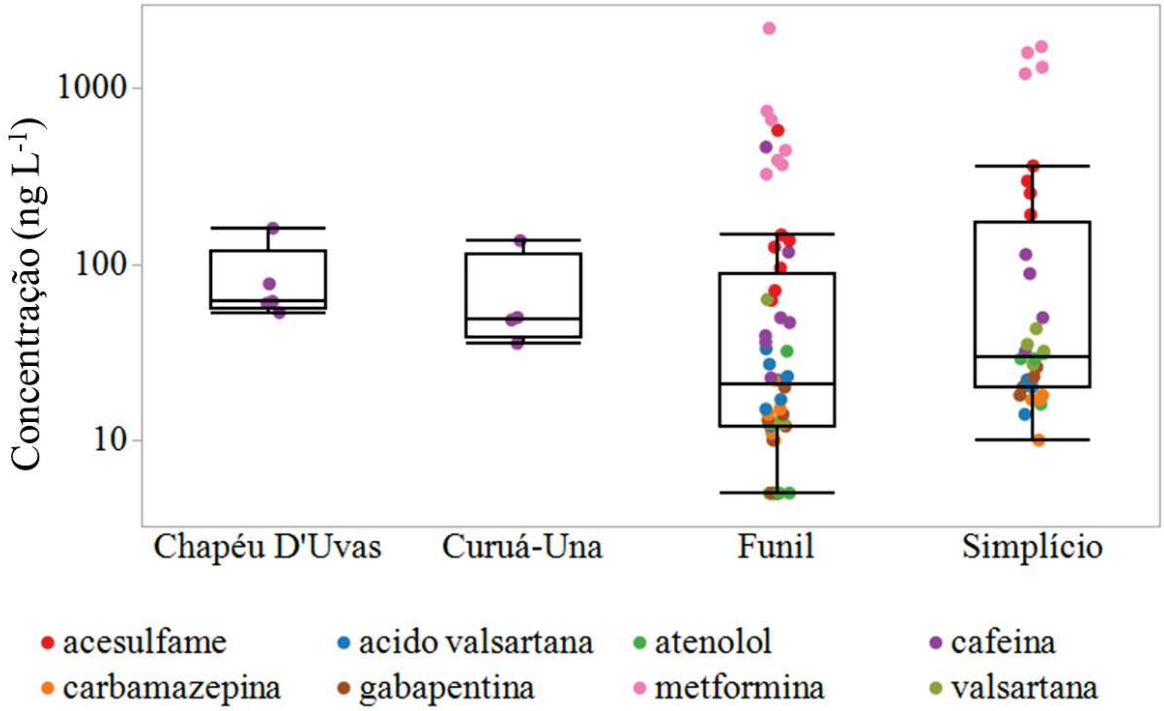

Figura 15. Concentrações dos contaminantes de preocupação emergente (ng L^{-1}) investigados nos reservatórios. As caixas foram definidas pelos quartis e as linhas representam a mediana dos compostos. As linhas representam os valores mínimos ou LQ e os máximos encontrados.

As concentrações dos contaminantes de preocupação emergente foram estatisticamente diferentes entre os reservatórios ($p < 0,0001$), demonstrando diferenças entre os reservatórios de FUN e SIM ($p = 0,0299$), mas semelhança entre CUN e CDU ($p = 0,9427$) (Figura 16). As diferenças encontradas entre FUN e SIM foram principalmente relacionadas as concentrações de atenolol ($p = 0,0496$) e gabapentina ($p = 0,0227$).

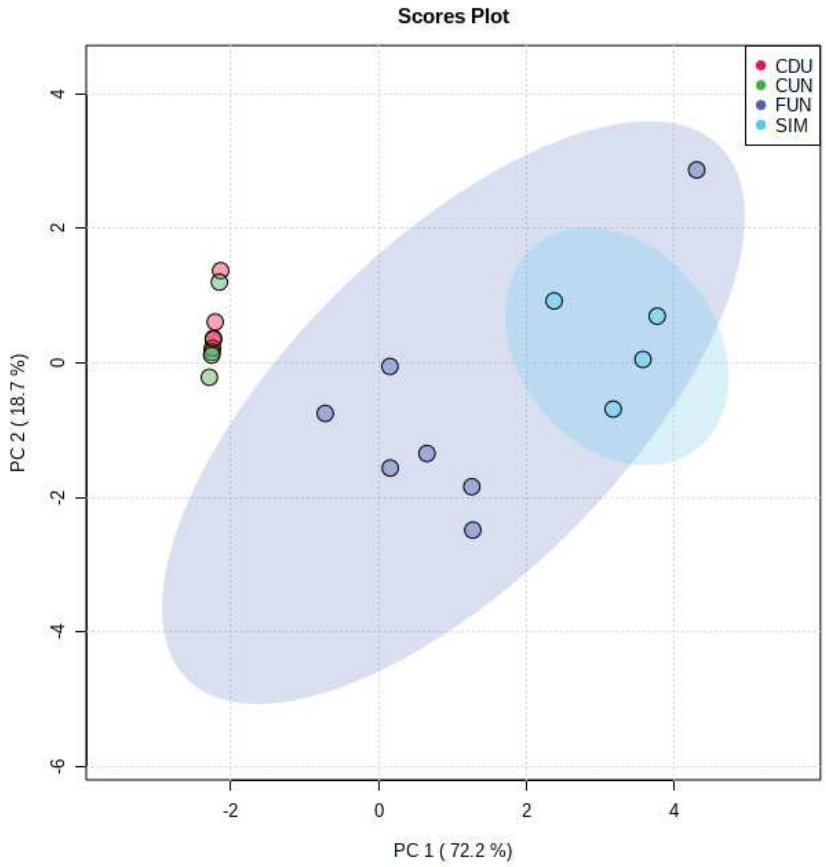

Figura 16. Análise dos compostos principais investigando a variação espacial dos contaminantes de preocupação emergente nos reservatórios investigados. CDU = Chapéu D'Uvas; CUN = Curuá-Una; FUN = Funil; SIM = Simplício.

Dentre os parâmetros físico-químicos investigados, a condutividade apresentou a maior variação entre os reservatórios, com maiores valores em FUN (104,6 ± 8,1 µs cm^{-1}, média ± DP) e SIM (90,5 ± 1,8 µs cm^{-1}) do que em CDU (12,6 ± 0,5 µs cm^{-1}) e CUN (10,3 ± 4.6 µs cm^{-1}) (Figura 17).

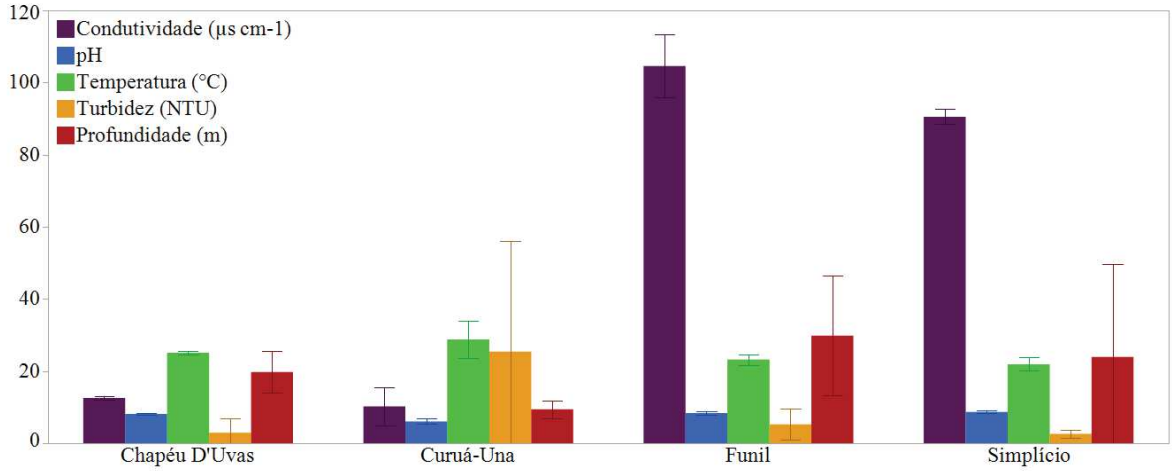

Figura 17. Parâmetros físico-químicos representados em média e desvio padrão nos reservatórios investigados.

A análise não alvo identificou mais 116 químicos além dos 10 detectados pelas análises alvo, ou seja, foram encontrados um total de 126 químicos (Tabela 11, Tabela 12). Esta abordagem confirmou que CDU e CUN são menos poluídos em termos de químicos do que FUN e SIM, uma vez que muitos químicos ficaram baixo do LQ artificial nos dois primeiros reservatórios. O perfil de contaminação foi bem semelhante ao estudo prévio do Rio Paraibuna (item 4.2), onde a maioria dos compostos foram fármacos, mas também produtos industriais, agrícolas, metabólitos e produtos naturais.

Tabela 11. Lista de compostos identificados pela análise não alvo com respectivos tempos de retenção (TR) e pontuação de combinação na biblioteca online (mzCloud).

ESI modo	Nome como na mzCloud	Aplicação	Fórmula	Peso molecular	TR [min]	mzCloud pontuação
ESI-	1-(Carboxymethyl)cyclohexanecarboxylic acid	Fármacos: Produtos de transformação	$C_9 H_{14} O_4$	186	4	86
ESI+	1-Methylbenzotriazole	Industrial	$C_7 H_7 N_3$	133	3	98
ESI+	1,1-Dimethyl-2-oxopropyl N-[2-(2-pyridyl)ethyl]carbamate	Fármacos	$C_{13} H_{18} N_2 O_3$	250	2	75
ESI+	1,3-di-o-Tolylguanidine	Fármacos	$C_{15} H_{17} N_3$	239	4	95
ESI+	10,11-Dihydro-10,11-dihydroxycarbamazepine	Fármacos: Produtos de transformação	$C_{15} H_{14} N_2 O_3$	270	3	86
ESI+	12-Aminododecanoic acid	Produtos naturais / Metabólitos humanos	$C_{12} H_{25} N O_2$	215	5	84
ESI+	16,16-Dimethyl prostaglandin A2	Produtos naturais / Metabólitos humanos	$C_{22} H_{34} O_4$	384	1	78
ESI+	2-Amino-1,3,4-octadecanetriol	Metabólitos humanos / Cosméticos	$C_{18} H_{39} N O_3$	317	7	83
ESI+	2-Methyl-4-isothiazolin-3-one	Industrial	$C_4 H_5 N O S$	115	1	86
ESI-	2-Naphthalenesulfonic acid	Industrial	$C_{10} H_8 O_3 S$	208	3	86
ESI+	2,2,6,6-Tetramethyl-4-piperidinol	Industrial	$C_9 H_{19} N O$	157	1	85
ESI+	2,3,4,9-Tetrahydro-1H-β-carboline-3-carboxylic acid	Produtos naturais / Metabólitos humanos	$C_{12} H_{12} N_2 O_2$	216	2	80
ESI+	2,4-Dimethylbenzaldehyde	Aditivos de alimentos	$C_9 H_{10} O$	134	4	91
ESI+	2'-Deoxyadenosine	Produtos naturais / Metabólitos humanos	$C_{10} H_{13} N_5 O_3$	251	1	96
ESI+	3,4-Dihydroxyphenylpropionic acid	Produtos naturais / Metabólitos humanos	$C_9 H_{10} O_4$	164	1	88
ESI+	4-Aminophenol	Industrial	$C_6 H_7 N O$	109	2	78
ESI-	4-Dodecylbenzenesulfonic acid	Industrial	$C_{18} H_{30} O_3 S$	326	8	87
ESI+	4-Guanidinobutyric acid	Produtos naturais / Metabólitos humanos	$C_5 H_{11} N_3 O_2$	145	1	97

ESI modo	Nome como na mzCloud	Aplicação	Fórmula	Peso molecular	TR [min]	mzCloud pontuação
ESI-	4-Hydroxybenzaldehyde	Aditivos de alimentos	$C_7 H_6 O_2$	122	4	78
ESI-	4-Hydroxybenzophenone	Fármacos	$C_{13} H_{10} O_2$	198	6	82
ESI+	4-Hydroxyephedrine	Fármacos: Produtos de transformação	$C_{10} H_{15} N O_2$	163	4	81
ESI-	4-Nitrophenol	Industrial	$C_6 H_5 N O_3$	139	4	84
ESI-	4-Oxoproline	Metabólitos humanos	$C_5 H_7 N O_3$	129	1	82
ESI+	6-Methylnicotinamide	Produtos naturais	$C_7 H_8 N_2 O$	114	1	81
ESI+	AB-CHMICA	Drogas de abuso	$C_{21} H_{29} N_3 O_2$	377	3	82
ESI-	Acesulfame	Aditivos de alimentos	$C_4 H_5 N O_4 S$	163	1	94
ESI+	Acetophenone	Industrial	$C_8 H_8 O$	120	4	83
ESI+	Acridine	Industrial	$C_{13} H_9 N$	179	3	76
ESI+	Adenine	Produtos naturais / Metabólitos humanos	$C_5 H_5 N_5$	135	1	76
ESI+	Adenosine	Produtos naturais / Metabólitos humanos	$C_{10} H_{13} N_5 O_4$	267	1	93
ESI-	Adipic acid	Industrial	$C_6 H_{10} O_4$	146	2	92
ESI+	Amfepramone	Fármacos	$C_{13} H_{19} N O$	205	7	77
ESI+	Aniline	Industrial	$C_6 H_7 N$	93	1	93
ESI+	Asparagine	Produtos naturais / Metabólitos humanos	$C_4 H_8 N_2 O_3$	132	1	94
ESI+	Atenolol	Fármacos	$C_{14} H_{22} N_2 O_3$	266	2	97
ESI+	Atenolol acid	Fármacos: Produtos de transformação	$C_{14} H_{21} N O_4$	267	2	95
ESI-	Azelaic acid	Aditivos de alimentos / Fármacos / Produtos naturais / Metabólitos humanos / Cosméticos	$C_9 H_{16} O_4$	188	4	84
ESI-	Bentazone	Agricultura	$C_{10} H_{12} N_2 O_3 S$	240	5	94
ESI-	Benzoic acid	Agricultura / Aditivos de alimentos / Fármacos / Cosméticos	$C_7 H_6 O_2$	122	3	78
ESI+	Benzotriazole	Fármacos / Cosméticos / Industrial	$C_6 H_5 N_3$	119	3	100

ESI modo	Nome como na mzCloud	Aplicação	Fórmula	Peso molecular	TR [min]	mzCloud pontuação
ESI+	Benzoylecgonine	Drogas de abuso	$C_{16}H_{19}NO_4$	289	3	93
ESI+	Betaine	Aditivos de alimentos / Fármacos	$C_5H_{11}NO_2$	117	1	92
ESI+	Bis(2-butoxyethyl) ether	Industrial	$C_{12}H_{26}O_3$	218	7	82
ESI+	Caffeine	Fármacos / Cosméticos / Aditivos de alimentos / Produtos naturais	$C_8H_{10}N_4O_2$	194	3	97
ESI+	Caprolactam	Industrial / Aditivos de alimentos	$C_6H_{11}NO$	113	2	97
ESI+	Carbamazepine	Fármacos	$C_{15}H_{12}N_2O$	236	5	97
ESI-	Citric acid	Fármacos / Cosméticos / Aditivos de alimentos / Produtos naturais	$C_6H_8O_7$	192	1	79
ESI+	Clarithromycin	Fármacos	$C_{38}H_{69}NO_{13}$	747	6	98
ESI+	Creatine	Fármacos / Produtos naturais / Metabólitos humanos	$C_4H_9N_3O_2$	131	1	75
ESI+	Crotonic acid	Aditivos de alimentos / Cosméticos / Produtos naturais / Metabólitos humanos	$C_4H_6O_2$	86	5	96
ESI+	Cytosine	Produtos naturais / Metabólitos humanos	$C_4H_5N_3O$	111	1	93
ESI+	D-(-)-Glutamine	Fármacos	$C_5H_{10}N_2O_3$	146	1	93
ESI+	D-(+)-Maltose	Cosméticos	$C_{12}H_{22}O_{11}$	364	1	95
ESI+	D-(+)-Proline	Fármacos / Cosméticos	$C_5H_9NO_2$	115	1	97
ESI+	D-Carnitine	Produtos naturais / Metabólitos humanos	$C_7H_{15}NO_3$	161	1	94
ESI+	D-Panthenol	Fármacos / Cosméticos	$C_9H_{19}NO_4$	205	4	98
ESI+	Decanamide	Produtos naturais / Metabólitos humanos	$C_{10}H_{21}NO$	171	7	90
ESI+	DEET	Agricultura	$C_{12}H_{17}NO$	191	6	98
ESI+	Diclofenac	Fármacos	$C_{14}H_{11}Cl_2NO_2$	295	7	99
ESI+	Diethanolamine	Industrial	$C_4H_{11}NO_2$	105	1	94
ESI+	Diethyl phthalate	Industrial / Cosméticos	$C_{12}H_{14}O_4$	222	6	84
ESI-	Dinoterb	Agriculturas	$C_{10}H_{12}N_2O_5$	240	7	84

ESI modo	Nome como na mzCloud	Aplicação	Fórmula	Peso molecular	TR [min]	mzCloud pontuação
ESI+	DL-Arginine	Fármacos / Cosméticos	$C_6 H_{14} N_4 O_2$	174	1	97
ESI-	DL-Lactic Acid	Aditivos de alimentos / Agricultura / Cosméticos	$C_3 H_6 O_3$	90	1	95
ESI+	DL-Lysine	Aditivos de alimentos	$C_6 H_{14} N_2 O_2$	146	1	97
ESI+	DL-Stachydrine	Produtos naturais / Metabólitos humanos	$C_7 H_{13} N O_2$	143	2	80
ESI+	DL-Tryptophan	Fármacos / Cosméticos	$C_{11} H_{12} N_2 O_2$	204	2	92
ESI-	Fumaric acid	Aditivos de alimentos / Fármacos / Industrial	$C_4 H_4 O_4$	116	1	98
ESI+	Gabapentin	Fármacos	$C_9 H_{17} N O_2$	171	2	92
ESI+	Guanine	Produtos naturais / Metabólitos humanos	$C_5 H_5 N_5 O$	151	1	89
ESI+	Guanylurea	Fármacos: Produtos de transformação	$C_2 H_6 N_4 O$	102	1	87
ESI+	Hypoxanthine	Fármacos / Metabólitos humanos	$C_5 H_4 N_4 O$	136	1	97
ESI+	Imazapic	Agricultura	$C_{14} H_{17} N_3 O_3$	275	3	93
ESI+	Indole-3-acrylic acid	Fármacos / Metabólitos humanos	$C_{11} H_9 N O_2$	187	2	95
ESI+	Isoamylamine	Aditivos de alimentos	$C_5 H_{13} N$	87	2	96
ESI+	Isoleucine	Aditivos de alimentos / Produtos naturaiss / Metabólitos humanos / Cosméticos	$C_6 H_{13} N O_2$	131	1	87
ESI-	Isorhamnetin	Produtos naturais / Metabólitos humanos	$C_{16} H_{12} O_7$	316	2	76
ESI+	L-(+)-Citrulline	Cosméticos / Fármacos / Produtos naturais / Metabólitos humanos	$C_6 H_{13} N_3 O_3$	175	1	95
ESI-	L-(+)-Lactic acid	Agricultura / Aditivos de alimentos / Fármacos / Cosméticos	$C_3 H_6 O_3$	90	1	96
ESI-	L-(+)-Tartaric acid	Aditivos de alimentos	$C_4 H_6 O_6$	150	1	89
ESI-	L-Aspartic acid	Aditivos de alimentos / Fármacos / Cosméticos	$C_4 H_7 N O_4$	133	1	86

ESI modo	Nome como na mzCloud	Aplicação	Fórmula	Peso molecular	TR [min]	mzCloud pontuação
ESI+	L-Glutamic acid	Aditivos de alimentos / Fármacos / Cosméticos	$C_5 H_9 N O_4$	147	1	95
ESI+	L-Histidine	Aditivos de alimentos / Fármacos / Cosméticos	$C_6 H_9 N_3 O_2$	155	1	87
ESI+	L-Phenylalanine	Aditivos de alimentos / Fármacos / Cosméticos	$C_9 H_{11} N O_2$	165	2	97
ESI+	L-Pyroglutamic acid	Cosméticos	$C_5 H_7 N O_3$	129	1	87
ESI+	L-Serine	Fármacos / Cosméticos	$C_3 H_7 N O_3$	105	1	93
ESI+	L-Threonine	Aditivos de alimentos / Fármacos / Cosméticos	$C_4 H_9 N O_3$	119	1	95
ESI+	L-Tyrosine	Aditivos de alimentos / Fármacos / Cosméticos	$C_9 H_{11} N O_3$	181	1	94
ESI+	Lactamide	Produtos naturais / Metabólitos humanos	$C_3 H_7 N O_2$	89	1	94
ESI+	Laurolactam	Cosméticos	$C_{12} H_{23} N O$	197	5	92
ESI-	Meclofenamic acid	Fármacos	$C_{14} H_{11} Cl_2 N O_2$	295	7	84
ESI+	Melamine	Agricultura	$C_3 H_6 N_6$	126	1	88
ESI+	Memantine	Fármacos	$C_{12} H_{21} N$	179	5	96
ESI+	Metamfepramone	Fármacos / Cosméticos	$C_{11} H_{15} N O$	177	5	79
ESI+	Metformin	Fármacos	$C_4 H_{11} N_5$	129	1	97
ESI+	Methionine sulfoxide	Produtos naturais / Metabólitos humanos	$C_5 H_{11} N O_3 S$	165	1	90
ESI-	Methylmalonic acid	Produtos naturais / Metabólitos humanos	$C_4 H_6 O_4$	118	1	87
ESI+	Mexiletine	Fármacos	$C_{11} H_{17} N O$	179	1	79
ESI-	Monobutyl phthalate	Industrial	$C_{12} H_{14} O_4$	222	5	79
ESI+	Mycophenolic acid	Fármacos	$C_{17} H_{20} O_6$	298	4	82
ESI+	N-Acetyl-L-leucine	Fármacos	$C_8 H_{15} N O_3$	173	1	75
ESI+	N-Cyclohexylidene-2-carbamylcyclohex-1-enylamine	Produtos naturais / Metabólitos humanos	$C_{13} H_{20} N_2 O$	220	2	94

ESI modo	Nome como na mzCloud	Aplicação	Fórmula	Peso molecular	TR [min]	mzCloud pontuação
ESI+	N,N-Diethylethanolamine	Industrial	$C_6 H_{15} N O$	117	1	80
ESI+	Nicotinamide	Produtos naturais / Metabólitos humanos / Fármacos	$C_6 H_6 N_2 O$	122	1	85
ESI+	Ornithine	Cosméticos	$C_5 H_{12} N_2 O_2$	132	1	87
ESI+	Panthenol	Cosméticos	$C_9 H_{19} N O_4$	205	1	81
ESI+	Paracetamol	Fármacos	$C_8 H_9 N O_2$	151	2	95
ESI+	Phenethylamine	Aditivos de alimentos	$C_8 H_{11} N$	121	2	87
ESI-	Pimelic acid	Produtos naturais / Metabólitos humanos	$C_7 H_{12} O_4$	160	2	85
ESI+	Propionylcarnitine	Fármacos	$C_{10} H_{19} N O_4$	217	1	86
ESI+	Pyridoxamine	Produtos naturais / Metabólitos humanos	$C_8 H_{12} N_2 O_2$	168	1	76
ESI-	Pyruvic acid	Produtos naturais / Metabólitos humanos	$C_3 H_4 O_3$	88	1	96
ESI+	Ranitidine	Fármacos	$C_{13} H_{22} N_4 O_3 S$	314	2	96
ESI+	Ricinine	Produtos naturais / Metabólitos humanos	$C_8 H_8 N_2 O_2$	164	2	87
ESI-	Suberic acid	Produtos naturais / Metabólitos humanos	$C_8 H_{14} O_4$	174	3	82
ESI+	Sulfamethoxazole	Fármacos	$C_{10} H_{11} N_3 O_3 S$	253	3	87
ESI+	Tertatolol	Fármacos	$C_{16} H_{25} N O_2 S$	295	1	80
ESI+	Tributyl phosphate	Industrial	$C_{12} H_{27} O_4 P$	266	8	81
ESI+	Triethanolamine	Industrial / Fármacos / Cosméticos	$C_6 H_{15} N O_3$	149	1	95
ESI+	Triisopropanolamine	Cosméticos	$C_9 H_{21} N O_3$	191	1	93
ESI+	Triisopropanolamine cyclic borate	Industrial	$C_9 H_{18} B N O_3$	199	2	92
ESI+	Tris(2-butoxyethyl) phosphate	Industrial	$C_{18} H_{39} O_7 P$	398	8	79
ESI-	Uric acid	Cosméticos / Produtos naturais / Metabólitos humanos	$C_5 H_4 N_4 O_3$	168	1	83
ESI+	Urocanic acid	Produtos naturais / Metabólitos humanos	$C_6 H_6 N_2 O_2$	138	1	96

ESI modo	Nome como na mzCloud	Aplicação	Fórmula	Peso molecular	TR [min]	mzCloud pontuação
ESI+	Valsartan	Fármacos	C_{24} H_{29} N_5 O_3	435	6	94
ESI-	Xanthine	Cosméticos / Produtos naturais / Metabólitos humanos / Fármacos	C_5 H_4 N_4 O_2	152	1	78
ESI-	β-D-Glucopyranuronic acid	Produtos naturais / Metabólitos humanos	C_6 H_{10} O_7	194	1	85

Tabela 12. Resultados da análise não alvo nos reservatórios de Chapéu D'Uvas (CDU), Curuá-Una (CUN), Funil (FUN) e Simplício (SIM). (Continua)

Nome como na mzCloud	CDU1	CDU2	CDU3	CDU4	CDU5	CUN1	CUN2	CUN3	CUN4
1-(Carboxymethyl)cyclohexanecarboxylic acid	28573	18317	14171	20074	15048	24787	26705	36379	38726
1-Methylbenzotriazole	2000	1990	1993	2317	1890	1966	2009	2230	1762
1,1-Dimethyl-2-oxopropyl N-[2-(2-pyridyl)ethyl]carbamate	2379	1925	2519	2510	2213	2642	2531	2071	2201
1,3-di-o-Tolylguanidine	4946	3216	3155	27323	10486	27508	11503	12883	6353
10,11-Dihydro-10,11-dihydroxycarbamazepine	3237	2841	3557	4715	3869	3178	2694	4640	4606
12-Aminododecanoic acid	32249	38438	52588	51917	36766	44438	44794	278051	32461
16,16-Dimethyl prostaglandin A2	31962	33508	31183	33017	30985	29233	28007	18461	33382
2-Amino-1,3,4-octadecanetriol	661	660	669	669	637	649	659	678	663
2-Methyl-4-isothiazolin-3-one	9269	9874	10501	12561	12478	16337	18460	21661	19431
2-Naphthalenesulfonic acid	55666	11432	8134	8991	7907	11419	12650	8649	7048
2,2,6,6-Tetramethyl-4-piperidinol	34682	13879	10278	8565	39089	26410	21186	13969	13829
2,3,4,9-Tetrahydro-1H-β-carboline-3-carboxylic acid	18221	1547	11517	40883	9774	29776	13241	6526	17208
2,4-Dimethylbenzaldehyde	55853	30707	18846	11323	10066	72631	40959	55521	42188
2'-Deoxyadenosine	176904	124880	132096	184450	314757	12793	9632	2722	46675
3,4-Dihydroxyphenylpropionic acid	20658	5958	13277	38464	11682	31461	13415	15903	10067
4-Aminophenol	4821	4830	5022	1330	5155	4710	4196	1235	5481
4-Dodecylbenzenesulfonic acid	175580	138819	135425	219432	121834	91331	88865	184537	94484
4-Guanidinobutyric acid	33183	11137	19027	19480	16585	144551	364364	18847	633450
4-Hydroxybenzaldehyde	10727	14514	10923	9791	10381	10500	11217	9131	17726
4-Hydroxybenzophenone	82804	91544	85091	83895	84912	83050	86028	90864	79009
4-Hydroxyephedrine	1228	1442	1128	1188	1304	3753	1745	1422	1435
4-Nitrophenol	244417	158064	222073	230140	290217	18251	8313	17022	11026
4-Oxoproline	707510	300889	697349	1111089	485005	524645	504098	368584	202772
6-Methylnicotinamide	50186	34770	32025	91795	32985	38210	29255	42355	34639
AB-CHMICA	2717	1998	2089	3799	2394	1865	2041	944	928
Acesulfame	800	774	775	788	800	942	918	829	1078

Nome como na mzCloud	CDU1	CDU2	CDU3	CDU4	CDU5	CUN1	CUN2	CUN3	CUN4
Acetophenone	4327	3227	3544	5364	3173	6805	5007	5466	3955
Acridine	8704	2167	2462	2776	3002	3528	1471	3426	3325
Adenine	1644	1452	1632	1446	62872	3413	96912	806	3403
Adenosine	80526	48135	65783	115583	191489	8357	6421	11290	13773
Adipic acid	48943	51477	55627	43548	47126	81533	59070	58555	45695
Amfepramone	99738	83512	81560	93714	78294	71820	66527	341101	111553
Aniline	19640	24755	36418	50303	14798	4527	1548	3615	2181
Asparagine	46446	17801	32475	44555	35790	19987	7388	15154	10479
Atenolol	2291	2303	2282	2317	2276	2244	2113	2152	2261
Atenolol acid	9949	8082	9302	10260	9302	8467	9054	3818	4095
Azelaic acid	440270	407387	419250	437207	490767	490183	544586	466801	327904
Bentazone	312	298	305	316	315	337	461	326	353
Benzoic acid	20885	8502	15399	14749	10100	47275	31871	13790	49432
Benzotriazole	1400	3016	1444	1537	1486	2096	1259	3145	3059
Benzoylecgonine	4040	5676	4374	3613	4700	3134	998	3827	3799
Betaine	97151	77285	91794	104237	73343	145000	54005	33918	137250
Bis(2-butoxyethyl) ether	20117	19266	17857	17088	16958	19617	20365	20328	20974
Caffeine	7946	3259	9594	24768	5328	9514	5201	2558	2854
Caprolactam	1020438	863811	627464	653048	889504	1237659	800055	1429411	1019394
Carbamazepine	3038	3103	3201	3210	3157	3124	3035	3246	2982
Citric acid	30792	16390	23183	20264	33220	37406	15109	11026	45203
Clarithromycin	1822	2199	2464	4518	663	956	652	6544	645
Creatine	65957	29232	63513	66133	50170	56108	43114	34347	42754
Crotonic acid	241500	213590	208763	158783	193358	249414	171456	297987	300229
Cytosine	163074	124032	139364	175250	197870	174339	65313	1754	170850
D-(-)-Glutamine	54588	26225	57264	193960	219631	132296	27270	72968	48834
D-(+)-Maltose	25317	26248	25992	108264	26473	27565	18456	18208	30778
D-(+)-Proline	479088	89003	297413	835817	207315	354775	111700	232728	110579

Nome como na mzCloud	CDU1	CDU2	CDU3	CDU4	CDU5	CUN1	CUN2	CUN3	CUN4
D-Carnitine	15136	7495	12437	15503	13280	71287	43080	74497	61886
D-Panthenol	15551	10331	20607	5530	12390	6570	14603	23621	6399
Decanamide	31790	13447	10085	11018	10218	26153	34992	35889	39563
DEET	153878	120453	2751769	149982	160924	626526	841837	219888	213159
Diclofenac	10197	11641	11023	12395	11807	12766	12928	13666	10979
Diethanolamine	41868	20529	20659	21789	69786	44880	31324	32503	36461
Diethyl phthalate	291964	313650	221375	282435	237162	528782	350865	254378	266239
Dinoterb	42922	43556	42693	23599	40797	23148	46718	50583	47075
DL-Arginine	111608	23130	79874	125218	102680	319852	8081	1238	157772
DL-Lactic Acid	63956	109936	111123	815969	42758	82580	74366	112139	46236
DL-Lysine	26702	27684	27413	27965	27920	22026	19551	15026	32461
DL-Stachydrine	3340	2377	1219	2429	3261	2386	2570	2668	1173
DL-Tryptophan	9095	6168	4070	13634	9246	26116	6131	11885	5417
Fumaric acid	52962	12461	18031	13638	15448	26254	23082	33032	33309
Gabapentin	3431	2849	3293	3572	3163	3502	3583	2048	2122
Guanine	286488	83291	84222	135375	95047	368074	124887	53132	181704
Guanylurea	11631	12515	11549	11269	11573	10919	10461	6895	12421
Hypoxanthine	32585	17697	31480	42388	35866	129224	54605	28308	101194
Imazapic	775	743	761	774	715	716	729	744	735
Indole-3-acrylic acid	5068	4943	3064	8267	5331	18350	3780	5959	3926
Isoamylamine	994	999	1029	1073	1061	2144	1599	1734	2578
Isoleucine	490967	162106	364510	772047	377047	839351	327093	357545	427421
Isorhamnetin	392	377	406	369	393	507	787	400	440
L-(+)-Citrulline	150978	31161	54277	256600	77845	122826	22798	31198	23775
L-(+)-Lactic acid	669094	306319	476470	1790391	382232	723446	733197	626307	653745
L-(+)-Tartaric acid	6525	3253	6017	3252	5045	4856	3687	5322	5509
L-Aspartic acid	54890	34308	75551	118875	66215	84103	48964	42505	32861
L-Glutamic acid	279059	115258	311996	453646	537763	192224	86814	64370	127383

Nome como na mzCloud	CDU1	CDU2	CDU3	CDU4	CDU5	CUN1	CUN2	CUN3	CUN4
L-Histidine	21063	22664	21891	22332	22296	25079	19226	36399	23867
L-Phenylalanine	186141	68728	151312	330216	150016	344197	127168	144792	145302
L-Pyroglutamic acid	287667	97356	192552	445289	132663	231977	178217	188770	95154
L-Serine	573696	167960	376460	977497	482987	270412	130196	221188	96276
L-Threonine	366480	59156	268941	505865	140965	129673	67515	62531	62486
L-Tyrosine	118221	42717	87094	224670	84910	191072	93778	106555	72093
Lactamide	198282	50050	121405	296953	121184	96738	45079	49658	63957
Laurolactam	17131	16465	25018	12477	9793	24546	25141	18812	11864
Meclofenamic acid	10666	13228	12798	12932	13280	12643	13153	13279	9849
Melamine	23228	8366	12979	19402	49696	44026	15668	12798	15991
Memantine	6930	8058	13037	6016	5353	12348	14376	8869	5944
Metamfepramone	8516	688	655	7421	679	7954	9898	643	9063
Metformin	26451	12158	20205	19731	20144	2544	2599	1993	3384
Methionine sulfoxide	54551	18350	41012	104887	48432	63276	17808	11528	26419
Methylmalonic acid	2038	2301	1992	2142	2545	1850	1818	1553	2540
Mexiletine	1398	1371	1451	1443	1639	1296	1325	1278	1399
Monobutyl phthalate	4590	3794	3912	3630	4026	8595	2814	3018	3278
Mycophenolic acid	215998	106117	68341	41304	39463	322698	156685	201643	217489
N-Acetyl-L-leucine	33740	5212	12318	7392	8132	9984	7254	9821	11535
N-Cyclohexylidene-2-carbamylcyclohex-1-enylamine	899	807	783	822	814	1133	839	738	726
N,N-Diethylethanolamine	236516	266328	48070	42226	290059	485810	124982	155643	137104
Nicotinamide	8956	3804	4734	8818	12251	4417	2886	5808	1514
Ornithine	41640	43171	42749	47137	43540	33994	30355	47087	49830
Panthenol	3251	1694	3231	1753	8515	3116	1922	2556	1893
Paracetamol	7421	7637	2547	7544	7198	6813	6588	2401	7796
Phenethylamine	56202	53721	3054	3043	55258	61331	57315	56550	54290
Pimelic acid	21971	27583	26762	16782	30430	39070	28202	31565	21288
Propionylcarnitine	15965	16737	15444	16331	15341	14602	13989	9221	16674

Nome como na mzCloud	CDU1	CDU2	CDU3	CDU4	CDU5	CUN1	CUN2	CUN3	CUN4
Pyridoxamine	6871	1190	1351	1633	3425	1361	6673	1319	13406
Pyruvic acid	5526	6872	4715	3440	6735	4433	3801	11997	5212
Ranitidine	6800	5503	7201	7175	6324	7551	7235	5919	6292
Ricinine	1046	721	824	712	847	759	1085	1056	658
Suberic acid	174574	164649	165025	163274	164825	195441	182136	198315	123225
Sulfamethoxazole	3742	4905	4229	3110	3559	3793	3904	3538	4095
Tertatolol	11500	8626	10805	11763	11050	6763	7917	2483	12011
Tributyl phosphate	11720	13500	12867	10745	11163	11232	10385	13912	10842
Triethanolamine	49794	6475	32129	170721	14964	176040	32194	11824	15405
Triisopropanolamine	2559047	1433329	1585958	1259104	5851584	1433871	1487698	3418160	1838444
Triisopropanolamine cyclic borate	24869	84364	18062	25660	125794	21060	86400	67959	10903
Tris(2-butoxyethyl) phosphate	112014	96548	143991	123489	164601	105080	103948	113978	106758
Uric acid	2156	8307	2173	3773	2451	4187	4317	4345	3733
Urocanic acid	1178166	69315	606287	2236809	88550	181470	652710	176040	80405
Valsartan	4040	3769	3962	3912	3636	3547	3535	2954	3349
Xanthine	18652	10907	19495	29940	32490	67264	18580	5011	21861
β-D-Glucopyranuronic acid	19039	10008	21940	15429	18693	11751	13283	11175	30692

Tabela 12. (Continuação) Resultados da análise não alvo nos reservatórios de Chapéu D'Uvas (CDU), Curuá-Una (CUN), Funil (FUN) e Simplício (SIM).

Nome como na mzCloud	FUN1	FUN2	FUN3	FUN4	FUN5	FUN6	FUN7	SIM1	SIM2	SIM3	SIM4
1-(Carboxymethyl)cyclohexanecarboxylic acid	9769	9062	40458	21407	7963	41505	16083	14946	8608	9815	10831
1-Methylbenzotriazole	91372	48853	71252	25504	66965	37371	51111	45749	69274	40886	
1,1-Dimethyl-2-oxopropyl N-[2-(2-pyridyl)ethyl]carbamate	1511	1591	1541	1323	1466	1285	1504	2618	1484	2100	
1,3-di-o-Tolylguanidine	15995	9064	6728	16332	10545	57648	10938	6259	18648	114443	

Nome como na mzCloud	FUN1	FUN2	FUN3	FUN4	FUN5	FUN6	FUN7	SIM1	SIM2	SIM3	SIM4
10,11-Dihydro-10,11-dihydroxycarbamazepine	12020	7068	10718	2869	8114	4534	6923	10127	8610	4889	
12-Aminododecanoic acid	47901	67133	44279	108151	59556	54417	50556	34432	50841	50555	
16,16-Dimethyl prostaglandin A2	20061	21042	22089	24383	22641	23498	21516	24313	22628	25756	
2-Amino-1,3,4-octadecanetriol	658	617	625	634	643	633	606	631	686	642	
2-Methyl-4-isothiazolin-3-one	18996	18440	42181	40262	32448	76320	55234	9787	33528	217611	
2-Naphthalenesulfonic acid	208891	4234	5796	11440	7563	6919	6092	36707	37096	74342	32598
2,2,6,6-Tetramethyl-4-piperidinol	40884	17324	16660	33490	24389	31171	29408	17962	15985	45710	
2,3,4,9-Tetrahydro-1H-β-carboline-3-carboxylic acid	27047	13119	10035	34164	20896	127679	28280	38857	5164	34199	
2,4-Dimethylbenzaldehyde	16244	41835	51961	24752	36071	33017	30660	18775	9465	13580	
2'-Deoxyadenosine	60614	10046	9443	20107	8513	8468	5541	926	1698	33490	
3,4-Dihydroxyphenylpropionic acid	48911	24624	16467	31958	22939	101306	26909	31770	10107	38830	
4-Aminophenol	4733	4393	1314	3583	1324	5222	1321	6919	13277	1317	
4-Dodecylbenzenesulfonic acid	142103	112494	163166	100394	116774	123153	101690	115211	208430	340053	145836
4-Guanidinobutyric acid	265493	98340	87869	60336	88659	142317	69377	238647	143360	262968	
4-Hydroxybenzaldehyde	8018	7381	14037	6237	7345	7636	5790	15311	17672	22933	17638
4-Hydroxybenzophenone	77994	80974	80151	83646	80279	82370	85333	82690	74558	80449	78194
4-Hydroxyephedrine	128764	214524	127007	11829	59425	29831	81477	1446	1265	1208	
4-Nitrophenol	13353	12984	13000	20258	13703	27564	10072	25866	10869	32605	20590
4-Oxoproline	62249	74441	33920	336564	75147	842436	149336	162867	49025	154317	50389
6-Methylnicotinamide	16757	21834	22920	57846	24136	134815	38908	30471	23480	30341	
AB-CHMICA	834	906	896	840	856	909	870	4539	1197	46896	
Acesulfame	122165	25706	28903	10959	33380	11900	24343	31352	43370	32963	66167
Acetophenone	3521	6488	5917	6137	6150	4467	5345	6348	4358	4576	
Acridine	5932	5518	6232	6475	5851	6588	5298	6622	6246	7307	
Adenine	2219	1287	1506	1386	1507	1374	4128	2386	1496	1468	
Adenosine	711830	39384	37128	57694	69412	44075	122169	16186	7850	93216	
Adipic acid	34650	26154	30626	133528	41808	789567	45946	52442	55938	116725	149772

Nome como na mzCloud	FUN1	FUN2	FUN3	FUN4	FUN5	FUN6	FUN7	SIM1	SIM2	SIM3	SIM4
Amfepramone	59583	142858	125608	104319	184189	104318	55394	663	721	675	
Aniline	13443	3206	2111	13345	1758	4955	12888	13139	10083	8801	
Asparagine	3361	2867	5173	9745	4752	6533	4011	6582	3408	1817	
Atenolol	30266	3513	7852	3373	8241	5619	7931	28126	25647	15293	
Atenolol acid	56096	31143	54132	14367	41480	23934	33195	55460	59088	36536	
Azelaic acid	401910	420658	425348	650962	424794	1549618	477397	368695	478803	522148	474699
Bentazone	77452	167560	218094	82697	205270	128560	153797	43068	39292	22700	36313
Benzoic acid	76787	16330	15637	18504	16079	27320	16134	51264	31498	46094	36147
Benzotriazole	40444	16780	24512	11331	22666	13347	19117	10520	7917	6829	
Benzoylecgonine	19613	2652	4973	1733	4959	1962	3722	17975	19701	4939	
Betaine	10797	58311	43150	45386	51802	178038	76360	402896	44216	91490	
Bis(2-butoxyethyl) ether	21656	21276	23527	20093	21120	21140	14931	25902	26442	24277	
Caffeine	71051	2773	4476	5556	2936	17124	5866	4274	1913	9017	
Caprolactam	1408294	1424149	1472135	1481607	1416885	1165247	796039	10412961	10134650	67794516	
Carbamazepine	23379	11509	17752	7213	14763	8270	12925	17717	18949	11572	
Citric acid	359355	243144	153330	53823	93982	86374	74019	70873	42302	96432	41432
Clarithromycin	636	5033	601	625	10469	8553	619	643	16248	869	
Creatine	8900	8895	10896	143953	22575	51987	16643	17885	14315	11822	
Crotonic acid	437041	400016	400216	354380	425969	257905	256274	232089	219565	236400	
Cytosine	147113	89694	2117	2552	2549	1638	1203	2469	4760	157531	
D-(-)-Glutamine	3678	3013	1500	28670	1540	7143	1752	1753	1350	3176	
D-(+)-Maltose	46171	48187	50471	18938	17677	17357	16889	20357	16556	17979	
D-(+)-Proline	34658	17133	11248	232534	28266	257653	36896	21640	10042	36822	
D-Carnitine	15702	14899	64855	21364	16850	54708	12415	49926	63794	92828	
D-Panthenol	14086	35375	28534	14295	7183	7726	10245	2243	2108	2222	
Decanamide	16134	12980	14201	15828	14715	13533	11558	330519	300405	383285	
DEET	133935	134706	209715	118683	206719	232372	143513	494626	141333	1102956	

Nome como na mzCloud	FUN1	FUN2	FUN3	FUN4	FUN5	FUN6	FUN7	SIM1	SIM2	SIM3	SIM4
Diclofenac	11779	13317	12112	9367	12900	8122	11208	12249	10509	12827	
Diethanolamine	373197	22504	60986	84983	59498	176919	79730	361699	275278	190129	
Diethyl phthalate	97346	86956	67313	66646	100254	102361	91982	156866	181128	197955	
Dinoterb	84847	67732	90518	101609	78583	94089	96350	174837	228941	256268	281322
DL-Arginine	1241028	131057	358700	128724	88609	92298	50934	64995	33120	68429	
DL-Lactic Acid	93061	35377	21011	261834	186217	1399316	177288	456803	92499	83782	82459
DL-Lysine	15769	15484	18048	18570	18644	18306	17813	21471	17461	18963	
DL-Stachydrine	2698	3059	2711	3071	2480	1231	2907	3126	2836	3050	
DL-Tryptophan	11126	11532	9197	16085	11102	17945	9274	10469	9014	16163	
Fumaric acid	20512	23829	18854	13669	14870	17889	9859	19045	18356	18345	19612
Gabapentin	11894	2633	5578	2035	8382	3683	4766	8837	10761	6521	
Guanine	25567	10303	11753	14747	17908	33500	13202	19747	23455	54878	
Guanylurea	5861	6038	6860	7512	7151	7215	15644	23941	41485	7837	
Hypoxanthine	78210	24941	13299	41515	23680	79984	22762	47900	21911	105052	
Imazapic	55849	1096	859	738	838	713	952	1358	1193	1024	
Indole-3-acrylic acid	8580	8275	4197	11327	7529	12781	5715	6131	5451	10891	
Isoamylamine	222103	37537	18325	12211	5156	8658	5174	3659	5040	3863	
Isoleucine	1177405	526858	382814	628483	417887	1908655	517606	858631	262968	1088170	
Isorhamnetin	210474	4106	2966	1211	948	1526	1915	10233	5756	20442	13122
L-(+)-Citrulline	18229	11379	19102	51976	18735	33963	16563	10999	14223	10939	
L-(+)-Lactic acid	356980	319176	209196	842258	405376	2361937	657977	807037	375158	642798	458379
L-(+)-Tartaric acid	11031	9361	10894	7326	13197	7849	9098	7726	7610	6791	7899
L-Aspartic acid	28745	17459	14474	40799	15247	122225	16586	17626	9291	25948	10327
L-Glutamic acid	62775	28501	26127	80863	19323	65122	19465	10512	6322	22119	
L-Histidine	11409	12276	12994	14280	13112	13522	11955	14956	12870	14491	
L-Phenylalanine	726806	290496	180387	268362	200178	826299	198992	340588	101500	369238	

Nome como na mzCloud	FUN1	FUN2	FUN3	FUN4	FUN5	FUN6	FUN7	SIM1	SIM2	SIM3	SIM4
L-Pyroglutamic acid	132400	119339	62127	299900	128617	884170	232348	272915	83340	191957	
L-Serine	8008	11243	9752	113292	14521	164859	21795	18116	6093	26671	
L-Threonine	9962	7482	4596	67503	8319	61352	8732	8165	4094	15545	
L-Tyrosine	316826	134004	88142	185194	128346	654824	139621	216000	54449	213763	
Lactamide	31810	18688	12051	59649	11305	87214	18731	15270	8849	33789	
Laurolactam	19675	26784	17674	52823	25004	14910	19069	5144	9560	9799	
Meclofenamic acid	14933	13891	13324	12682	13250	13609	14072	13235	13865	14851	13088
Melamine	261074	165829	393303	295057	479429	721655	1310938	265912	433938	232439	
Memantine	8378	13667	8575	30964	12778	9265	9644	4216	4156	5536	
Metamfepramone	9761	8910	8680	610	8706	628	9357	8757	670	8973	
Metformin	1175652	171369	412168	211209	370586	219166	271492	826284	644291	691771	
Methionine sulfoxide	2003	1603	1361	22181	1397	6460	1072	1186	1132	2284	
Methylmalonic acid	12818	7572	20219	3229	6439	6126	5604	11416	18754	18276	9943
Mexiletine	1521	1342	1583	1413	1404	1729	1329	1350	1339	1450	
Monobutyl phthalate	4437	4314	2927	3989	3479	6415	3808	6485	4420	42826	4967
Mycophenolic acid	119323	189002	251777	105739	185474	139210	170506	58440	45047	52189	
N-Acetyl-L-leucine	10290	9095	10129	4919	7392	6372	6666	4774	6026	3369	
N-Cyclohexylidene-2-carbamylcyclohex-1-enylamine	740	731	758	709	728	699	685	17113	14205	20594	
N,N-Diethylethanolamine	144239	91318	405100	387658	197046	304291	405192	5160	3648	3612	
Nicotinamide	5969	10324	8319	9974	10447	15270	8407	20758	21926	24416	
Ornithine	24591	24147	28146	28959	29074	77516	27778	33482	27230	29571	
Panthenol	3328	2023	353813	49917	2938	1864	2487	2295	2308	2734	
Paracetamol	7319	6483	6357	7480	6272	6683	6915	2652	4746	8901	
Phenethylamine	1465827	1462478	912672	128390	491467	261054	460051	57569	56468	57977	
Pimelic acid	13363	10088	10231	54056	15835	203833	22605	25351	16810	25144	24214
Propionylcarnitine	12129	10510	9357	12179	10950	11737	11326	10915	9938	20925	
Pyridoxamine	30691	10850	9657	6821	14637	9217	10272	1469	1334	19339	

Nome como na mzCloud	FUN1	FUN2	FUN3	FUN4	FUN5	FUN6	FUN7	SIM1	SIM2	SIM3	SIM4
Pyruvic acid	11971	8858	12275	6932	12487	7427	8609	7310	7201	6426	8499
Ranitidine	5088	4547	4579	3782	4433	4790	4299	7484	4241	5654	
Ricinine	18945	8537	10595	10644	8213	4370	5642	33189	27031	15150	
Suberic acid	157356	149122	152860	282704	140891	999782	174239	137094	197161	195406	218878
Sulfamethoxazole	3751	3635	3829	3796	2903	4220	4239	3569	3910	4674	
Tertatolol	7218	7571	7947	8773	8146	8454	7741	11098	8141	9267	
Tributyl phosphate	14613	21258	20979	10609	17232	18485	9071	27772	18815	20665	
Triethanolamine	114552	14760	36654	46764	34859	165119	48609	88500	52084	87525	
Triisopropanolamine	1429324	1679243	5770662	2980455	2486329	1858726	2016667	236429	188831	240978	
Triisopropanolamine cyclic borate	26868	69366	98657	147980	28252	74511	78252	35872	51357	47259	
Tris(2-butoxyethyl) phosphate	101134	116358	70998	100529	145053	84732	105497	114188	101203	93837	
Uric acid	655	1468	1645	3757	20215	24100	10836	51911	3147	6654	1602
Urocanic acid	89397	675093	328336	1707493	165174	5221952	186977	247021	105853	1084009	
Valsartan	9631	3749	4095	3660	3510	3875	4004	6712	5271	5781	
Xanthine	8566	5525	4300	7873	7364	28984	5126	11261	4048	27107	6151
β-D-Glucopyranuronic acid	19732	20339	20600	17547	21132	18262	19954	14807	15501	14471	15282

4.4 Consumo de medicamentos pela população brasileira

Em 2018, aproximadamente 70% da população brasileira era composta por indivíduos com mais de 18 anos de idade (IGBE, 2018), o que resultou em um mínimo tamanho amostral de 421 participantes para representar a população brasileira. No total, tivemos 540 respostas, sendo que a maioria estava localizada na região sudeste brasileira (88,3%), seguido pela região centro-oeste (6,1%), sul (3%), nordeste (1,5%) e norte (1,1%).

Dentre os 26 estados e distrito federal da divisão política brasileira, 19 estados e o distrito foram representados, sendo que os estados Espirito Santo (ES), Maranhão (MA), Mato Grosso (MT), Pará (PA), Piauí (PI), Rondônia (RO) e Roraima (RR) não tiveram representatividade. A faixa etária mais representada foi entre 26 e 40 anos (47,4%) e a menos representada acima de 61 anos (4,1%) (Figura 18). Em relação a escolaridade, participantes com pós-graduação foram os que mais responderam (45,4%) e a menor representação de ensino médio incompleto (0,6%) (Figura 18).

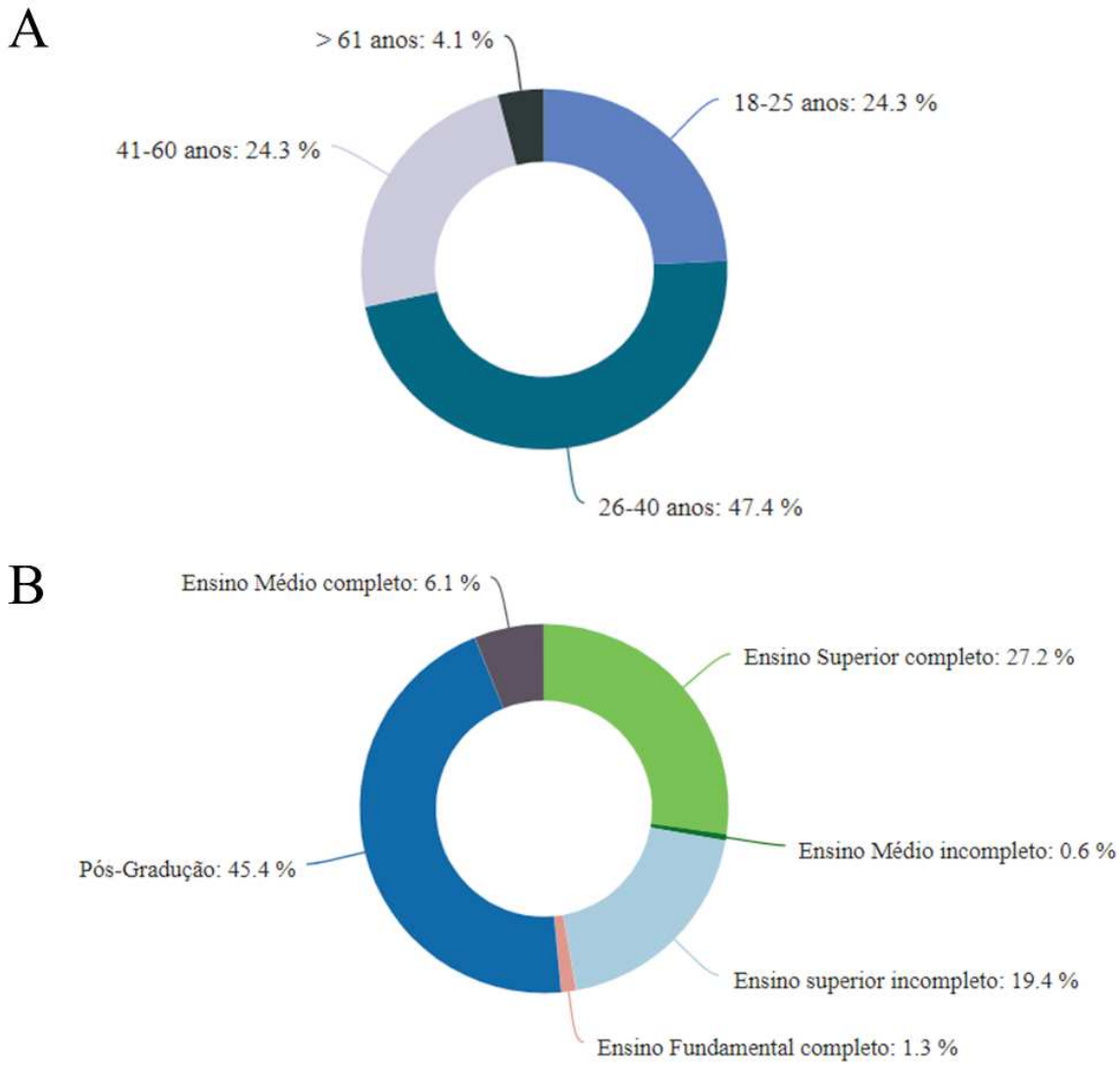

Figura 18. Respostas das (A) idades e da (B) escolaridade dos participantes.

Dentre os participantes que estavam tomando alguma medicação (57,4%), a maioria tomava entre um a dois medicamentos por dia (41,7%) (Figura 19). Ainda foi verificado o hábito de automedicação entre os participantes (64%) e muitos já sentiram algum efeito adverso ao tomar um medicamento (40,2%). Dentre a parcela que sentiu algum efeito adverso, 15% trocaram o tratamento, o que pode resultar em excesso de sobra de medicamentos. Os analgésicos foram a classe de medicamentos mais mencionada pelos participantes (30%) (Figura 19).

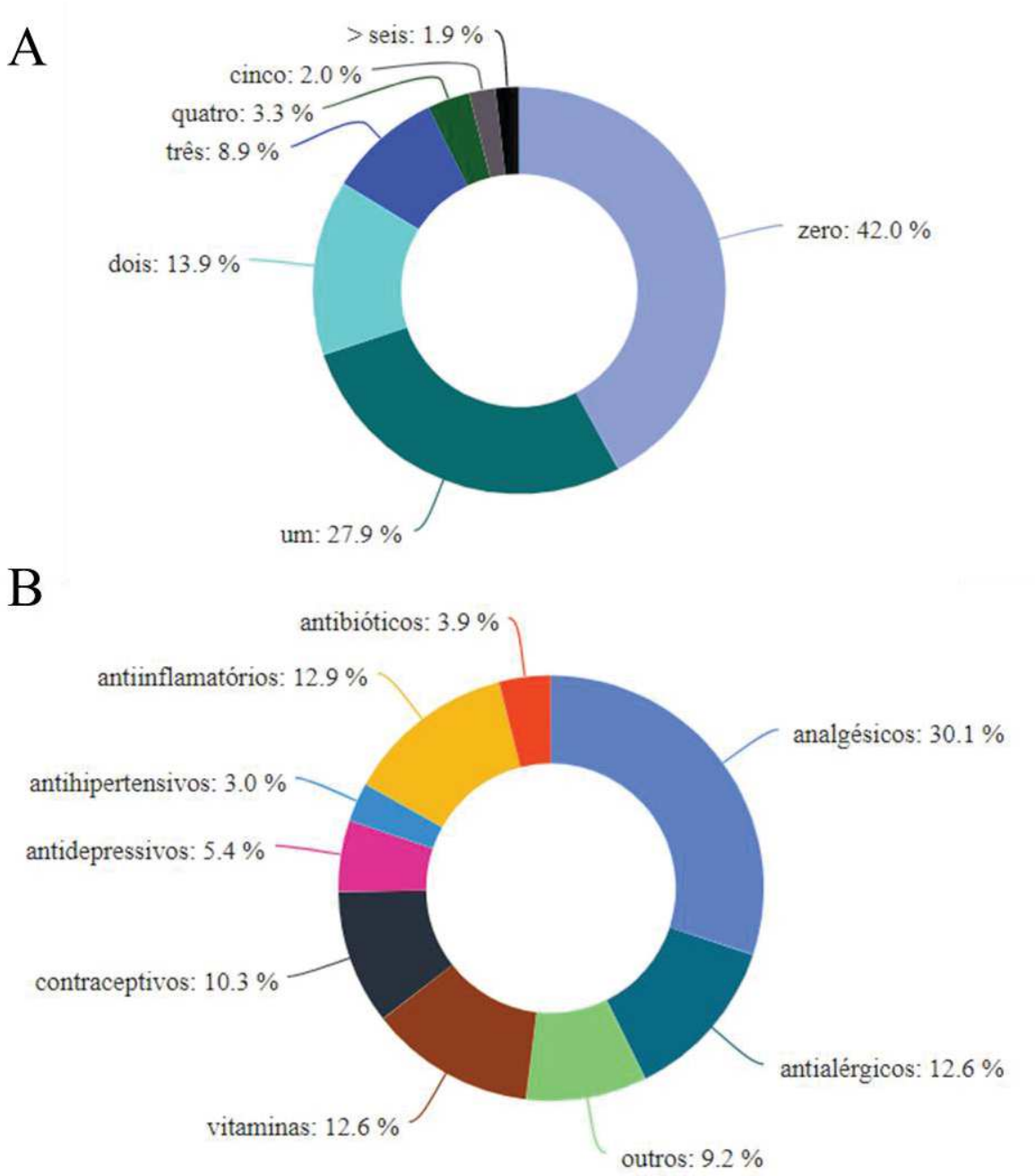

Figura 19. Respostas do (A) número de medicamentos consumidos e das (B) classes terapêuticas normalmente consumidas pelos participantes.

Quando a destinação dos medicamentos, um total de 66% dos participantes descarta os produtos em desuso ou vencidos no lixo comum (Figura 20). Um total de 54,4% das respostas não sabia informar se as suas cidades apresentavam coletores específicos para medicamentos, sendo que a grande maioria (71,9%) dos participantes nunca recebeu nenhuma informação sobre o descarte correto de medicamentos.

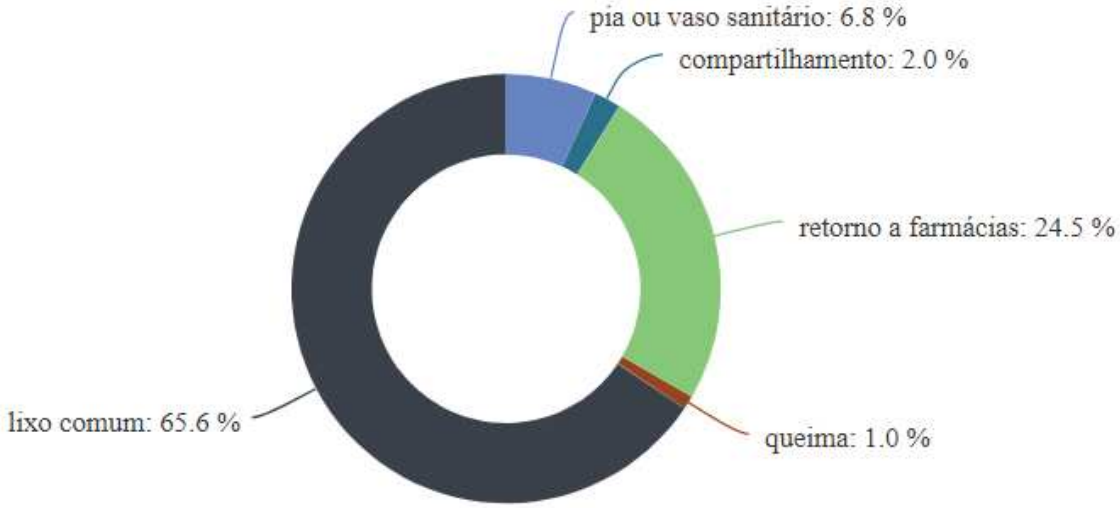

Figura 20. Respostas da destinação aos medicamentos vencidos ou em desuso pelos participantes.

5 Discussão

5.1 Consumo e concentrações de cafeína ao redor do mundo

Os hábitos culturais são importantes em termos de consumo regional de cafeína e, como esperado, diferentes padrões foram observados ao redor do mundo. Os países em desenvolvimento com maior aumento de consumo per capita de cafeína ao longo dos anos provavelmente são *hotspots* de contaminação do composto, visto que normalmente existe precariedade nos sistemas de rede de esgoto e tecnologia para tratamento, como o Brasil, Etiópia, Indonésia, Vietnã, Turquia e Tunísia. Obviamente as altas concentrações não estão necessariamente ligadas somente ao consumo, mas também a produção de café, como no caso da Costa Rica, que registra o maior valor para águas superficiais de 1.100 $\mu g\ L^{-1}$ (SPONGBERG et al., 2011), mas apresentou um padrão de consumo negativo ao longo dos anos no presente estudo. No Brasil, uma das correlações mais fortes encontradas, as concentrações de cafeína detectadas na água superficial apresentaram uma das maiores médias em comparação com outros países (~130 $\mu g\ L^{-1}$) (Figura 21). Outros países onde também foram encontradas altas correlações de consumo ao longo do tempo também apresentam relativamente altas concentrações de cafeína em suas águas superficiais ou residuais, como no Vietnã, Turquia e Tunísia (AYDIN; TALINLI, 2013; CHAU et al., 2018; KURODA et al., 2015; MOSLAH et al., 2018) (Figura 21).

No entanto, os países da Europa e América do Norte, como a Suíça, Noruega e Estados Unidos, não apresentaram uma correlação positiva de consumo de cafeína ao longo dos anos, mas apresentaram concentrações altas nos ambientes aquáticos (Figura 21). Apesar destes países apresentarem maior nível de saneamento e tecnologia nas estações de tratamento de esgoto, países da América do Norte e da Europa são grandes consumidores de café (INTERNATIONAL COFFEE ORGANIZATION, 2020). Por outro lado, países da África não são grandes consumidores (INTERNATIONAL COFFEE ORGANIZATION, 2020) e a tendência é de diminuição ao longo do tempo. É importante mencionar que alguns continentes, como a África, apresentam lacunas na quantificação da cafeína nas matrizes ambientais e, mesmo que a tendência de consumo não esteja aumentando, a ausência de saneamento básico adequado acoplado a alta produção de café pode representar um risco ambiental. Dessa forma,

países em desenvolvimento provavelmente são *hotspots* de contaminação de cafeína e os padrões de consumo precisam ser levados em consideração em outros países.

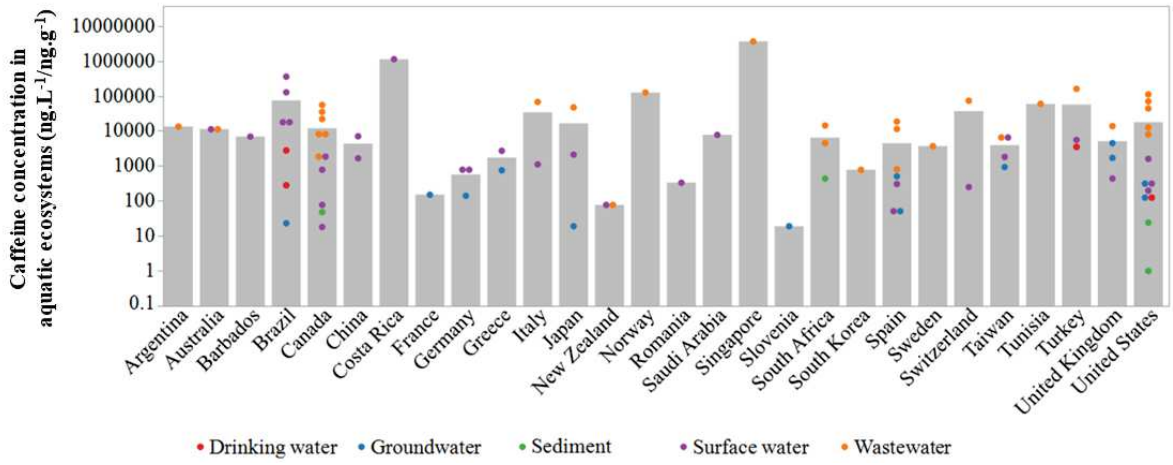

Figura 21. Média das concentrações ambientais de cafeína em diferentes países representadas pelas barras cinzas. Os pontos representam as quantificações em água potável (vermelho), água subterrânea (azul), sedimentos (verde), água superficial (roxo) e águas residuais (laranja). Matrizes líquidas apresentaram os resultados em ng L^{-1} e sedimentos em ng g^{-1}. O eixo y está representado em escala logarítmica.

Apesar de utilizarmos o café como indicador de cafeína no ambiente, a cafeína também é utilizada em muitos outros produtos, como os medicamentos. Os medicamentos que tem como base a cafeína, como os analgésicos, são normalmente vendidos sem prescrição médica (AFOLABI, 2012), tornando a automedicação um agravante importante para contaminação de cafeína nos ecossistemas aquáticos. O aumento da produção industrial e o descarte incorreto de medicamentos também podem ser fontes potenciais de cafeína para o ambiente (KLATTE; SCHAEFER; HEMPEL, 2017; QUADRA et al., 2019a, 2017). Porém, não foi observado uma relação direta entre os maiores consumidores de medicamentos e as concentrações ambientais de cafeína, com exceção do Brasil, que ocupa uma das posições mais altas de consumidores de medicamentos no mundo (AITKEN; KLEINROCK, 2015). Portanto, a venda e consumo de medicamentos também deve ser considerada em termos de contaminação de cafeína.

Apesar de ser considerado uma substância segura para a saúde humana, o consumo exagerado pode trazer complicações, especialmente em populações mais vulneráveis (EFSA, 2015; NAWROT et al., 2003). No entanto, os níveis aceitáveis no ambiente ainda não são bem estabelecidos e, apesar de sua alta taxa de degradação, os níveis são constantemente retornados

devido ao input contínuo (THOMAS; FOSTER, 2005). Dessa foram, efeitos crônicos são mais esperados de acontecer do que os efeitos agudos. Os dados ecotoxicológicos demonstram uma variação de efeitos desde a ordem de ng L^{-1} para testes mais sensíveis, como os comportamentais (STEELE; MOLE; BROOKS, 2018), até mg L^{-1} (CHEN et al., 2008; YEH et al., 2012). Portanto, essa alta variação dos resultados dificulta o estabelecimento de um valor limitante que não resultem em riscos ambientais.

Concentrações preditas para não causar efeito em organismos aquáticos representativos de três níveis tróficos (alga, Daphnia e peixe) foram definidas em 15 µg L^{-1} de cafeína para efeitos agudos e 4 µg L^{-1} para efeitos crônicos (RODRÍGUEZ-GIL et al., 2018). Utilizando estes valores, os maiores riscos foram encontrados em efluentes e nas águas superficiais (RODRÍGUEZ-GIL et al., 2018), como encontrado no presente estudo, onde 35% das matrizes ambientais ultrapassaram o limite estabelecido para efeitos crônicos e 18% para efeitos agudos, sendo que a maior parte dos riscos foram encontrados em águas residuais (Figura 21). Porém, as avaliações de risco baseadas em um único composto podem não ser adequadas, visto que os contaminantes são encontrados como misturas no ambiente. A biomassa de algas e bactérias diminuíram quando expostas a uma mistura de cafeína, acetaminofeno e diclofenaco a 5 µg L^{-1}, bem como a população de protozoários e um aumento da atividade predatória de nematoides e rotíferos (LAWRENCE et al., 2012). Porém, ainda são necessários outros estudos investigando efeitos de mistura nos ecossistemas. Um outro estudo demonstrou alto risco da exposição de cafeína em corpos hídricos da Espanha e sugerem medidas de mitigação quando as concentrações são superiores a 1 ng L^{-1} (DI LORENZO et al., 2019). Levando em consideração este valor proposto, praticamente todos os ecossistemas aquáticos teriam concentrações acima deste limite, visto que a cafeína é um composto ubíquo em ambientes aquáticos e geralmente encontrado em concentrações um pouco mais altas comparando a outros contaminantes de preocupação emergente. Os efeitos da cafeína na fisiologia e comportamento de organismos aquáticos a longo prazo, bem como efeitos de mistura a nível ecossistêmico são pouco conhecidos, mas podem resultar em desequilíbrios ecológicos e perda de serviços ecossistêmicos. Dessa forma, controlar os níveis de cafeína que chegam até o ambiente é extremamente importante.

5.2 Concentrações de contaminantes de preocupação emergente no Rio Paraibuna

As concentrações de contaminantes de preocupação emergente detectados no Rio Paraibuna não são altas comparando com outros valores no Brasil (Figura 22). Por exemplo, as maiores concentrações de atenolol registradas em água superficial no Brasil, de acordo com a UBA database (AUS DER BEEK et al., 2016), foi de 8.199 µg L^{-1} em um rio no estado de São Paulo (CAMPANHA et al., 2015). O mesmo estudo também encontrou uma concentração de carbamazepina de 215 ng L^{-1} (Figura 23). Estes altos valores foram registrados em um rio que recebe efluentes não tratados da cidade de São Carlos que, apesar de ser menor do que a cidade de Juiz de Fora, os pontos amostrados estavam mais próximos da fonte suspeita (CAMPANHA et al., 2015). Altas concentrações de diclofenaco e acetaminofeno foram encontradas em um riacho depois da cidade de Campinas, também no estado de São Paulo, que possui o dobro da população de Juiz de Fora (MONTAGNER; JARDIM, 2011). Os dois tributários do Rio Paraibuna (Rio do Peixe e Rio Preto) podem contribuir para a diluição das concentrações dos contaminantes de preocupação emergente encontradas, mas um ponto de amostragem antes da entrada dos rios é necessário para confirmação.

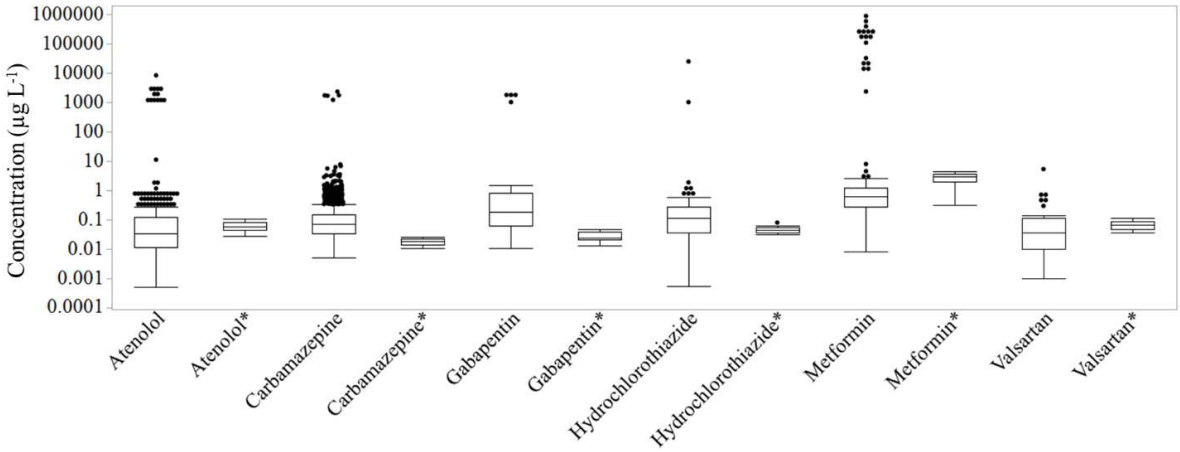

Figura 22. Concentrações em água superficial (rios e riachos, µg L^{-1}) de atenolol, valsartana, carbamazepina, gabapentina, hidroclorotiazida e metformina mundialmente. O Segundo boxplot apresentado para cada composto, representado com um asterisco, são os valores registrados no Rio Paraibuna por este estudo. As caixas representam os quartis enquanto as linhas o valor de mediana. As barras de erro indicam os valores de mínimo e máximo registrados e os pontos representam os outliers. Esta figura foi construída com base nos valores de água superficial (rios e riachos) do banco de dados da UBA (AUS DER BEEK et al., 2016).

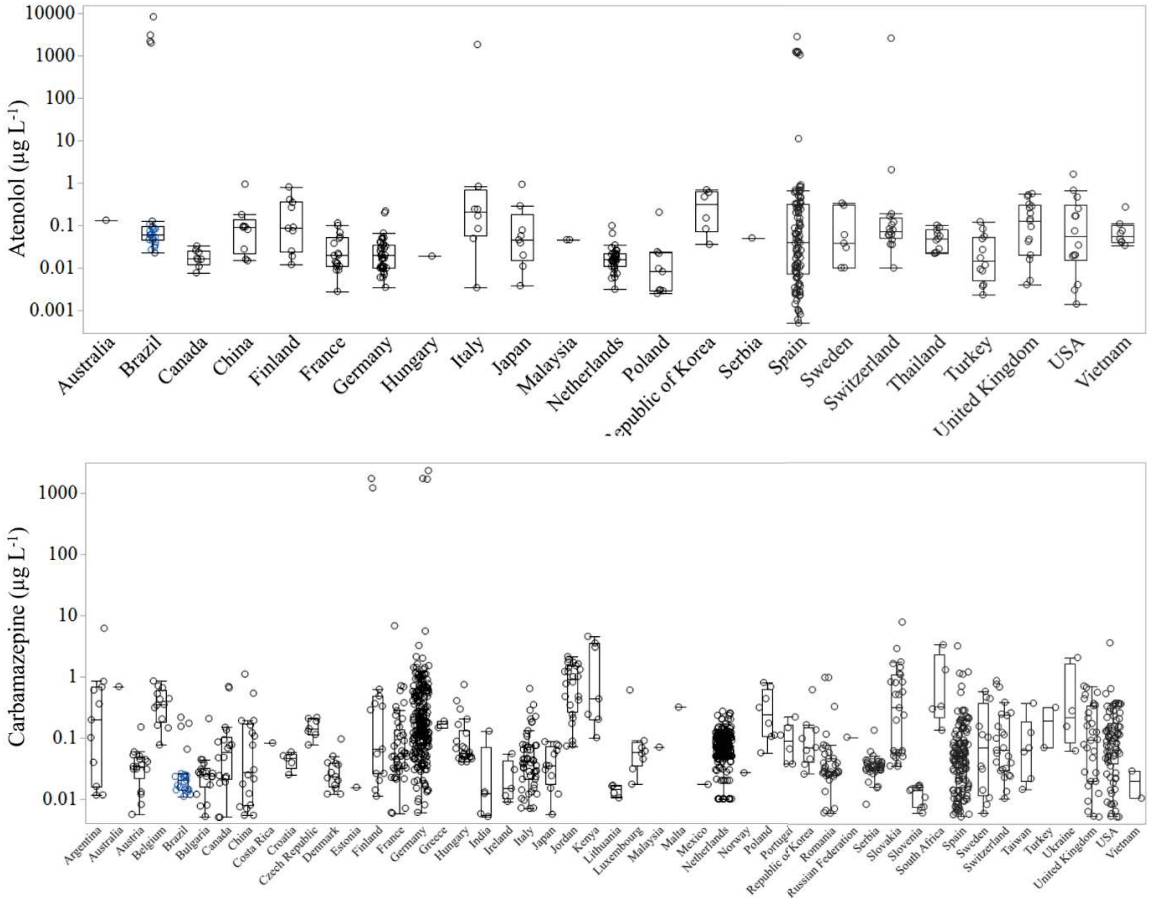

Figura 23. Concentrações em água superficial (rios e riachos, µg L^{-1}) de atenolol e carbamazepina mundialmente. As caixas representam os quartis enquanto as linhas o valor de mediana. As barras de erro indicam os valores de mínimo e máximo registrados e os pontos representam os outliers. Os pontos azuis definem os valores registrados no Rio Paraibuna. Esta figura foi construída com base nos valores de água superficial (rios e riachos) do banco de dados da UBA (AUS DER BEEK et al., 2016).

O presente estudo contribui para novos dados de gabapentina, hidroclorotiazida, metformina e valsartana em rios brasileiros (Figura 24, Figura 25). Em relação a cafeína, estudos anteriores também desenvolvidos no estado de São Paulo, reportaram concentrações de 32.400 a 127.092 ng L^{-1} (MONTAGNER; JARDIM, 2011; SODRÉ et al., 2007). As concentrações de atenolol, carbamazepina, gabapentina, hidroclorotiazida, metformina e valsartana encontradas no Rio Paraibuna podem ser comparadas a outras ao redor do mundo. No entanto, essas comparações mundiais demonstram como a variação dos registros pode ser bem alta dentro de um mesmo país.

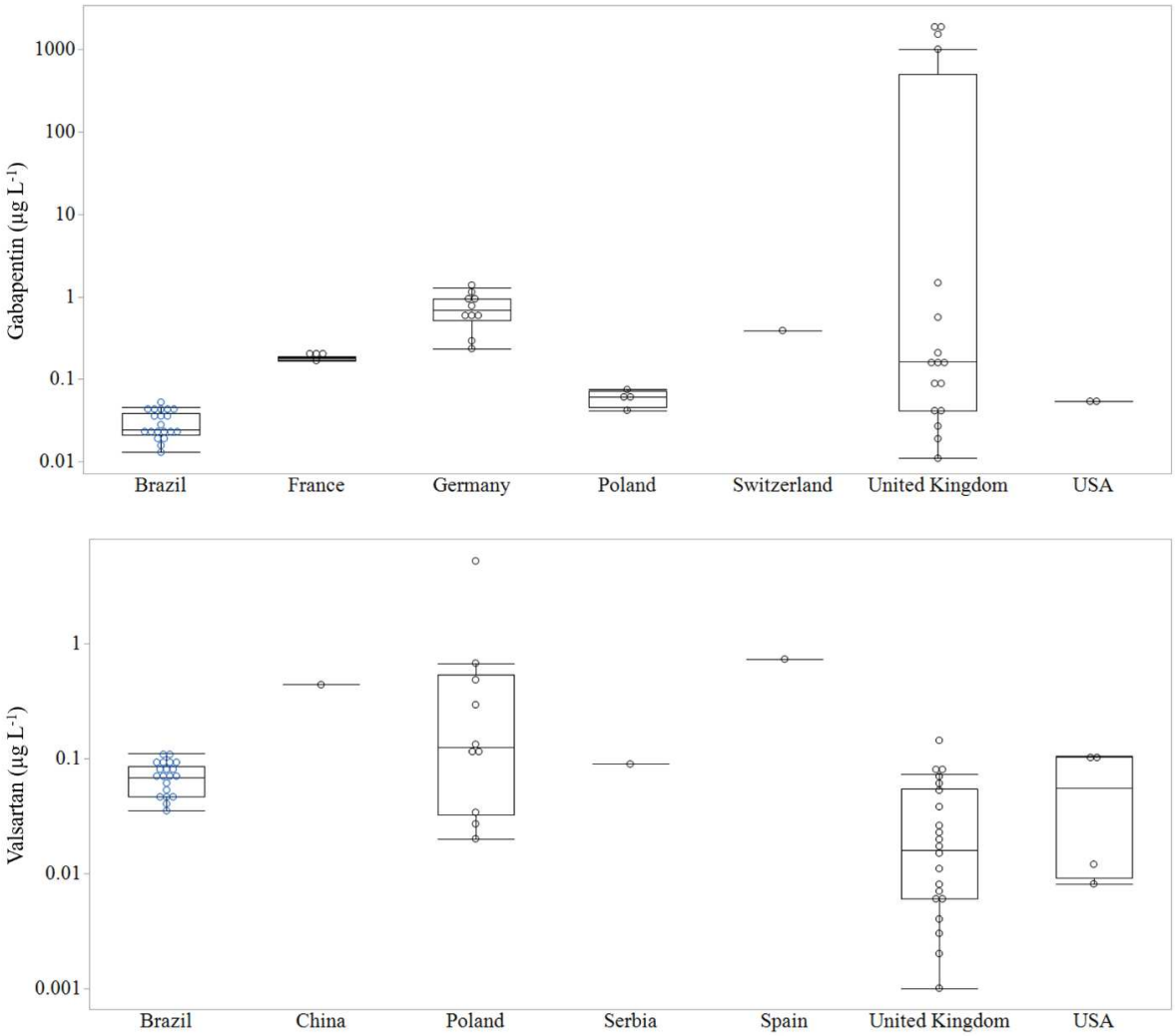

Figura 24. Concentrações em água superficial (rios e riachos, µg L^{-1}) de gabapentina e valsartana mundialmente. As caixas representam os quartis enquanto as linhas o valor de mediana. As barras de erro indicam os valores de mínimo e máximo registrados e os pontos representam os outliers. Os pontos azuis definem os valores registrados no Rio Paraibuna. Esta figura foi construída com base nos valores de água superficial (rios e riachos) do banco de dados da UBA (AUS DER BEEK et al., 2016).

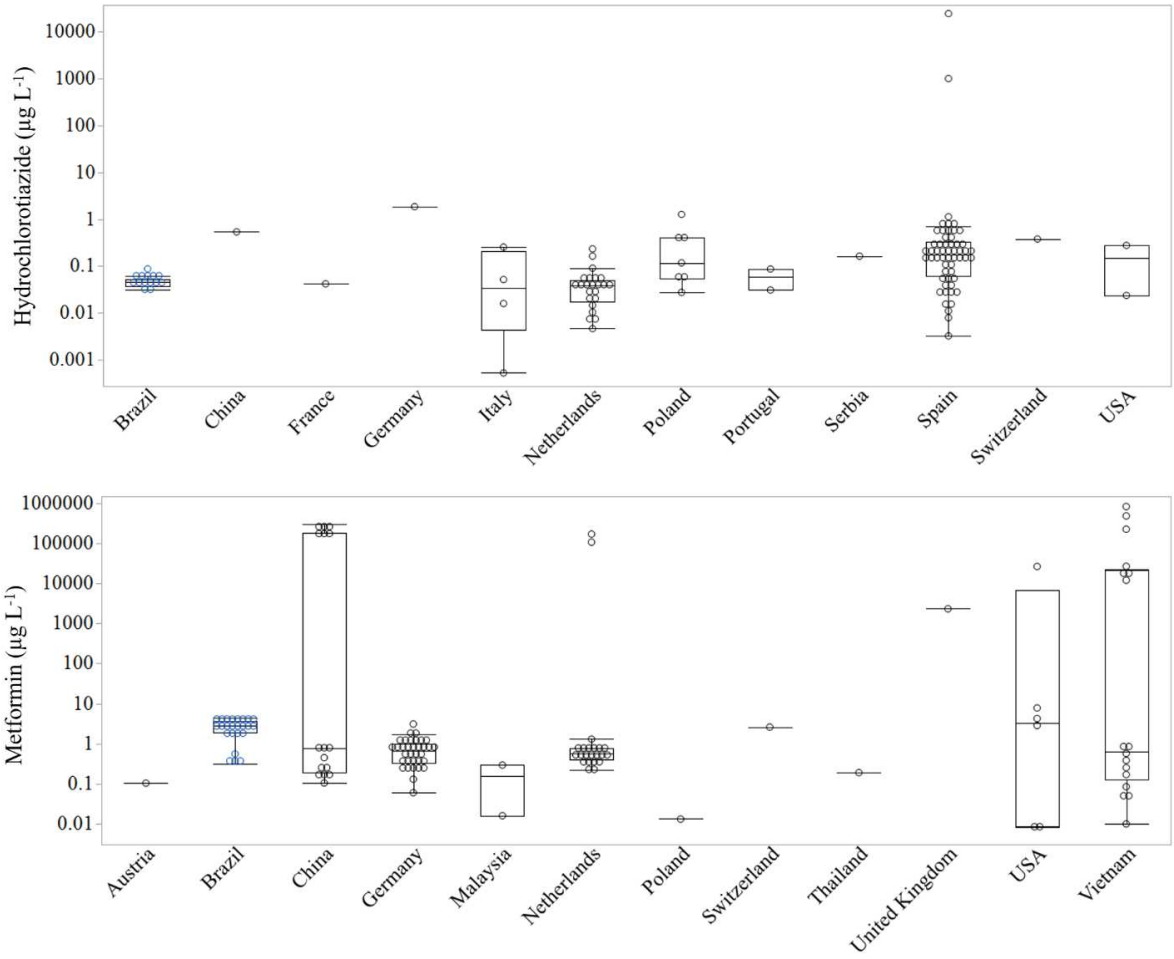

Figura 25. Concentrações em água superficial (rios e riachos, µg L^{-1}) de hidroclorotiazida e metformina mundialmente. As caixas representam os quartis enquanto as linhas o valor de mediana. As barras de erro indicam os valores de mínimo e máximo registrados e os pontos representam os outliers. Os pontos azuis definem os valores registrados no Rio Paraibuna. Esta figura foi construída com base nos valores de água superficial (rios e riachos) do banco de dados da UBA (AUS DER BEEK et al., 2016).

As concentrações de cafeína compiladas anteriormente demonstram que as concentrações máximas do Rio Paraibuna estão dentro da mesma faixa de variação (Figura 26). Como demonstrado no artigo anterior (QUADRA et al., 2020), as concentrações de cafeína no ambiente podem aumentar em um futuro próximo, especialmente em países com aumento do consumo per capita ao longo dos anos e com deficiência de saneamento básico, como o Brasil, o que pode representar um risco para os ecossistemas aquáticos.

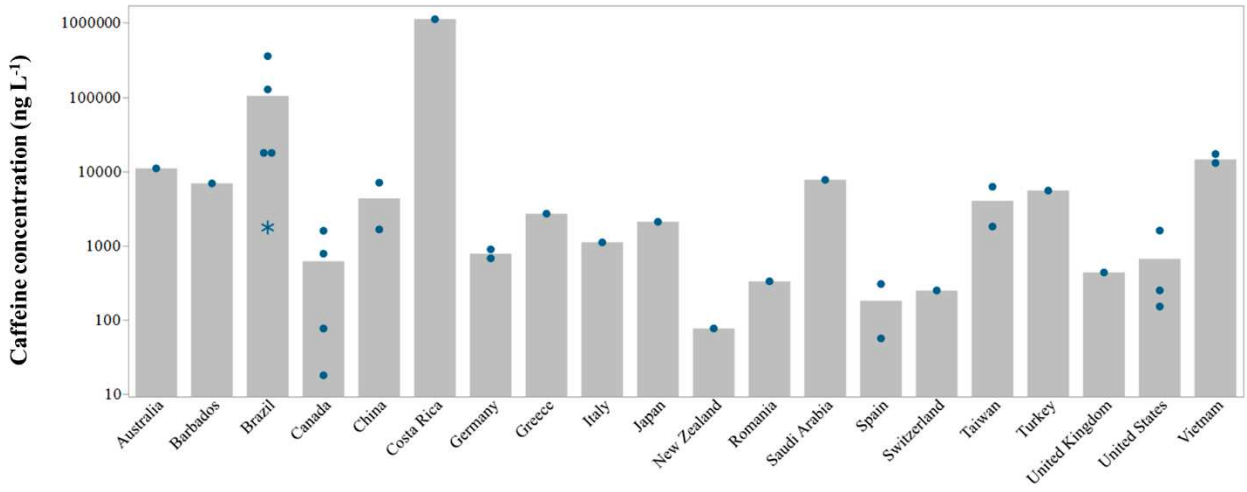

Figura 26. Concentrações ambientais de cafeína (ng L^{-1}) em águas superficiais de diferentes países. As barras representam as medias e os pontos os valores individuais. O asterisco no Brasil representa a concentração máxima reportada no Rio Paraibuna. Os outros dados foram retirados do artigo anterior (QUADRA et al., 2020).

O composto caprolactam, um produto industrial e aditivo de alimentos, bem como o DEET, um inseticida, chamaram a atenção na análise não alvo devido às suas áreas de pico maiores do que a metformina nas amostras de água. O DEET é comumente utilizado como ingrediente de repelentes no Brasil, cosméticos muito utilizados para evitar doenças tropicais. Além disso, a benzoylecgonina – metabólito da cocaína – também chamou atenção, uma vez que realmente é muito consumido e produzido no Brasil, o que resulta em altas concentrações já detectadas na costa Brasileira, tanto do metabólito quando do seu composto parental (PEREIRA et al., 2016; UNODC, 2020).

Como os compostos não foram encontradas no ambiente de referência, com exceção da cafeína, que mesmo assim apresentou concentrações muito menores antes de passar pela cidade de Juiz de Fora, podemos dizer que o esgoto doméstico da cidade é provavelmente a principal fonte de contaminantes de preocupação emergente para o Rio Paraibuna. Durante as campanhas, somente 20% do esgoto da cidade de Juiz de Fora estava sendo tratado pelas duas estações de tratamento ativas. Também foi percebido que os valores medidos na primeira campanha em junho de 2017 foram similares ou maiores do que as medidas um ano depois, em junho de 2018 (Tabela 4). Apesar da lei municipal (Lei 13.442 – de 10 de agosto de 2016) a respeito do descarte correto de medicamentos, os dados provavelmente ainda não foram afetados pela legislação, sendo necessário um maior acompanhamento. O quarto estudo desta

tese (QUADRA et al., 2019a), demonstrou que a principal via de descarte pela população brasileira é o lixo comum e, portanto, as águas subterrâneas devem ser diretamente afetadas pela nova legislação, havendo, provavelmente, redução das concentrações. Porém, é necessária avaliação desta matriz ambiental para confirmação.

O Brasil tem estado sempre entre os maiores consumidores de medicamentos do mundo (AITKEN; KLEINROCK, 2015; BASAK, 2018), sendo que na cidade de Juiz de Fora existem 3 vezes mais farmácias (239 no total) do que o recomendado pela Organização Mundial de Saúde (TRIBUNA DE MINAS, 2018). O alto consumo de metformina pela população brasileira já foi reportado anteriormente (NEVES; PAULO; MOL, 2019; VOSGERAU; CABRERA; SOUZA, 2011). Os três fármacos mais consumidos dentre os avaliados (metformina, hidroclorotiazida e atenolol) correspondem as maiores concentrações encontradas no Rio Paraibuna e os dois menos consumidos (furosemida e propranolol) não foram detectados no rio. O consumo dos medicamentos não variou ao longo do tempo, o que faz sentido uma vez que os compostos mais encontrados são utilizados para tratar doenças crônicas (Figura 10). Os dados de consumo podem ajudar a priorizar as substâncias para as quantificações ambientais, porém, estudos de maior extensão em relação ao consumo e concentrações ambientais são necessários para tornar essa ligação mais robusta.

A baixa variação espacial encontrada muito provavelmente é explicada pela alta vazão do rio que resulta em uma alta velocidade de deslocamento da água e partículas de um ponto amostral até o outro. Por outro lado, a alta variação temporal pode ser explicada pela diluição das concentrações de contaminantes de preocupação emergente, o que já foi reportado por outros estudos (BENOTTI; BROWNAWELL, 2007; KOLPIN et al., 2004; MEI et al., 2018). A cafeína foi o único composto que não apresentou variação temporal ($F = 1,5107$, $p = 0,0685$), provavelmente por sua maior variabilidade entre os pontos de amostragem ($F = 2,0523$, $p = 0,1389$) comparando aos outros. Este achado foi oposto ao encontrado por estudos prévios onde a variação da cafeína ao longo do tempo foi encontrada, com maiores concentrações na época seca (GONÇALVES; RODRIGUES; SILVA-FILHO, 2017; MONTAGNER; JARDIM, 2011).

Como os parâmetros físico-químicos apresentam relação entre si, não é possível diferenciar qual destes apresenta maior impacto nas concentrações dos contaminantes de preocupação emergente no Rio Paraibuna. Porém, a diluição é um processo que afeta todos os contaminantes de preocupação emergente avaliados, ao contrário da sorção ao material

particulado, dissociação por mudanças de pH ou degradação por temperatura ou sorção, os quais afetam os compostos de diferentes formas e magnitudes.

As concentrações do antibiótico sulfametoxazol provavelmente não estão causando resistência bacteriana, já que o PNEC sugerido para tal risco é de 16 $\mu g\ L^{-1}$ (BENGTSSON-PALME; LARSSON, 2016). De maneira geral, um baixo risco ambiental foi encontrado para os compostos investigados, sendo que para os riscos moderados encontrados, somente a metformina foi quantificada efetivamente no Rio Paraibuna e, portanto, o risco dos outros compostos é incerto. O moderado risco de misturas encontrado pode superestimar o risco visto que não leva em consideração o modo de ação de cada composto. É necessário o desenvolvimento de ferramentas mais relevantes em termos ecológicos para trazer mais informação sobre o riscos levando em consideração outros efeitos ecotoxicológicos, a longo prazo e de misturas (ÅGERSTRAND et al., 2015; CLEUVERS, 2004; RIBBENSTEDT et al., 2017).

5.3 Concentrações de contaminantes de preocupação emergente em reservatórios brasileiros

As diferenças nas ocorrências e concentrações de contaminantes de preocupação emergente encontradas nos reservatórios provavelmente estão relacionadas as suas diferentes características. FUN apresenta uma maior área e volume de água comparando a SIM, o que pode diluir as concentrações dos contaminantes de preocupação emergente. Além disso, a população estimada de SIM é maior do que a de FUN, indicando, provavelmente, uma maior descarga destes resíduos em SIM. A ocorrência de contaminantes de preocupação emergente, portanto, foi maior em FUN e SIM do que em CDU e CUN (Figura 16) e a característica mais contrastante entre estes grupos formados é o número de habitantes na bacia. CDU e CUN estão localizados em regiões menos urbanizadas, com uma população estimada de 1.800 e 1.900 habitantes, respectivamente, com pequenas vilas nas bacias em comparação a SIM e FUN, com população estimada de 4 milhões e 2,1 milhões de pessoas, respectivamente. Dessa forma, como mostrado com os dados do Rio Paraibuna, as cidades são as principais fontes de contaminantes de preocupação emergente para as águas superficiais.

A cafeína foi o único composto detectado em CDU e CUN, que apesar de possuir menos pessoas vivendo ao redor, ainda menos tratamento de efluentes é esperado, uma vez que os reservatórios são povoados por pequenas vilas e casas e não de grandes cidades. Dessa forma,

as concentrações encontradas são provavelmente relacionadas ao esgoto que vai direto para o ambiente sem qualquer atenuação. Por este motivo, a cafeína é utilizada como traçador de esgotos domésticos em ecossistemas aquáticos (BUERGE et al., 2003; MONTAGNER et al., 2014). Além disso, como mostrado no primeiro estudo da presente tese (QUADRA et al., 2020), os brasileiros estão bebendo cada vez mais café ao longo do tempo, o que corrobora para a cafeína ser um contaminante ubíquo nas águas superficiais. Além disso, o consumo de medicamentos para doenças crônicas pode ser menor em pequenas vilas pelo acesso ao sistema de saúde e pela preferência por métodos tradicionais. No entanto, é necessária uma investigação social para confirmar isso.

Caprolactam novamente chamou a atenção na análise não alvo pelos altos picos encontrados, bem como Triisopropanolamina, um produto cosmético. No entanto, uma análise alvo é necessária para investigar suas concentrações e riscos associados. Além do metabólito da cocaína também encontrado no estudo anterior, a droga de abuso AB-CHMICA também foi encontrada especialmente em SIM, um canabinóide sintético classificado como uma nova substância psicoativa.

Outros estudos prévios encontraram uma relação positiva da condutividade com as concentrações dos contaminantes de preocupação emergente (SOUSA et al., 2014) e este parâmetro é importante em termos de qualidade da água apresentando alto potencial de indicar a entrada de esgoto doméstico (THOMPSON; BRANDES; KNEY, 2012). Dessa forma, a alta condutividade encontrada em SIM e FUN pode indicar a entrada de efluentes domésticos que trazem uma complexa mistura de contaminantes, incluindo contaminantes de preocupação emergente. No entanto, outros fatores influenciam diretamente a condutividade no ambiente, inclusive fatores geomorfológicos, geológicos e hidrogeológicos.

O Brasil já tem se mostrado um grande consumidor de medicamentos nos últimos anos (AITKEN; KLEINROCK, 2015; BASAK, 2018), sendo que medicamentos para doenças cardiovasculares e diabetes, bem como analgésicos, estão entre os mais vendidos (ANVISA, 2018). De fato, as maiores concentrações encontradas nos reservatórios de FUN e SIM foram relacionadas a doenças cardiovasculares, como o atenolol, bem como o antidiabético metformina, enquanto outros fármacos presentes em antifúngicos, reguladores lipídicos e antidepressivos permaneceram abaixo do LQ. Estudos anteriores demonstraram um alto consumo da metformina pela população brasileira (NEVES; PAULO; MOL, 2019; VOSGERAU; CABRERA; SOUZA, 2011), e compostos que são pouco metabolizados no

corpo humano, como a metformina e o atenolol (ASHLEY; CURRIE, 2009), pode favorecer a entrada destes fármacos no ambiente.

Comparando com os dados reportados para o Rio Paraibuna, os rios são normalmente mais investigados em termos de poluição por fármacos do que lagos e reservatórios, muito provavelmente devido aos maiores tempos de residência nos últimos que pode favorecer a degradação e decantação para os sedimentos, diminuindo as concentrações ambientais. No entanto, é essencial investigar a contaminação por contaminantes de preocupação emergente em reservatórios que são utilizados como fonte de água para a população humana, bem como para aquicultura e irrigação de agricultura. Apesar dos fármacos não apresentarem um alto potencial de biomagnificação, pouco ainda é conhecido sobre as vias de exposição humana, a biodisponibilidade e captação, ou ainda de efeitos a longo prazo para a saúde humana e ambiental (BOXALL et al., 2012; ZENKER et al., 2014).

Comparando com outros reservatórios brasileiros, a concentração de acetaminofeno variou entre 130 e 254 ng L^{-1} (POMPEI et al., 2019; SHIHOMATSU et al., 2017) e diclofenaco atingiu 50 ng L^{-1} (POMPEI et al., 2019). Comparando com outros estudos mundiais, 0,3 µg L^{-1} de diclofenaco foram detectados em um reservatório mexicano (GONZÁLEZ-GONZÁLEZ et al., 2014) e sulfametoxazol atingiu 280 ng L^{-1} e uma frequência de detecção de 100 % foi registrada em reservatórios chineses (CUI et al., 2018; WOLF; BERGMANN; WILKEN, 2013). Todos estes compostos permaneceram abaixo do LQ nos reservatórios investigados deste estudo. No entanto, diclofenaco e triclosan não foram encontrados no reservatório Guarapiranga localizado no estado de São Paulo (Brasil) (SHIHOMATSU et al., 2017). Ketoprofeno, diclofenaco e o ácido clofíbrico também não foram detectados em um reservatório chinês (WOLF; BERGMANN; WILKEN, 2013), ao passo que os dois últimos também não foram encontrados em um reservatório de abastecimento público da Colômbia (ARISTIZABAL-CIRO et al., 2017).

Atenolol atingiu uma concentração de 177 ng L^{-1} e carbamazepina 358 ng L^{-1} no reservatório Guarapiranga (SHIHOMATSU et al., 2017), valores 5 e 16 vezes maiores do que o máximo registrado no reservatório de FUN, respectivamente. Os autores associaram estas altas concentrações encontradas no reservatório Guarapiranga com a intensa urbanização ao redor do reservatório e pobre saneamento na bacia (SHIHOMATSU et al., 2017). Apesar da população da bacia do reservatório estar estimada em cerca de 755 mil habitantes, o reservatório está inserido na cidade de São Paulo, enquanto os reservatórios investigados aqui estão

localizados um pouco mais distante de grandes cidades. Dessa forma, os rios precisam cobrir um alto curso entre a descarga dos efluentes até chegar aos reservatórios, sendo que os contaminantes de preocupação emergente tendem a degradar ao longo deste caminho.

A cafeína no reservatório Guarapiranga registrou valores entre 4.726 e 27.386 ng L^{-1} (LÓPEZ-DOVAL et al., 2017; SHIHOMATSU et al., 2017), 10 e 59 vezes maiores do que ao máximo registrado em FUN. Este composto também já foi detectado em um reservatório australiano de abastecimento público (30 ng L^{-1}) (HAWKER et al., 2011) e variou de 89 a 620 ng L^{-1} em reservatórios chineses (JIANG et al., 2018; ZHANG et al., 2018). O máximo de cafeína detectado nos reservatórios é 15 vezes maior do que o registrado na Austrália e similar aos valores registrado na China.

De acordo com estudos ecotoxicológicos, a variação das concentrações ambientais dos contaminantes de preocupação emergente encontrados nos reservatórios não colocaria em risco os organismos aquáticos. Isso foi demonstrado pelos estudos testando acesulfame (REN et al., 2016), atenolol (HAMPEL et al., 2010; PAROLINI et al., 2011), cafeína (AGUIRRE-MARTÍNEZ et al., 2013; STEELE; MOLE; BROOKS, 2018), carbamazepina (ALMEIDA et al., 2014), gabapentina (LI et al., 2018a), metformina (CLEUVERS, 2003) e valsartana (BAYER et al., 2014). Porém, os efeitos ecotoxicológicos do acesulfame, gabapentina, metformina e valsartana são pouco estudados e não completamente entendidos. Além disso, já foi demonstrado a necessidade de se considerar os metabólitos do acesulfame, por exemplo, já que eles demonstraram capacidade de causar estresse oxidativo em *Carassius auratus* (REN et al., 2016). Uma outra questão essencial de se levar em conta são os efeitos de mistura (VASQUEZ et al., 2014). Por exemplo, uma mistura de oito compostos farmacêuticos, incluindo carbamazepina e cafeína causaram fitotoxicidade em *Lemna gibba* e *Myriophyllum sibiricum* (BRAIN et al., 2004). Um outro estudo testando 13 compostos, incluindo carbamazepina e atenolol, também afetou o crescimento de algas e o conteúdo de pigmento (VANNINI et al., 2011). Ainda assim, um outro estudo de misturas com 16 diferentes compostos, incluindo carbamazepina e atenolol, demonstrou que a mistura global foi mais tóxica em relação a imunocapacidade de *Lymnaea stagnalis* do que as misturas somente das classes terapêuticas (GUST et al., 2013).

5.4 Consumo de medicamentos pela população brasileira

O maior número de respostas da região sudeste era esperado, uma vez que essa região possui mais de 40% da população brasileira (IBGE, 2018). Apesar do questionário ter sido divulgado por meio eletrônico, como os autores estão inseridos dentro da rede acadêmica, muito provavelmente houve influência no número de respostas de pós-graduados. Este fato implica que os resultados são conservativos, visto que o *background* educacional pode influenciar o consumo e descarte de medicamentos.

Um estudo semelhante nos Estados Unidos com 301 participantes encontrou resultados similares, onde 68,9% dos participantes estavam tomando de um a cinco medicamentos por dia (SEEHUSEN; EDWARDS, 2006). Os analgésicos, que foramaltamente reportados como consumidos, normalmente são vendidos sem receita médica, consequentemente, são encontrados em recursos hídricos mundialmente (AUS DER BEEK et al., 2016; HEBERER, 2002; QUADRA et al., 2017).

Os resultados demonstraram que, apesar do alto grau de escolaridade das respostas, o número de participantes que descartam medicamentos da forma incorreta foi substancialmente alto. Outros estudos ao redor do mundo encontraram resultados semelhantes. Nos Estados Unidos, por exemplo, 77,1–86% dos pacientes não retornavam os medicamentos em desuso para os serviços de saúde e 53,8% descartavam no vaso sanitário (SEEHUSEN; EDWARDS, 2006). Outro estudo na Irlanda, que entrevistou 398 pessoas, demonstrou que 51% descartavam os medicamentos no lixo comum, 29% na pia e 14% no vaso sanitário (VELLINGA et al., 2014). Na Inglaterra, 392 pessoas foram entrevistadas e 63,2% dos participantes descartavam os medicamentos no lixo, 11,5% na pia ou vaso sanitário e 21,8% retornavam as farmácias (BOUND; VOULVOULIS, 2005).

Uma revisão sobre o descarte de medicamentos em desuso ou vencidos realmente demonstrou resultados similares mundialmente (TONG; PEAKE; BRAUND, 2011), onde os participantes dos Estados Unidos parecem apresentar a maior porcentagem da população que descartam medicamentos na pia ou vaso sanitário (SEEHUSEN; EDWARDS, 2006), enquanto no Kuait a maior porcentagem de descarte no lixo comum foi encontrada (97%) (ABAHUSSAIN; BALL, 2007). Por outro lado, na Suécia, uma porcentagem de 43% dos participantes retornam os medicamentos para as farmácias (PERSSON; SABELSTRÖM; GUNNARSSON, 2009), a maior porcentagem comparando a outros países (TONG; PEAKE;

BRAUND, 2011). Mesmo que os resultados sejam conservativos, foram similares a outros locais do mundo, o que, na verdade, demonstra ainda mais preocupação visto que se atingíssemos um maior número em regiões mais carentes do país e com menor índice de escolaridade, estes números podem ser ainda maiores. Dessa forma, é possível inferir que o alto grau acadêmico teve pouca influência nestes resultados de descarte dos medicamentos.

Estes números demonstram a grande ausência da logística reserva para medicamentos no Brasil, o que deve mudar com o novo Decreto Nº 10.388, assinado em junho de 2020. O novo decreto está inserido na Política Nacional de Resíduos Sólidos (Lei nº 12.305, de 2 de agosto de 2010) e institui o sistema de logística reversa de medicamentos vencidos ou em desuso de uso humano.

A maioria dos participantes (95,2%) acredita que os resíduos dos medicamentos podem causar efeitos adversos no ambiente, o mesmo encontrado nos Estados Unidos e Inglaterra (BOUND; KITSOU; VOULVOULIS, 2006; SEEHUSEN; EDWARDS, 2006).

A educação ambiental deve ser considerada em currículos escolares, levando em consideração diferentes tipos de poluição e como uma mudança de hábitos pode ajudar a reduzir os impactos ambientais. Um estudo desenvolvido em Massachusetts demonstrou que uma breve intervenção educacional foi efetiva em mudar a atitude e conhecimento de farmacêuticos em relação as consequências ambientais de práticas de descarte incorreta (JARVIS et al., 2009). A educação ambiental é um dos pilares mais importantes em termos de manejo da saúde ambiental e pública e, portanto, esforços para aumentar a conscientização ambiental podem afetar diretamente de maneira benéfica as práticas de descarte de medicamentos (KOTCHEN et al., 2009). Os achados contribuem para o conhecimento a respeito dos hábitos de consumo e descarte de medicamentos pela população brasileira, demonstrando que mesmo com uma maior parcela de respostas com alto grau de escolaridade, o descarte incorreto é uma realidade. As atividades de educação ambiental podem instruir a respeito da poluição por fármacos e é fundamental.

6 Conclusões e considerações finais

Foi observado, portanto, que (1) países em desenvolvimento podem ser considerados *hotspots* de contaminação de cafeína, mas a preocupação se estende a todos os países, sendo necessário maior investimento em saneamento básico, uma vez que as concentrações de cafeína já encontradas nos ecossistemas aquáticos podem representar um risco ambiental. (2) As concentrações de contaminantes de preocupação emergente encontradas no Rio Paraibuna são comparáveis a outros estudos mundiais, no entanto, o trecho investigado está localizado 40 km abaixo da fonte suspeita, que é a cidade de Juiz de Fora, sendo que outros estudos investigam trechos mais próximos das fontes suspeitas. Portanto, futuros trabalhos mais próximos a fonte suspeita podem ajudar a melhor compreender a contribuição da cidade para o Rio Paraibuna em termos de poluição por contaminantes de preocupação emergente. As maiores concentrações encontradas foram de fármacos voltados para doenças cardiovasculares e diabetes, usados para doenças crônicas, e foram inversamente proporcionais a precipitação, que dilui as concentrações no rio. A metformina, composto que apresentou as maiores concentrações, representa um risco ecológico moderado para o rio, bem como a mistura de contaminantes de preocupação emergente avaliados. (3) A alta ocorrência e concentrações de contaminantes de preocupação emergente no reservatório de Funil e Simplício em contraste aos reservatórios de Curuá-Una e Chapéu D'Uvas, demonstra a influência do tamanho populacional da bacia para contribuição da entrada destes compostos para os reservatórios. Apesar das concentrações parecerem baixas quando comparadas aos estudos ecotoxicológicos, ainda há muito o que conhecer sobre os efeitos dos fármacos no ambiente, como efeitos de mistura e de seus metabólitos, que podem colocar em risco a saúde humana via consumo de água e alimento vindo dos reservatórios. (4) A maioria dos brasileiros descarta os medicamentos vencidos ou em desuso no lixo comum. Muitos países ainda não possuem regulação em relação ao descarte de medicamentos e a população ainda não desconhece as consequências do descarte incorreto, não sendo diferente para o Brasil. Além da regulação, é extremamente necessário um maior investimento na educação ambiental, o que pode reduzir significativamente os impactos ambientais da poluição por fármacos.

Importante ressaltar a importância de futuros estudos para fortalecer os resultados encontrados nesta tese. Por exemplo, o aprofundamento dos efeitos de misturas, tanto em testes ecotoxicológicos quanto em modelos e cálculos para tornar os resultados mais robustos são

essenciais para entender essa problemática. Com inclusão, inclusive, dos estressores múltiplos, ou seja, além de combinar diferentes químicos sintéticos, entender a influência das variações de temperatura (mudanças climáticas) e concentrações de nutrientes (eutrofização), por exemplo, são essenciais. No Rio Paraibuna, avaliar pontos amostrais mais próximos a cidade, bem como ampliar os pontos de monitoramento para estações de tratamento de esgoto e água potável, pode ampliar o entendimento da contribuição da cidade de Juiz de Fora em termos de contaminação ambiental por contaminantes de preocupação emergente. De fato, nós investigamos uma ampla lista de compostos, mas uma investigação mais robusta focando na lista de compostos não-alvo também é importante. Para os reservatórios, uma avaliação temporal, incluindo medições em diferentes profundidades da coluna d'água podem complementar este primeiro estudo de maneira substancial. Por fim, avaliar as águas subterrâneas visando entender possíveis consequências ambientais do descarte incorreto de medicamentos via lixo comum trará subsídios importantes para o melhor entendimento desta via de contaminação ambiental.

Os quatro estudos apresentados demonstram a necessidade da inclusão de contaminantes de preocupação emergente nas regulações globais, levando em consideração todos os químicos ao invés de compostos isolados. Apesar da necessidade de uma reformulação total da forma que avaliamos a poluição, estudos envolvendo modelos de exposição e predição das emissões, assim como testes ecotoxicológicos sensíveis a misturas podem auxiliar nesse desafio. Dessa forma, o Pacto Ecológico Europeu poderia ser expandido para um tratado mundial, visando a busca por um desenvolvimento e hábitos sustentáveis. O tratado é um plano de ação para impulsionar a utilização dos recursos de forma eficiente por meio de economia limpa e circular, visando restaurar a biodiversidade e diminuir a poluição (COMISSÃO EUROPÉIA, 2019). O manejo dos recursos hídricos não pode levar em consideração somente o ambiente em questão, mas sim, toda a sua bacia. A visão total dos ecossistemas pode auxiliar em buscas de ferramentas mais eficazes para a gestão dos recursos naturais. Dessa forma, os pensadores da Ecologia Profunda, que trazem a visão de um todo, podem auxiliar também nessa jornada (SILVA, 2004). A Ecologia Profunda traz o conceito de gestão ambiental na base da gestão de hábitos e desejos humanos ao invés da gestão da natureza, bem como a base transpessoal cosmológica que aceita todas as vidas como partes autónomas de um mesmo processo, que é a vida, identificando todos os seres vivos de uma forma interiorizada (SILVA, 2004). Assim, se observarmos que a natureza é indistinta dos seres humanos, teremos uma poderosa motivação para conservação. As pessoas, de um modo geral, não percebem que suas

ações prejudicam o ambiente, nem como as consequências de suas ações vão contra as suas convicções e, expor estas inconsistências, ajudará a efetuar mudanças construtivas, ao invés de gerar conflito (SILVA, 2004). A ecologia profunda como estilo de vida traz preceitos de utilização de meios simples, atitude anti-consumista, ausência ou baixo grau de novofilia, apreço por bens existentes em quantidades suficientes, solidariedade, apreço pelas diferenças étnicas e culturais, procura pela profundidade e riqueza das experiências, trabalho com sentido e não como modo de ganhar vida, satisfazer necessidades vitais e não desejos, viver na natureza mais do que visitar lugares belos. Assim, poderemos encontrar um equilíbrio num ponto diferente do atual (SILVA, 2004).

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APÊNDICES DA TESE

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Water pollution: one of the main Limnology challenges in the Anthropocene

Poluição hídrica: um dos principais desafios da Limnologia no Antropoceno

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Abstract: Humankind is defining a new geological time. The Anthropocene epoch is marked by changes in the geological processes, hydrological regimes, biosphere structure, among other processes, due to human expansion over the landscape worldwide. Biogeochemical cycle's acceleration, the high load of pollutants in water resources, rampant deforestation, increase in the greenhouse gas emissions to the atmosphere, eutrophication and biodiversity losses are some indications that reflect human's pressure over several ecosystems, especially aquatic ones. Therefore, here we reviewed some aspects from a huge anthropogenic influence on ecosystems: water pollution. For decades, humankind has increasingly placed demands on aquatic environments without any concern. As an effect, lakes, rivers, and reservoirs are being globally degraded. Although the interactive effects of future anthropic processes are complex, much of current knowledge suggests that these pressures are likely to increase in magnitude and frequency over the next years. Hence, scientific results need to be articulated in an integrative perspective to expand our understanding of the aquatic resources management. The ecological knowledge generated by scientists must be applied to solve environmental problems enabling human progress sustainably. It is urgent to improve communication and understanding among different sectors of society in favor of water management. Therefore, it will be possible to ensure the preservation of natural resources for future generations by using transdisciplinary tools to understand, mitigate and recover the water resources from these anthropogenic pressures.

Keywords: aquatic ecosystems; biogeochemical cycles; eutrophication; pollutants.

Resumo: A humanidade está definindo um novo período geológico. A era do Antropoceno é marcada por mudanças nos processos geológicos, nos regimes hidrológicos, na estrutura da biosfera, dentre outros processos devido às expansões humanas sobre a paisagem ao redor do mundo. A aceleração dos ciclos biogeoquímicos, a grande carga de poluentes nos recursos hídricos, o desflorestamento desenfreado, o aumento das emissões de gases de efeito estufa para a atmosfera, a eutrofização e a perda da biodiversidade são algumas evidências que refletem as pressões humanas sobre diversos tipos de ecossistemas, especialmente os ecossistemas aquáticos. Desta maneira, neste estudo nós revisamos alguns aspectos da grande influência antrópica sobre os ecossistemas: a poluição hídrica. Durante décadas, a humanidade tem colocado cada vez mais demandas sobre os ambientes aquáticos sem qualquer

preocupação. Como efeito, lagos, rios e reservatórios estão sendo degradados globalmente. Embora os efeitos interativos dos processos antrópicos futuros sejam complexos, muito do conhecimento atual sugere que essas pressões provavelmente aumentarão sua magnitude e frequência nos próximos anos. Consequentemente, os resultados científicos precisam ser articulados em uma perspectiva integradora buscando expandir o nosso entendimento sobre o manejo dos recursos hídricos. O conhecimento ecológico gerado pelos cientistas deve ser aplicado para solucionar os problemas ambientais permitindo o progresso humano de uma forma sustentável. É urgente a melhora da comunicação entre diferentes setores da sociedade em prol do manejo dos ecossistemas aquáticos. Assim, será possível garantir a preservação dos recursos naturais para futuras gerações aplicando ferramentas transdisciplinares para entender, mitigar e recuperar os recursos hídricos destas pressões antropogênicas.

Palavras-chave: ciclos biogeoquímicos; ecossistemas aquáticos; eutrofização; poluentes.

1. Introduction

Human activities have profoundly altered ecosystems worldwide creating a new geological epoch, known as Anthropocene (Griggs et al., 2013; Steffen et al., 2007; Steffen et al., 2011). The Anthropocene is divided into three periods: *"The Industrial Era (1800 – 1945)"*, *"The Great Acceleration (1945 – 2015)"*, and *"Stewards of the Earth System (2015 – ?)"* (Steffen et al., 2007). The indications for this new epoch are many, such as population growth, deforestation, changes in biogeochemical cycles, climate and environmental changes, hydrological regimes modifications, increases in greenhouse gases emissions, environmental pollution, biodiversity loss, among others. The period known as *"Stewards of the Earth System"* is a signature of human knowledge on such anthropic impacts. Moreover, it highlights the time to develop strategies to support life on Earth in face of many stressors (Griggs et al., 2013; Steffen et al., 2007; Steffen et al., 2011).

Despite warnings from researchers about anthropogenic pressures on ecosystems worldwide, which it may be exceeding the Earth's support capacity (UCS, 1992), it seems that most of the 'decision-makers' over the globe still do not care or take concrete actions to halt or revert global changes. As a consequence, new warnings continue to come up over and over, pointing out the same problems above-mentioned (Ripple et al., 2017; Rockström et al., 2009). For instance, a recent alert has just come out exposing the need for more care on the management of wetlands (Finlayson et al., 2018). For lakes, reservoirs, and rivers, the challenges are the same. Freshwater ecosystems sustain many kind of life and play key roles in the cycling of matter and energy (Cardoso et al., 2019; Cole et al., 2007; Tranvik et al., 2009). Therefore, it is undoubted that humankind depends on watercourses due to ecosystem services provided, such as climate regulation, purification process, watering, and food production (Ray, 2011; Schwarzenbach et al., 2010). Despite its importance, aquatic ecosystems have been suffering great deteriorations, compromising the water quality and availability (Smith et al., 2006; Smith & Schindler, 2009; Schwarzenbach et al., 2010).

The impacts on aquatic ecosystems are numerous, and among them, we can highlight the disposal of not-properly treated effluents, resulting in chemical pollution and eutrophication (Schwarzenbach et al., 2010), in which make the limnological challenges more complex. Accordingly, here we compile knowledge available in the literature about one of the major anthropogenic influences that are affecting ecosystem worldwide: *water pollution*. We described the main causes and consequences of water pollution as well as ways for mitigation. In addition, we have gathered some examples of chemical contamination in the Brazilian aquatic ecosystems through a literature review.

2. Eutrophication

The nutrient enrichment, or eutrophication, have greatly increased since the industrial revolution, and human activity has profoundly altered the global cycles of nitrogen (N) and phosphorus (P) in aquatic environments (Smith et al., 1999; Vitousek et al., 1997). The external inputs of N and P into the aquatic environments come from several sources, including groundwater, leaching, untreated and partially treated sewage, agriculture runoff, atmospheric deposition and/or fixation, among others. Many studies indicate that eutrophication related to human population growth has triggered the occurrence of harmful algal blooms in aquatic environments around the world (Anderson et al., 2002; Hallegraeff, 1993; Heisler et al., 2008). However, the harmful algal blooms are characterized by a complex event, which is not caused by a single environmental change but rather by multiples factors occurring synergistically

(Heisler et al., 2008). This phenomenon implies the deterioration of water resources, which have direct and indirect effects on the global economy, as well as human and environment health. Some aspects of eutrophication are characterized by shifts in the composition of non-toxic phytoplankton species to toxic ones, increasing of the pH, oxygen depletion, fish mortality, reduction in water transparency, changes in the aesthetic value and odor, among others (Smith et al., 1999).

As the eutrophication problem has been studied for several years, some practical approaches have been applied in experiments from microcosm to whole-ecosystems scales, to reverse the eutrophication. For instance, mineral compositions have been applied into lakes to immobilize P in the sediment (for details, see Zamparas & Zacharias 2014). These techniques are succeeding in many locations, according to short-term studies. However, it is still unclear how its long-term applications may compromise the aquatic ecosystem health. Besides that, it has also been tested the efficiency of performing trophic manipulations to reduce eutrophication, i.e., to reduce internal nutrients upwelling from the sediments to the water column in shallow tropical lakes. For example, the replacement of a benthivorous native fish by an invasive planktivorous fish (Nile tilapia) has shown significant reduction of P release from the sediment to the water column in mesocosm experiment performed in a tropical eutrophic semi-arid reservoir. As a consequence, a reduction in the phytoplankton biomass was observed, restoring transparency conditions (Dantas et al., 2019). Therefore, one critical tool to mitigate eutrophication in aquatic ecosystems is to control nutrient loads, mainly N and P (Carpenter, 2008; Schindler et al., 2008). Thus, there are examples of possible management actions that can be important tools to mitigate eutrophication and restore aquatic ecosystems services.

3. Chemical Pollution

Industrial development and uncontrolled urbanization lead to land cover change, soil erosion, and waste production. These impacts trigger chemical loads into the water bodies, in which metals and organic pollutants have a prominent place due to their capacity to alter the ecosystems functioning, quality and steady-state (Filser, 2008; Förstner & Wittman, 1983; Harrad, 2009; Reemtsma & Jekel, 2006; Welch, 2002).

3.1. Metals overview

Metals (e.g. cadmium, chromium, zinc, copper, lead) may represent a direct risk to human and environmental health depending on environmental concentrations (Förstner & Wittman, 1983). Metals have natural and anthropic sources to the freshwater ecosystems. Among the natural sources, mineral weathering of rocks and soils are the most important ones (Förstner & Wittman, 1983; Salomons & Förstner, 1984). Anthropogenic sources include smelting processes, fuel combustion via atmospheric deposition and waste discharges (Förstner & Wittman, 1983; Salomons & Förstner, 1984). In addition to these sources, mining waste can also cause huge ecological damages, even more if there is a dam failure (Segura et al., 2016; Hatje et al., 2017; Quadra et al. 2019a). Clearly, this type of accident should not happen and the safety of tailings dams needs to be improved with greater investments (Lopes et al., 2019). Aquatic communities are continually exposed to metals due to their continuously dumping into the environment, and humans are exposed to these metals through lifelong drinking water consumption. Accordingly, the emission and the accumulation of metals in aquatic ecosystems need to be appropriately addressed by society since they affect growth, reproduction and cause genotoxic effects on all life forms depending on their concentrations (Hadjiliadis, 2012; Moore & Ramamoorthy, 2012; Mason, 2013).

3.2. Organic pollutants overview

The group of organic pollutants includes compounds that present a combination of carbon, hydrogen, oxygen, nitrogen, sulfur and the halogens (e.g. fluorine, chlorine, bromine, iodine) in their molecular formulas. They present an enormous complexity of molecular structures, and here we will discuss about some of those groups.

3.2.1. Pharmaceuticals and Personal Care Products (PPCPs)

The intensification of medicines production and consumption makes pharmaceuticals and personal care products (PPCPs) an environmental concern (Locatelli et al., 2011; Quadra et al., 2017a). Some aggravating factors on PPCPs pollution are self-medication, inversion of the population pyramid and the improper discarding (Daughton & Ruhoy 2013; Quadra et al., 2017a; Quadra et al., 2019b). Most PPCPs pass through water and sewage treatment plants and are not completely removed. As a result, PPCPs may end up

in aquatic ecosystems (Tambosi et al., 2010) and are seldom required by regular water quality guidelines. Once in the aquatic environment, PPCPs may cause ecotoxicological effects on the biota and reach humans through drinking water or food consumption (Monteiro et al., 2016). It is alarming the magnitude of concentrations, such as those derived from pain killers and hormones, which have been found in natural aquatic ecosystems. It is worth to emphasize the potential chronic effects caused by their exposures, since hormones, antidepressants, and antibiotics have already been tested and the results suggest changes in growth rates, behavior, and reproduction of aquatic organisms, which may lead to profound changes in the ecological structure of aquatic ecosystems (Doerr-MacEwen & Haight, 2006; Kümmerer, 2008). Thus, the chronic effects can be or become a health issue in a near future and it is urgent to better understand the role and fate of these contaminants in the water, aquatic organisms and humans (Brausch et al., 2012).

3.2.2. Pesticides

The application of pesticides in agriculture is an inefficient process, given that only a small fraction of the amount-applied pesticide is retained by the crops. Then, farmers end up applying even more pesticides to increase its absolute retention, resulting in more residues to flow throughout the land (runoff) into aquatic ecosystems (Matthews, 2015). As a consequence, contamination of surface water and groundwater by pesticides is a worldwide reality (Cerejeira et al., 2003; Ritter, 1990; Turgut, 2003). Pesticides residues have already been found in drinking water in several countries, and even in the fat and milk of humans (Carlile, 2006). Several non-target organisms are affected by the indiscriminate use of pesticides, and negative effects have already been described for bees, earthworms, arthropods, aquatic invertebrates, fish, amphibians, reptiles, birds, and mammals (Carlile, 2006). The widespread use of DDT, for example, was responsible for the population decline of birds, among them, the US symbol, the bald eagle (*Haliaeetus leucocephalus* - Linnaeus, 1766) (D'Amato et al., 2002).

3.3.3. A few more examples

Obviously, organic pollutants are not limited to PPCPs and pesticides. Some pesticides, for example, are included in the list of persistent organic pollutants (POPs). POPs are of great concern, because they are stable and persist in the environment for long periods. In addition, they present a great tendency for bioaccumulation, have high toxicity, and are transported over long distances (Harrad, 2009; Reemtsma & Jekel, 2006). The Stockholm Convention aims to protect human health and the environment from those chemicals (Stockholm Convention, 2019), but many of them are not yet on the list to be eliminated or have the use reduced. Researchers face a real challenge to understand the fate and effects of these compounds on humans and in the environment (Sobek & Undeman, 2019).

Polychlorinated biphenyls (PCBs), for example, are compounds that have many industrial applications, such as cooling substances for electrical apparatus, and its biomagnification is a great issue for some organisms, such as polar bears, fishes and even humans (Pavlova et al., 2016; Sobek et al., 2006). Polycyclic aromatic hydrocarbons (PAHs) are well–studied compounds, which are presented in the aquatic environment by effluents and atmospheric deposition and may alter the reproduction and development of organisms (Abdel-Shafy & Mansour, 2016). Brominated flame retardants (BFRs) are used to decrease material flammability and their main environmental sources are the diffusive leaching from households and industries. Humans are exposed to BFRs by indoor air and even household dust (for details see Wit (2002) and Harrad (2009)). Perfluoroalkyl compounds (PFAs) have a huge industrial application in different materials to create resistance for water, stain, oil, among others. PFAs reach the environment by direct disposal, spills and releases during production and application (for details see Ahrens (2011) and Harrad (2009)). Dioxins and furans are known for their toxicity and they are by-products of the manufacturing other chemicals and are being released into the environment by incineration reactions (for more details see Fletcher and McKay, 1993 and Harrad, 2009). Therefore, organic pollution is a vast area of research that needs more investment to understand their interactions within the environment.

4. Probably, the Biggest Challenge: Multiple Stressors

We present here some examples of water pollution, but it is important to keep in mind that the number of existing industrial products is huge. Therefore, it is noteworthy to think that there is a combination of such pollutants in the environment. Aquatic ecosystems are exposed to a pool of various

pollutants (Sobek & Undeman, 2019). How to consider the different exposures that aquatic ecosystems are facing, such as eutrophication and chemical pollution? For chemical pollution, mixtures effects have already been demonstrated and the existence of synergies is unquestionable (Chu & Chow 2002; Cleuvers, 2003, 2004; Mejía-Saavedra et al., 2005; Fleeger et al., 2007; Qian et al., 2009). However, how can we deal with these huge pollutant varieties that present different chemicals structures and their behavior in the environment?

Here we put together few examples of chemicals in Brazilian ecosystems to show how they are usually found in the aquatic environment. Typically, metals are found in higher magnitude in the aquatic ecosystems than pesticides and PPCPs, respectively (Figure 1). Moreover, generally, metals presented higher concentrations in sediments than surface water, as well as pesticides, while PPCPs are hydrophilic (Figure 1).

The ecotoxicological data may give a misinterpretation that those concentrations may not pose a risk to aquatic organisms (Figure 1). However, for all the compounds is important to consider long-term and mixture effects, since different chemicals are continuously discharged in the environment. Then, studies considering the complex mixtures of chemicals are crucial for water quality criteria to protect organisms adequately (Salomons and Förstner, 1984; Sobek & Undeman, 2019). Moreover, different species exhibit different tolerances and some end-points are more sensitive, such as behavior. All these variabilities should be take into account.

5. What Shall We Do, Then?

Considering the Anthropocene epoch and its causes and consequences, modern limnology faces challenges and needs to dedicate efforts to understand the ecological implications of multiple stressors in the aquatic ecosystems. The demand for water is rising, while the number of residues produced grows in the same constancy. So, first of all, we need to re-evaluate where and how we dispose of our residues, since, with the increasing demand for water quantity and quality, it is contradictory to the unsustainable use of water resource. All our waste end up in the aquatic ecosystems and we use the same water for supply and irrigation, a big counter-census (Figure 2).

There are several personal and collective attitudes that can also help to reduce the anthropogenic impacts on water resources, such as collaborative consumption, organic food production, law enforcement for reverse logistics, restric fertilizers and pesticides use in watersheds, control groundwater uses, investment in technology for other energy sources and pollutants removal in treatment plants, green products, among others (Abdel-Shafy & Mansour, 2016; Anastas et al., 2000; Griggs et al., 2013; Pereira et al., 2017; Quadra et al.,

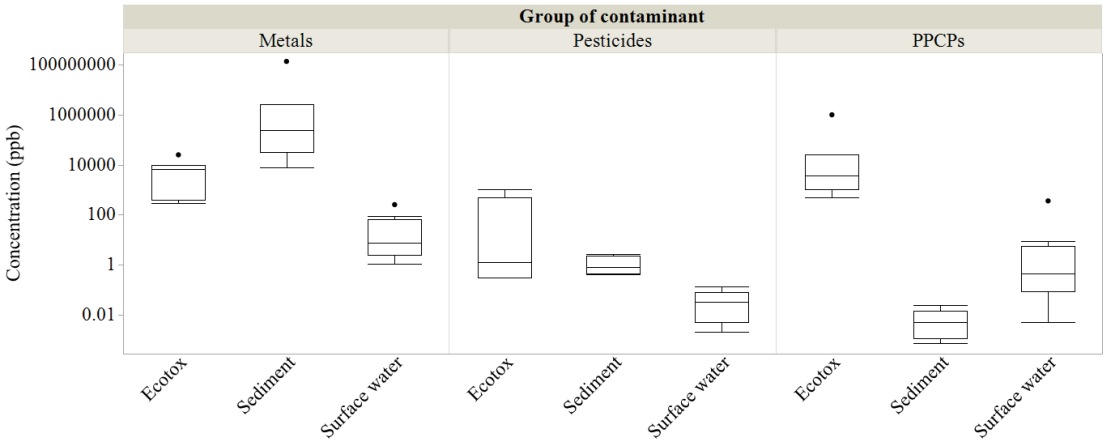

Figure 1. Concentrations of metals, pesticides and pharmaceuticals and personal care products (PPCPs) in the Brazilian aquatic ecosystem and ecotoxicological data. Sources: Almeida & Weber (2009); Alves et al. (2014); Beretta et al. (2014); Bonai et al. (2009); Brix et al. (2011); Costanzo et al. (2005); Ferreira (2005); Ghiselli (2006); Gibson et al. (2009); Gonçalves (2016); Han et al. (2010); Imai et al. (2005); Kim et al. (2012); Koprivnikar & Walker (2011); Kouyoumjian & Uglow (1974); Laabs et al. (2002); Lee et al. (2011); Liao et al. (2003); Locatelli et al. (2011); Montagner & Jardim (2011); Montagner et al. (2014); Monteiro et al. (2016); Oliveira et al. (2009); Partridge & Lymbery (2009); Pascoe et al. (2002); Pereira et al. (2016); Pestana et al. (2007); Pickering et al. (1962); Devi Prasad & Devi Prasa (1982); Rissato et al. (2006); Sanders et al. (1981); EPA (2007).

Figure 2. Different sources of chemicals to aquatic ecosystem.

2017a; Quadra et al., 2017b; Steffen et al., 2007; Steffen et al., 2011). The implementation of pollution prevention is also crucial. Pollution prevention reduces the generation of pollutants and wastes, prioritizing recycling and treatment, and minimize the use of harmful products, which includes more restrictive and effective laws on their regulations (Mulholland & Dyer 2010).

The challenges to preserve the water quality in ecosystems are many and includes the need for transdisciplinary work, such as the reforestation of riparian zones with native species and investment in environmental education and social programs (Tundisi, 2005). However, it is truly necessary to improve the communication and action among different sectors of the society (Sobek & Undeman, 2019), so that mutual attitudes can be taken, since we have the same propose: preserve water. For instance, the Brazilian water legislation provides that an effluent must have at least similar water quality, or better, than the water taken. However, the lack of supervision allows that this simply is not fulfilled. Since we use the water resources for multiple uses, it is essential that all parts involved work together to fulfill this gap. For example, it is not interesting for those who use water resources for navigation that the environment is taken of macrophytes, as well as for hydroelectric generation. Similarly, those who use the resource for animal desedentation or human use, water quality is crucial. Therefore, working together for a healthy environment is essential for a better water management. Thus, scientists also need to be together showing its results and how poor water quality generates short- and long-term losses, as well as helping to apply the ecological knowledge to generate new solutions to solve environmental problems. In order to better develop solutions for the Anthropocene issues, the transdisciplinary efforts are essential, seeking a vision of aquatic ecosystems as a whole.

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REVIEW ARTICLE

Do pharmaceuticals reach and affect the aquatic ecosystems in Brazil? A critical review of current studies in a developing country

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Abstract Pharmaceutical residues are not completely removed in wastewater treatment plants (WWTPs) becoming contaminants in aquatic ecosystems. Thereby, it is important to investigate their concentrations in the environment and the possible consequences of their occurrence, including for human health. Here, we briefly reviewed the paths of pharmaceuticals to reach the environment, their behavior and fate in the environment, and the possible consequences of their occurrence. Moreover, we synthetized all the studies about the detection of pharmaceuticals in Brazilian water bodies and the available ecotoxicological knowledge on their effects. In this study, when we compare the data found on these compounds worldwide, we observed that Brazilian surface waters present considerable concentrations of 17α-ethinylestradiol, 17β-estradiol, and caffeine. In general, concentrations found in aquatic systems worldwide seems to be low; however, ecotoxicological tests showed that even these low concentrations can cause sublethal effects in biota. The knowledge about the effects of continuous exposure and mixtures is sparse. In summary, new research is urgently required about the effects of these compounds in biota—including long-term exposition and mixture tests—and on specific technologies to remove these compounds in water bodies and WWTPs, besides the introduction of new policies for pharmaceutical use.

Keywords Contaminants · Drugs · Ecotoxicological tests · Exposure · Health · Pollutants · Residues · WWTPs

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Introduction

Aquatic ecosystems behave as both purifiers and dispersers of anthropogenic pollutants. Nowadays, many compounds that are reaching the aquatic environment have compromised their depuration capabilities (Santos 2011). Freshwater systems, for example, despite being a small portion in the water balance of the world, they are the main source of water for most human uses and are extremely important in natural water depuration and in nutrient cycling (Cole et al. 2007; Tranvik et al. 2009). Among anthropogenic pollutants, some new classes of compounds are being studied, the so-called emerging pollutants. While not usually monitored, and lacking regulatory legislation, they present potential risks to human and environmental health (Farré et al. 2008; Geissen et al. 2015). Pharmaceuticals—the active principles of drugs (ANVISA 2016)—are included in this class and present now an environmental problem. The increase in their production and consumption, due mainly to population growth, coupled to

improper discarding, raises concern about the extension of this problem.

Self-medication is also an aggravating factor in the increased production and consumption of drugs (Daughton and Ruhoy 2013) and their discharge into the environment (Locatelli et al. 2011). The World Health Organization (2011) showed that there is an urgent need for regulation and rational use of medicines, including those for veterinary use, especially by antimicrobials. In Brazil, incorrect use of drugs results in 40 % of all poisoning cases in emergency rooms (ANVISA 2005). The most common drugs for self-medication are antimicrobials, analgesics, and vitamins (WHO 2001). The random distribution of free samples, changes on prescribed treatments, poor inventory management, and lack of information (ANVISA 2005) also contribute to enhance the discharge of pharmaceutical residues into the environment. The World Health Organization alerts about the lack of information mainly by prescribers, which need updated information to make the best decision on which medicines to prescribe, and by the population that should be made aware of the correct disposal of expired or disused pharmaceuticals. For antimicrobials, for example, lack of knowledge is the main factor responsible for inappropriate use worldwide (WHO 1999; WHO 2001; WHO 2011).

The intensive use of drugs for human and veterinary applications as well as their improper discard produces wastes that may often pass through wastewater treatment plants (WWTPs) and thus are not completely removed; therefore, they may contaminate the receiving water bodies (Tambosi et al. 2010). The main concern about the occurrence of pharmaceuticals in the environment is the possibility of causing ecotoxicological effects on organisms and reaching the human food supply (Monteiro et al. 2016b). In Brazil, there are few studies investigating the occurrence of pharmaceuticals in aquatic environments (Montagner and Jardim 2011; Sodré et al. 2010b), and as we found in this review, the knowledge of the ecotoxicological effects of these compounds is even smaller. In order to understand the ecological risks of pharmaceuticals in aquatic environments and to implement mitigation strategies to this problem, the occurrence of such compounds should be closely monitored, avoiding human health and environmental risks (Monteiro et al. 2016a). Furthermore, the establishment of regulations about emerging contaminants in water resources has not been considered a priority by the Brazilian government despite major basic sanitation problems (Locatelli et al. 2011; Montagner and Jardim 2011; Monteiro et al. 2016b; Machado et al. 2016; Pereira et al. 2016). In this context, the aim of this paper is to summarize the available information about drugs in the Brazilian environment, their sources and fates, discussing the possible consequences and solutions, with the purpose of exposing the occurrence of this problem in the Brazilian environmental scene. Besides, this scenario is possibly representative of that from other developing countries that have access to modern medicines but do not apply the correct procedures to handle them safely in the environmental aspect.

Pharmaceutical production and population growth

Brazil is the ninth largest producer of medicines in the world (Febrafarma 2011; Abrafarma 2013), and its southeast region is responsible for the majority of the pharmaceutical product commerce. Population growth is one of the most important factors to increase the consumption of medicines. In Brazil, this consumption increases proportionally with population growth over time (Fig. 1). In 2015, the consumption per capita reached 16 boxes per person per year (Fig. 2). Many pharmacies and drugstores frequently sell drugs without prescription in Brazil (Locatelli et al. 2011), thus self-medication is a well-established habit among Brazilians, which makes the use of these products indiscriminate (Filho et al. 2004). Beyond this problem, the disposal of expired products happens randomly (Beretta et al. 2014).

Another important factor that leads to increased production and consumption of medicines is the inversion of the population pyramid of age worldwide (An and Jeon 2006). The immune system of the older population does not work as well as of youngsters and the incidence of chronic diseases increases (Linjakumpu et al. 2002; Tummala et al. 2010). Because of these factors, the older population is responsible for an important increase of consumption of medicines. According to data collected by the National Center for Health Statistics (USA), while general people use an average of 7 medications per person, people over 65 years of age use 20 medications per person. As the world population age tends to increase, the use of drugs to alleviate related conditions is expected to increase

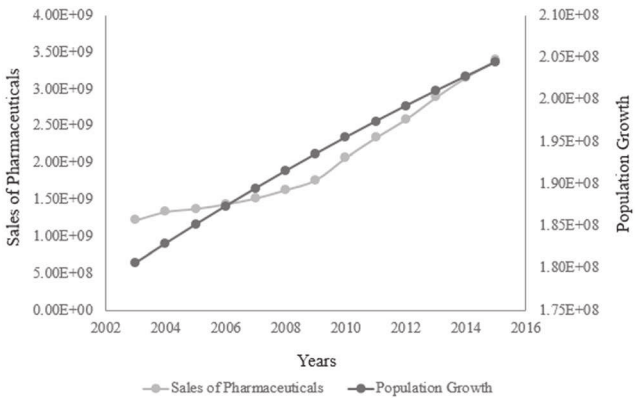

Fig. 1 Brazilian population growth and pharmaceutical market sales. Increase of Brazilian population accompanied with pharmaceutical market sales during the last 13 years. Brazilian population growth is reported as millions of people per year and sales of pharmaceuticals are indicated by billion units of boxes sold per year. Source: IBGE and Sindusfarma (IBGE: Brazilian Institute of Geography and Statistics; Sindusfarma: Pharmaceutic Products Industry Sindicate, Sao Paulo, Brazil)

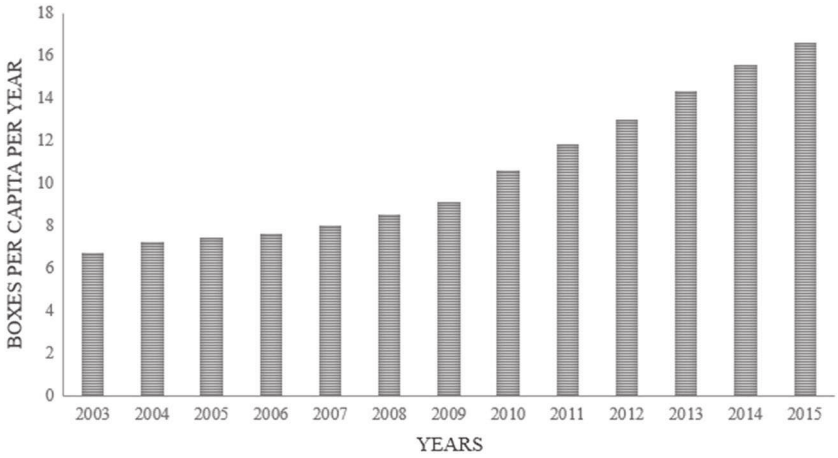

Fig. 2 Increasing use of pharmaceuticals (per capita number of boxes per year). Increase in use of pharmaceuticals indicated as a per capita value. This value was obtained using the same data of the previous graph, dividing the number of boxes of pharmaceuticals sold by the increase in Brazilian population in the same year

also (Williams and Brooks 2012). Life expectancy among older adults in Brazil has increased in recent decades. Life expectancy increased from 51 to 72 years from 1950 to 2010, and is expected to reach 77.4 years by 2030. During the same period, the proportion of older adults grew from 5 % of the total population to 10 %. In 2030, the older population is expected to more than double, reaching 40.7 million people or 17.1 % of the total Brazilian population (Andrade et al. 2016). This same tendency would apply for medicine consumption, and the related environmental loads, if no other changes in this situation happens.

Properties of pharmaceuticals

Pharmaceuticals are included in the class of emerging pollutants because they are not currently covered by regulations, and their effects on the environment and human health are still poorly understood (Corcoll et al. 2014). Furthermore, they actually emerged as important market products only by some 40 years ago (Johnson and Sumpter 2015).

The pharmaceutical industry produces many classes of drugs and each composition is designed for one specific purpose, then we have a huge variation of physicochemical properties and structures that are used both in human and veterinary medicine worldwide (Monteiro and Boxall 2010; Williams and Brooks 2012). Most of these are solid, designed as salts to improve solubility in water and its bioavailability and thus may be present in the environment in dissolved or absorbed state (Monteiro and Boxall 2010; Boxall and Ericson 2012). Besides, pharmaceuticals enter the environment at almost continuous rates, thus exposing aquatic organisms lifelong (Nash et al. 2004; AMWA and NACWA 2010; Petrović et al. 2005). Pharmaceuticals are lipophilic to pass membranes and facilitate the absorption and are in many instances persistent to maintain active properties until reaching the desired effects. Thereby, they have the properties to bioaccumulate (Mezzelani et al. 2016) and to cause negative effects in aquatic or terrestrial ecosystems, such as mortality, immobilization, growth inhibition, and reproduction inhibition (Halling-Sorensen et al. 1998; Minguez et al. 2016; Estévez-Calvar et al. 2016; Watanabe et al. 2016).

Main sources and fate of drugs in the environment

Tons of drugs are produced and applied every year in human and veterinary medicine (Bila and Dezotti 2003). Pharmaceuticals may reach aquatic ecosystems through many pathways. Because of this, many water bodies contain measurable concentrations of pharmaceuticals (Fig. 3). Depending on the properties of pharmaceuticals, some of these residues are not completely removed in WWTPs (Petrović et al. 2005; Ternes 1998; Daughton and Ternes 1999; Zwiener et al. 2000; Heberer 2002; Roberts and Thomas 2006; Suárez et al. 2008). Then, the effluent of WWTPs is a commonly recognized pathway for pharmaceutical residues to reach aquatic ecosystems (Monteiro and Boxall 2010; Rosi-Marshall and Royer 2012). These residues can cause pollution in groundwater, river water, sediment, seawater, and soil (Halling-Sorensen et al. 1998).

After the application of pharmaceuticals and personal care products (PPCPs) in human and veterinary medicine, the metabolites formed and residues reach surface waters through excretion and rinsing of PPCPs. Excretion of drugs in veterinary medicine gets into the soil and groundwater directly, without any treatment. Improper disposal of medicines is another important pathway to contaminate the environment. Depending on the hydrology of the system, pharmaceuticals can infiltrate groundwater. In many instances, waters of lakes, rivers, and reservoirs, loaded with these residues, are used as drinking water and for agriculture irrigation (WHO 1999; Bound and Voulvoulis 2005; Glassmeyer et al. 2008; Boxall and Ericson 2012).

Currently, Brazil still faces big problems related to sanitation and the urban population does not stop to grow, which aggravates the problem. This reflection is mainly due to the deficiency of proper policies to solve this problem about basic

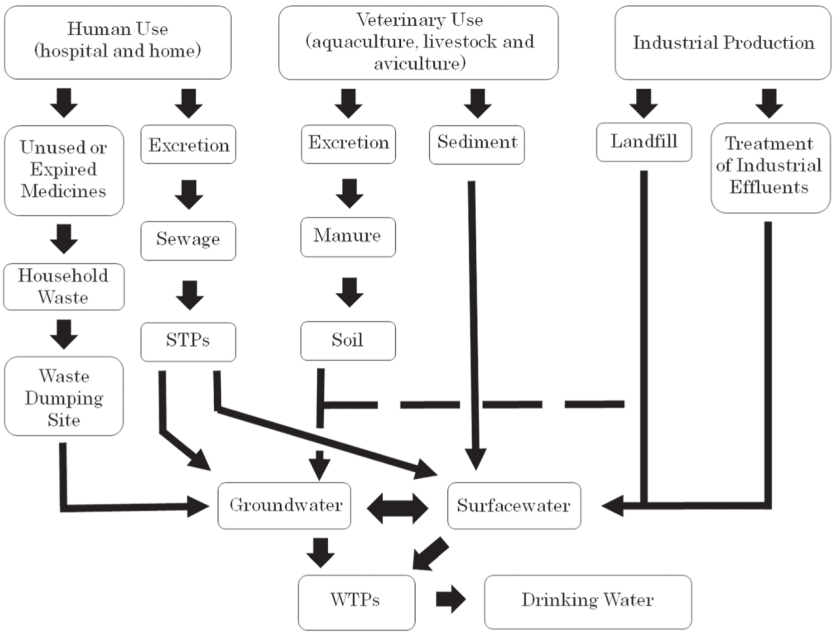

Fig. 3 Possible sources and fates of pharmaceuticals in the environment. *STPs* sewage treatment plants, *WTPs* water treatment plants. Adapted and modified from Halling-Sorensen et al. (1998); Bila and Dezotti (2003). Other sources to information on pathways: Richardson and Bowron (1985); Kümmerer (2001); Heberer (2002); Monteiro and Boxall (2010)

sanitation (Machado et al. 2016). In Brazil, in many municipalities, it is common to see discharges of raw-sewage directly into water resources (Montagner and Jardim 2011; Locatelli et al. 2011; Montagner et al. 2014). Moreover, only a minor portion of the collected wastewater passes through treatment plants, which, in Brazil, are mainly designed to decrease the organic content of the effluents, most of them using only conventional processes (Machado et al. 2016; Pereira et al. 2016). According to Aquino et al. (2013), the efficiency in the removal of pharmaceuticals is higher in tertiary treatment (reaching >90 %) because it has some measure of physicochemical process, like activated carbon adsorption and/or chemical oxidation (conventional and advanced). Even presenting a higher efficiency, tertiary treatment is rare in Brazil because it is more expensive (Aquino et al. 2013). Hence, raw-sewage discharges are among the most important sources of pollution for water resources in Brazil, causing water pollution and consequently compromising the quality of drinking water (Locatelli et al. 2011; Machado et al. 2016). This seems to be a very common scenario in the Third World, even in the beginning of the twenty-first century.

In Brazil, veterinary use is also an important source of drugs to the environment. Animal production is a very important activity in Brazilian agribusiness, and the use of drugs for therapeutic and prophylactic purposes is common to maintain strong business (Monteiro et al. 2016b). Many antibiotics are used in veterinary medicine, especially in livestock. Because of the possible consequences of overuse, Brazilian researchers have tried to show how these residues behave in the environment and their tendency to sorption and desorption in the soil. Peruchi et al. (2015) studied norfloxacin and found a high affinity by clay soils, and they suggested that this compound could be easily retained. Beyond the livestock, fish farming is also an important activity in Brazil. Monteiro et al. (2016a) studied the occurrence of antibiotics in fish farms located in Ilha Solteira Reservoir (SP, Brazil) and showed that concentrations decreased downstream from the cages but presented high levels at the cages.

Once in the environment, many factors influence the behavior of pharmaceuticals, like chemical structure, persistence, solubility, sorptive behavior, environmental degradation, climatic factors (temperature, precipitation), water body properties (pH, redox potential, organic carbon content), and composition of sediments (Boxall and Ericson 2012; Ying et al. 2013). Because of this immense complexity, it is difficult to know previously the behaviors of drugs in environment and more research in this field is required.

In summary, drugs in the environment may pass for transportation, sequestration, or degradation (Richardson and Bowron 1985; Halling-Sorensen et al. 1998; Glassmeyer et al. 2008). The process of sequestration includes partitioning and drugs could be found in the biomass (sludge) of sewage treatment plants and in living organisms (Boxall and Ericson 2012). This sludge generates biosolids that might be used as fertilizers in agriculture (Boxall and Ericson 2012), and this is an important source of contamination for the terrestrial environment. Once in the soil, these residues might be transported to aquatic ecosystems again carried by runoff, subsurface flow, drainage flow, and leaching (Boxall and Ericson 2012; Glassmeyer et al. 2008). They also can be found in sediments, and once there, they can return to the water column through several pathways, such as clearance by aquatic life, wind, and currents of water (Glassmeyer et al. 2008). Because of this possibility to return to water column, it is important to

investigate the concentration of these compounds in sediments. In Brazil, for example, all samples of sediments from Todos os Santos Bay have shown concentrations of carbamazepine, ibuprofen, diclofenac, atenolol, diazepam, and erythromycin, at levels of parts per billion of dry sediment (Beretta et al. 2014).

During the degradation process, it is important to consider that some classes of pharmaceuticals may undergo photolysis, hydrolysis, and biodegradation. Some drugs are sensitive to sunlight, such as diclofenac and naproxen (Ying et al. 2013). Hydrolysis is very important in determining the fates of antibiotics, for instance, but steroids and acid drugs cannot undergo hydrolysis (Ying et al. 2013). In sewage treatment plants, bacteria are responsible for most biodegradation processes, playing an important role in the dissipation of most pharmaceutical loads (Kümmerer 2008; Ying et al. 2013). The products of this degradation can be even more stable than the starting compounds, show variable toxicities, and have different potential of accumulation (Kümmerer 2008).

Because of the complex behavior of pharmaceuticals in the environment, a lot of information about compound degradation rates and half-lives in environmental compartments is required (Ying et al. 2013). The anti-inflammatory ibuprofen, for example, requires approximately 412 days to be degraded by photolysis and 200 days for biodegradation in river water (Yamamoto et al. 2009). The lipidic regulator clofibric acid, on the other hand, needs 119 days to be biodegraded in the sediment-water interface (Packer et al. 2003; Löffler et al. 2005). Another example is the anxiolytic diazepam that needs approximately 300 days to be biodegraded in this same environmental compartment (Löffler et al. 2005; West and Rowland 2012).

It is possible to observe that pharmaceuticals have different behaviors in the environment depending on environmental matrices, climatic factors, and chemical properties. The degree to which a pharmaceutical will be transported to different environmental compartments depends specially on the sorption behavior in soils, sediment-water systems, and treatment plants, which varies widely across pharmaceuticals (Boxall et al. 2004).

Regulation, law and correct disposal

In Brazil, effective regulations considering drugs as possible pollutants are not available, and this subject is not a priority for the government environmental organs (Machado et al. 2016; Monteiro et al. 2016b; Pereira et al. 2016). The government does not require safety tests or define concentration limits for drugs in any environmental matrix (Beretta et al. 2014). There are laws about the proper disposal of medicines in Brazil, but the laws need urgent revision about the maximum concentrations of pharmaceuticals that could be accepted in different aquatic systems (Monteiro et al. 2016a).

Legislation on healthcare product waste management has been in force in Brazil for 10 years; however, this does not address the specificities of waste management in primary healthcare, especially with regard to household-generated waste (Alves et al. 2014). After all, technical, economic, and institutional issues make it difficult for Brazilian municipalities to conduct integrated, sustainable management of the waste under their responsibility, such as urban, civil construction, and healthcare waste produced by them (Jacobi and Besen 2011), which makes the proper treatment of biological and chemical waste almost impossible (Sodré et al. 2007).

The Brazilian population has often a habit of discarding drugs in toilets and/or sinks (Lameira 2012) or directly in the trash (Bila and Dezotti 2003). As in many places, there is no garbage collection system and it is common to burn urban residues, a practice that also includes medications that may release toxic substances (Schwarzbauer et al. 2002). On the other hand, drugstores did not have the responsibility to receive and properly dispose of medicines that are no longer used, and hospitals and local health centers cannot accept medicines, even if within the validity period (Hoppe and Araújo 2012). However, much more attention on this subject is required in Brazil because the occurrence of medicines in wastewater could be considered an imminent risk to the population, since the sewage treatments, when used, are usually ineffective (Chiarello et al. 2016).

Occurrence of pharmaceuticals in aquatic ecosystems of Brazil

The groups of pharmaceuticals more commonly found in the environment worldwide between 1997 and 2009 were non-steroidal anti-inflammatory drugs (16 %), antibiotics (15 %), lipid regulators (12 %), hormones (9 %), antiepileptics (8 %), and β-blockers (8 %) (Santos et al. 2010). There are some Brazilian studies focused on the occurrence of pharmaceuticals in the environment. We tried to put them all together in order to provide a review of what had been found in Brazil (Table 1).

Our results have shown that studies about the occurrence of pharmaceuticals in the environment are punctual in the country, Sao Paulo being the state that has more studies about detection of these compounds in aquatic ecosystems. We found that hormones are more studied and found in higher concentrations in the environment compared to other compounds. One hypothesis for this is that there are more researches focused on this class of drugs, since its consequences for humans can be potentially bigger, though still mostly unknown. We found that among the 22 pharmaceuticals detected in surface waters around the world, about 13 are common between Brazil and other countries. When comparing our findings with those of the review from Monteiro and Boxall (2010), it is possible to observe that Brazil show considerably high concentrations of 17β-estradiol (6000 ng L^{-1}), 17α-ethinylestradiol (35,000 ng L^{-1}), and caffeine (357,000 ng L^{-1}).

Table 1 Presence of pharmaceuticals in Brazilian water bodies

Therapeutic class	Compound	Place	Value (ng L^{-1})	References
Anxiolytics	Diazepam	Billings Reservoir (SP)	0.2–4.8	Almeida and Weber (2005)
Antipyretic and stimulants	Acetaminophen	Billings Reservoir (SP)	0.3–10.3	Almeida and Weber (2005)
	Acetaminophen	Atibaia River (SP)	280	Montagner and Jardim (2011)
	Acetaminophen	Santos Bay (RJ)	29.1	Pereira et al. (2016)
	Acetaminophen	São Domingos Stream (RJ) 50 m before the STP	3031	Gonçalves (2012)
	Caffeine	Billings Reservoir (SP)	0.35–28.3	Almeida and Weber (2005)
	Caffeine	Guanabara Bay (RJ)	134,000–147,000	Ferreira (2005)
	Caffeine	Leopoldina Basin (RJ)	160,000–357,000	Ferreira (2005)
	Caffeine	Alto Iguaçu Basin (PR)	170–22,840	Ide et al. (2013)
	Caffeine	Atibaia River (SP)	200–127,000	Raimundo (2007)
	Caffeine	Atibaia River (SP)	1100–16,800	Ghiselli (2006)
	Caffeine	Ribeirão Anhumas (SP)	35,300–106,000	Ghiselli (2006)
	Caffeine	Santos Bay (RJ)	511.3	Pereira et al. (2016)
	Caffeine	Tap water of Campinas (SP)	0.22 ± 0.06	Sodré et al. (2010a)
Analgesics and anti-inflammatories	Diclofenac	Billings Reservoir (SP)	8.1–394.5	Almeida and Weber (2005)
	Diclofenac	Resende (RJ) (Paraíba do Sul river)	20	Stumpf et al. (1999)
	Diclofenac	Vargem Alegre (RJ) (Paraíba do Sul river)	60	Stumpf et al. (1999)
	Diclofenac	Barra do Piraí (RJ) (Paraíba do Sul river)	60	Stumpf et al. (1999)
	Diclofenac	Três Rios (RJ) (Paraíba do Sul river)	50	Stumpf et al. (1999)
	Diclofenac	Além Paraíba (RJ) (Paraíba do Sul river)	40	Stumpf et al. (1999)
	Diclofenac	Itaocara (RJ) (Paraíba do Sul river)	30	Stumpf et al. (1999)
	Diclofenac	Cambuci (RJ) (Paraíba do Sul river)	20	Stumpf et al. (1999)
	Diclofenac	Atibaia River (SP)	2440–5900	Ghiselli (2006)
	Diclofenac	Atibaia River (SP)	106 ± 13	Montagner and Jardim (2011)
	Ibuprofen	Billings Reservoir (SP)	10.0–78.2	Almeida and Weber (2005)
	Ibuprofen	Paquequer River and affluents (RJ) Main canal	478.4	Gonçalves (2012)
	Ibuprofen	Sarapuí-Iguaçu Rivers (RJ) Mounth of system	640.5	Gonçalves (2012)
	Ibuprofen	Santos Bay (RJ)	2094.4	Pereira et al. (2016)
	Salicylic acid	São Domingos Stream (RJ) 2 km after the STP	1219.1	Gonçalves (2012)
	Salicylic acid	Paraíba do Sul River and affluents (RJ) Main canal/Resende	606	Gonçalves (2012)
	Salicylic acid	Guandu River and affluents (RJ)	1208	Gonçalvez (2012)
	Salicylic acid	Sarapuí-Iguaçu Rivers (RJ) Mouth of the Sarapuí river	8341.2	Gonçalves (2012)
	Salicylic acid	Atibaia River (SP)	828 ± 295	Montagner and Jardim (2011)
	Naproxen	Resende (RJ) (Paraíba do Sul river)	30	Stumpf et al. (1999)
	Naproxen	Vargem Alegre (RJ) (Paraíba do Sul river)	50	Stumpf et al. (1999)
	Naproxen	Além Paraíba (RJ) (Paraíba do Sul river)	30	Stumpf et al. (1999)
	Naproxen	Itaocara (RJ) (Paraíba do Sul river)	20	Stumpf et al. (1999)
	Naproxen	Campos (RJ) (Paraíba do Sul river)	20	Stumpf et al. (1999)
	Naproxen	São Domingos Stream (RJ) 50 m before the STP	1004.8	Gonçalves (2012)
	Naproxen	Ribeirão Santissímo STPs (RJ)	1578.9	Gonçalves (2012)
Antibiotics	Norfloxacin	Piracicaba River (SP)	8–26/18	Torres (2014)
	Norfloxacin	Atibaia River (SP)	2.2	Locatelli et al. (2011)

Table 1 (continued)

Therapeutic class	Compound	Place	Value (ng L^{-1})	References
	Norfloxacin	Anhumas Creek (SP)	51	Locatelli et al. (2011)
	Amoxicillin	Atibaia River (SP)	17	Locatelli et al. (2011)
	Cefalexin	Atibaia River (SP)	29	Locatelli et al. (2011)
	Cefalexin	Anhumas Creek (SP)	133	Locatelli et al. (2011)
	Ciprofloxacin	Atibaia River (SP)	2.5	Locatelli et al. (2011)
	Ciprofloxacin	Anhumas Creek (SP)	119	Locatelli et al. (2011)
	Sulfamethoxazole	Atibaia River (SP)	1.8	Locatelli et al. (2011)
	Sulfamethoxazole	Anhumas Creek (SP)	106	Locatelli et al. (2011)
	Sulfamethoxazole	Pedras River (RJ)	467	Monteiro et al. (2016b)
	Tetracycline	Atibaia River (SP)	11	Locatelli et al. (2011)
	Trimethoprim	Atibaia River (SP)	5.3	Locatelli et al. (2011)
	Trimethoprim	Anhumas Creek (SP)	484	Locatelli et al. (2011)
	Oxytetracycline	Ilha Solteira Reservoir (SP) 0 m at the cages	220 ± 8	Monteiro et al. (2016a)
	Oxytetracycline	Ilha Solteira Reservoir (SP) 100 m downstream from the cages	27 ± 2	Monteiro et al. (2016a)
	Oxytetracycline	Pedras River (RJ)	44.1	Monteiro et al. (2016b)
	Florfenicol	Ilha Solteira Reservoir (SP) 0 m - at the cages	425 ± 46	Monteiro et al. (2016a)
	Florfenicol	Ilha Solteira Reservoir (SP) 100 m downstream from the cages	10 ± 1	Monteiro et al. (2016a)
Antidiabetic	Buformin	Billings Reservoir (SP)	2.6–18.4	Almeida and Weber (2005)
Beta blockers and diuretics	Atenolol	Billings Reservoir (SP)	0.9–16.4	Almeida and Weber (2005)
	Atenolol	São Domingos Stream (RJ) 50 m after the STP	821,7	Gonçalves (2012)
	Atenolol	São Domingos STP (RJ)	1437.3	Gonçalves (2012)
	Propranolol	São Domingos Stream (RJ) 50 m after the STP	15.2	Gonçalves (2012)
	Valsartan	Santos Bay (RJ)	20.5	Pereira et al. (2016)
	Valsartan	Sarapuí-Iguaçu Rivers (RJ) Mouth of the Sarapuí river	593.4	Gonçalves (2012)
	Losartan	São Domingos Stream (RJ) 50 m after the STP	574.9	Gonçalves (2012)
	Valsartan	Domingos Stream (RJ) 50 m after the STP	215.2	Gonçalves (2012)
	Furosemide	São Domingos STP (RJ)	7543.6	Gonçalves (2012)
Lipid regulators	Bezafibrate	Billings Reservoir (SP)	1.2–3.7	Almeida and Weber (2005)
	Bezafibrate	São Domingos Stream (RJ) 50 m before the STP	201.5	Gonçalves (2012)
	Bezafibrate	Paraíba do Sul River and affluents (RJ) Main canal/ Resende	606	Gonçalves (2012)
	Acid clofibric	Resende (RJ) (Paraíba do Sul river)	20	Stumpf et al. (1999)
	Acid clofibric	Itaocara (RJ) (Paraíba do Sul river)	20	Stumpf et al. (1999)
	Acid clofibric	Cambuci (RJ) (Paraíba do Sul river)	30	Stumpf et al. (1999)
Hormones	17β-estradiol	Penha STP (RJ)	21	Ternes et al. (1999)
	17β-estradiol	Atibaia River (SP)	1900–3000	Ghiselli (2006)
	17β-estradiol	Ribeirão Anhumas (SP)	2000–6000	Ghiselli (2006)
	17β-estradiol	Campinas WTP (raw water)	3–9.7	Gerolin (2008)
	17β-estradiol	Campinas WTP (potable water)	0.78–1.05	Gerolin (2008)
	17β-estradiol	Sumaré WTP (raw water)	5.25–7.27	Gerolin (2008)
	17β-estradiol	Sumaré WTP (potable water)	1.02–1.48	Gerolin (2008)
	17β-estradiol	Araraquara (SP)	31	Araújo (2006)
	17β-estradiol	Córrego Rico (SP)	8.6–30.6	Lopes (2007)
	17β-estradiol	Campo Grande (MS)	6.5–6.8	Souza (2008)
	17β-estradiol	Piracicaba River (SP)	nd – 87	Torres et al. (2015)
	17β-estradiol	Atibaia River (SP)	464	

Table 1 (continued)

Therapeutic class	Compound	Place	Value (ng L^{-1})	References
				Montagner and Jardim (2011)
	17β-estradiol	Atibaia River (SP)	nd – 7.3	Sodré et al. (2010b)
	17α-ethinylestradiol	Campinas WTP (raw water)	444	Gerolin (2008)
	17α-ethinylestradiol	Campinas WTP (potable water)	275	Gerolin (2008)
	17α-ethinylestradiol	Sumaré WTP (raw water)	798	Gerolin (2008)
	17α-ethinylestradiol	Sumaré WTP (potable water)	472	Gerolin (2008)
	17α-ethinylestradiol	Atibaia River (SP)	1200–1700	Ghiselli (2006)
	17α-ethinylestradiol	Ribeirão Anhumas (SP)	1400–3500	Ghiselli (2006)
	17α-ethinylestradiol	Campo Grande (MS)	6.25–25	Souza (2008)
	17α-ethinylestradiol	Piracicaba River (SP)	nd–150	Torres et al. (2015)
	17α-ethinylestradiol	Atibaia River (SP)	981	Montagner and Jardim (2011)
	17α-ethinylestradiol	Atibaia River (SP)	nd–25	Sodré et al. (2010b)
	Estriol	Campinas WTP (raw water)	3–3.93	Gerolin (2008)
	Estriol	Campinas WTP (potable water)	0.43–1.24	Gerolin (2008)
	Estriol	Sumaré WTP (raw water)	1.09–6.1	Gerolin (2008)
	Estriol	Sumaré WTP (potable water)	1.48–2.05	Gerolin (2008)
	Estriol	Piracicaba River (SP)	nd–46	Torres et al. (2015)
	Estriol	Atibaia River (SP)	nd–2.3	Sodré et al. (2010b)
	Estriol	Rivers in Rio de Janeiro State	3.68	Kuster et al. (2009)
	Estrone	Penha (RJ)	40	Ternes et al. (1999)
	Estrone	Campinas WTP (raw water)	0.15–11.6	Gerolin (2008)
	Estrone	Campinas WTP (potable water)	0.1	Gerolin (2008)
	Estrone	Sumaré WTP (raw water)	0.33–0.54	Gerolin (2008)
	Estrone	Sumaré WTP (potable water)	0.07–0.1	Gerolin (2008)
	Estrone	Ribeirão Anhumas (SP)	3500	Ghiselli (2006)
	Estrone	Piracicaba River (SP)	nd–14	Torres et al. (2015)
	Estrone	Atibaia River (SP)	2.2–39	Sodré et al. (2010b).
	Progesterone	Piracicaba River (SP)	nd–26	Torres et al. (2015)
	Progesterone	Atibaia River (SP)	195	Montagner and Jardim (2011)
	Progesterone	Rivers in Rio de Janeiro State	9.35	Kuster et al. (2009)
Antidepressants and psychiatric medication	Venlafaxine	Ribeirão Santissímo STP (RJ)	40.1	Gonçalves (2012)
	Carbamazepine	Paraíba do Sul River and affluents (RJ) Main canal/ Resende	309.8	Gonçalves (2012)
Personal care products	Triclosan	Rivers in Sao Paulo State	2.2–66	Montagner et al. (2014)

nd not detected, *SP* São Paulo, *RJ* Rio de Janeiro, *PR* Paraná, *MS* Mato Grosso do Sul

Anxiolytics

Formerly, not many years ago, people (patients and health professionals) believed that anxiety disorders were rare. However, in the 1990s, an explosion of research into anxiety occurred, especially with childhood and adolescence (Rapee et al. 2009). In this context, the use of anxiolytics has increased, and among these, the drug diazepam standing out between the others. Diazepam is used in humans as a hypnotic, tranquilizer, and anticonvulsant (Bautitz et al. 2012).

Almeida and Weber (2005) detected diazepam in Billings Reservoir (São Paulo, Brazil) (Table 1). Ecotoxicological effects of diazepam were not found in Brazil, but Oggier et al. (2010) found that diazepam at 235 ng L^{-1} was able to alter the expression of 51 genes in the brain of zebrafish (*Danio rerio*), in which 61 % of genes were downregulated and 39 % were upregulated. Despite the higher concentrations than those found in the environment, including in Brazil, these results are concerning because organisms can fix the damages in subsequent generations, and the errors would affect the species in the long-term.

Antipyretics and stimulants

Caffeine is one of the most consumed stimulants around the world and is a common component of foods, drinks, and drugs (Chen et al. 2002). Humans only use caffeine, and then many researchers are using this compound as indicator of sewage effluent (Gardinali and Zhao 2002). After all, caffeine is stable, not completely metabolized, and is easily determined (Berreta et al. 2014). It is possible to observe in Table 1, comparing with data from Monteiro and Boxall (2010), that Brazil has the highest concentration of caffeine in surface waters in the world, and this observation could be related to high consumption, as it could be expected because of the long tradition of Brazil in the coffee industry (Camargo 1999).

Machado et al. (2016) used 100 samples of drinking water spread across 22 Brazilian state capitals to analyze emerging pollutants. In these samples, the most frequently detected substance was caffeine. They found a maximum concentration of 2769 ng L^{-1} of caffeine in Porto Alegre. In this capital, as well as in the entire state of Rio Grande do Sul, people have the cultural habit to take a hot drink made of yerba mate, in which caffeine is the most important component. The presence of caffeine in 93 % of samples of treated water indicates a contamination by domestic sewage in water sources, as it is known that this substance has anthropogenic origin (Machado et al. 2016). Nevertheless, no ecotoxicological effect of caffeine has been detected yet in Brazil. Moore et al. (2008) found that 57 ± 3.3 mg L^{-1} of caffeine was lethal to 50 % of *Ceriodaphnia dubia* (microcrustacean) in a 48-h exposure. Moore et al. (2008) also evaluated the sublethal effects and found that reproduction of 50 % of *C. dubia* reproduction was impaired at 44 mg L^{-1} and also showed a growth inhibition of 50 % of *Pimephales promelas* (fathead minnow) at 71 mg L^{-1}. Despite the higher concentrations in this study than those found in the environment, is it not prudent to ignore the possibility of synergistic effects with other substances and more intense effects at long exposure? For instance, recently, Li et al. (2012) found that the activity of acetylcholinesterase in the brain of *Carassius auratus* (goldfish) was significantly inhibited by higher concentrations (mg L^{-1} magnitude) of caffeine and sulfamethoxazole after 2 days of exposure, showing that both drugs coupled can inhibit the enzyme.

Normally in Brazil, only psychotropic and antibiotic medications have the prescription retained at the time of purchase. Antipyretic drugs do not require a prescription or the prescription is presented but not retained, allowing a new use (Silva et al. 2012). Because of this situation, self-medication with antipyretics becomes common. A study conducted in Brazil by Silva et al. (2012) showed that in a group of university students, the drug most used by those interviewed is acetaminophen, although they discouraged friends and relatives from self-medication. Acetaminophen was determined in Sao Paulo and Rio de Janeiro surface waters in the range of 0.3–280 ng L^{-1} (Almeida and Weber 2005, Montagner and Jardim 2011, Pereira et al. 2016). David and Pancharatna (2009) showed that 50 μg L^{-1} of acetaminophen affected embryonic development of zebrafish (*D. rerio*). Galus et al. (2013) found that a mixture of equal concentrations of acetaminophen, carbamazepine, gemfibrozil, and venlafaxine was capable to reduce embryo production and embryo mortality and increase the incidence of regressive changes within the kidney tubule in zebrafish. All these results are a concern about the concentrations found in the environment, because endpoints tested can implicate in ecological imbalances and loss of biodiversity at long term.

Analgesics and anti-inflammatories

Analgesics are used to relieve pain and many are sold without prescription; thus, self-medication is very common. The half-life of these drugs in the environment is short (a few hours); however, they can cause chronic effects on aquatic biota since its introduction into surface waters is almost continuous (Lameira 2012). In Brazil, Lameira (2012) showed that water temperature can influence the toxicity of dipyrone and a concentration of 21.1 and 4.59 mg L^{-1} can cause growth inhibition on 50 and 25 % of *Daphnia similis* (microcrustacean) embryos, respectively.

Diclofenac was detected in some cities of Rio de Janeiro state along Paraíba do Sul river and both diclofenac and ibuprofen were found in the Billings Reservoir (São Paulo) (Table 1). Ibuprofen is one of the most prescribed medications in the treatment of rheumatic pains and fevers (Almeida and Weber 2005) and is one of the most commonly used anti-inflammatory drugs (Colaço 2013). Its world production was estimated at 15,000 t per year (Myers 2007). Furthermore, 70 to 80 % of therapeutic dose is excreted (Hutt and Caldwell 1983) and because of its physical and chemical properties, this drug may have mobility in aquatic environments (Almeida and Weber 2005). Cleuvers (2003) showed that a mixture of diclofenac at 68 mg L^{-1} and ibuprofen at 108 mg L^{-1} could cause more immobilization in *D. magna* (microcrustacean) and inhibition of the average growth rate for algae in

comparison to the singly measured toxicities, thus having a synergistic effect.

Anti-inflammatories are among the most important and commonly used groups of pharmaceuticals in the world. They are estimated to be produced in an annual basis of several thousands of tons, and many formulations can be purchased without prescription, so the consumption is equally high (Cleuvers 2003; Jill 2015). Because of this, compounds of the anti-inflammatory group are commonly found in sewage-impacted waters (Corcoll et al. 2014). Corcoll et al. (2014) found that biofilms could acquire tolerance of the mixture ibuprofen + diclofenac, corroborating the synergetic effects of this mixture showed also by Cleuvers (2003). Pharmaceuticals, combined with many other contaminants and environmental factors, could change the algal community, as well as the microbial metabolic profile, and have potential to cause adverse effects on aquatic ecosystems (Corcoll et al. 2014). In Brazil, naproxen was found in water bodies (Table 1) and the toxicology of paracetamol and dipyrone was tested in cladocerans. According to Lameira (2012), paracetamol was able to cause a growth inhibition in 25 % of *D. similis* at 4.15 mg L^{-1}, a similar effect being observed at 4.47 mg L^{-1} in *C. dubia* and the more sensible organism tested being *C. silvestrii* , affected at 2.96 mg L^{-1} for the same endpoint. Lameira (2012) also tested dipyrone and found effects at 3.59, 2.79 and 1.12 mg L^{-1} in *D. similis*, *C. dubia*, and *C. silvestrii*, respectively, causing growth inhibition in 25 % of tested organisms. With this ecotoxicological tests, we observed that dipyrone was more toxic than paracetamol was and *C. silvestrii* was the more sensible organism in both cases.

Antibiotics

Antibiotics are natural or synthetic compounds able to inhibit growth or kill bacteria and fungi (Walsh 2003). These drugs have high solubility in water (Sasaki 2012) and, as many other drugs, are designed to be persistent. The concern about antibiotics in the environment is that they can change the genetic composition of microorganisms and could lead to the development of resistant pathogens (Jones et al. 2005). In Brazil, Torres (2014) showed that norfloxacin, sulfadiazine, and erythromycin are able to cause immobility in *D. magna* at concentrations in the order of milligrams per liter. Torres (2014) also detected the presence of norfloxacin in six points of Piracicaba River in concentrations ranging from 8 to 26 ng L^{-1} (Table 1), thus six orders of magnitude less than those that can cause immobility to the test organisms. However, cytotoxicity tests developed by Pomati et al. (2006) revealed that the human embryonic cell growth was inhibited by a mixture of drugs (atenolol, bezafibrate, carbamazepine, cyclophosphamide, ciprofloxacin, furosemide, hydrochlorothiazide, ibuprofen, lincomycin, ofloxacin, ranitidine, salbutamol, and sulfamethoxazole) at environmental levels (ng L^{-1}) after 48 h by 10 to 30 % compared to controls.

Antidiabetics

Buformin was found in Billings Reservoir (São Paulo, Brazil) at 2.6–18.4 ng L^{-1} (Table 1). These kinds of medicine act on insulin synthesis (Almeida and Weber 2005). In this review, we did not find ecotoxicology Brazilian studies using antidiabetics. Metformin was found in aquatic systems in other countries such as Germany and USA. This compound is more studied than Buformin is, due to the high consumption, persistence, and capability to bioaccumulate. Its elimination in sewage treatment plants is between 80 and 98 % (Chiarello 2014). However, experiments performed by Carlsson et al. (2006) have demonstrated that high concentrations of metformin are required to cause toxic effects on biota. Nevertheless, it still needs attention because we know very little about the effects of mixtures and continuous exposure in long-term periods.

β-blockers

β-Blockers are widely used to treat hypertension and heart failure (Bonnineaua et al. 2010). Propranolol showed a mean value of 96 % of elimination in sewage treatment plants (Ternes 1998; Ternes et al. 1999; Heberer 2002). In Brazil, atenolol was found in Billings Reservoir at 0.9–16.4 ng L^{-1} (Sao Paulo, Brazil) (Almeida and Weber 2005) and Valsartan at 20.5 ng L^{-1} in Santos Bay (Rio de Janeiro, Brazil) (Pereira et al. 2016)(Table 1). In Brazil, Rosa (2008) tested propranolol in *C. silvestrini* and found a lowest observed effect concentration of 2.5 mg L^{-1} using mortality and immobility as endpoints. Pomati et al. (2008) showed that atenolol has effect on prokaryotic and eukaryotic cells at environmentally relevant exposure levels (ng L^{-1} to μg L^{-1}). They indicated a potential hazard for some particular human conditions, such as pregnancy or infancy, in the case of chronic exposure via contaminated drinking water by atenolol and other pharmaceuticals.

Lipid regulators

Lipid regulators are used to decrease levels of cholesterol and triglycerides in blood (Aquino et al. 2013). Almeida and Weber (2005) detected bezafibrate in Billings Reservoir (Sao Paulo, Brazil) and Stumpf et al. (1999) found clofibric acid in Resende, Itaocara, and Cambuci (Rio de Janeiro, Brazil) (Table 1). Bezafibrate also has also been found in pesticide composition (Roque 2009).We did not find Brazilian studies about the effects of these compounds in organisms. Clofibric acid was not biologically degraded in experimental test during

the period of 21 days (Winkler et al. 2001) and has a very persistent behavior in aquatic environments (Buser and Muller 1998). Ferrari et al. (2003) showed that until a concentration level of 246 μg L^{-1} of clofibric acid effects in reproduction of *Brachionus calycifloru* (rotifer) after 48-h exposure were not observed. Another study conducted by Runnalls et al. (2007) showed that concentrations of 0.1 μg L^{-1}, 1 μg L^{-1}, and 1 mg L^{-1} of clofibric acid were able to increase the number of non-viable (dead) sperm of fathead minnow, and the highest concentration also decreased the swimming velocity in the fish.

Hormones

Estrogens affect the functions of the endocrine system and are used as contraceptives and in hormonal replacement therapy. There are compounds that have a greater environmental concern, such as the natural estrogens 17β-estradiol, estriol and estrone, and the synthetic estrogen 17α-ethinylestradiol (Filho et al. 2006). According to Bila and Dezotti (2007), estrogens are found in the environment in concentrations ranges from μg L^{-1} to ng L^{-1} and can cause adverse effects on human and animal health. These hormones are often metabolized and excreted in inactive forms; however, the action of bacteria in waste disposal areas can transform them into biologically active compounds (Tyler and Routledge 1998). If we compare our data with those of the Monteiro and Boxall (2010) review, we can observe that Brazil has showed considerable concentrations of 17β-estradiol and 17α-ethinylestradiol in surface waters, even when compared with other countries such as Germany and United States.

In Brazil, Torres (2014) developed ecotoxicological testing with hormones and observed that estriol is able to cause immobility in *D. magna* at a concentration of 94.6 mg L^{-1}. According to Bila and Dezotti (2003), fish are often used as test organisms for ecotoxicological studies with estrogens in other countries. In this context, we noted that Brazil has a shortage of studies about effects of pharmaceuticals in fishes despite ecological and economic relevance. Pawlowski et al. (2004) studied the effects of 7α-ethinylestradiol in fathead minnow (*P. promelas*) and found that environmental concentrations, in order of ng L^{-1}, can be a problem for the health of fish. For example, exposure resulted in a significant decrease in gonadosomatic index and umber of batches of eggs and their fertilization rate between 10and 100 ng L^{-1}. They were then exposed to various nominal concentrations of the synthetic estrogen 17α-ethinylestradiol (0, 0.1, 1, 3, 10, 100 ng/L). After 3 weeks of chemical exposure, effects on plasma vitellogenin, secondary sex characteristics, gonad growth (gonadosomatic index), and condition factor were assessed. This research is worrying, because the concentrations found in Brazilian surface waters were demonstrated to be capable to cause many problems in *P. promelas* reproduction.

Antidepressants and psychiatric medications

The use of drugs to control anxiety and depression in Brazil has become abusive. Among the antidepressants, fluoxetine hydrochloride is the most widely used and is applied for the treatment of depression, obsessive-compulsive disorder, nervous bulimia, and panic disorder, being also improperly used to provide a measure of weight control (Myers 2007). According to Silva (2014), this is one of the most prescribed medications in Brazil (and in the world). The fluoxetine metabolism originates norfluoxetine, which is a primary and active metabolite. Due to the extensive use of the parent compound, this compound has been also detected in the aquatic environment, and ecotoxicological data demonstrated the potential effects that it may cause in the biota, which has already been noted in *Ceriodaphnia dubia* causing a reduction in reproduction (Brooks et al. 2003). Despite being found at low concentrations (in the range of ng L^{-1}), fluoxetine has low biodegradability, is persistent, and has potential to bioaccumulate, then negative effects to biota could be expected (Silva 2014).

In Brazil, Wolff (2011) tested fluoxetine in *D. similis* and obtained an effective concentration to affect 50 % of organisms of 8900 ng L^{-1} using immobility as endpoint. Wolff also saw that 100 ng L^{-1} of fluoxetine was able to cause growth inhibition in 50 % of *Pseudokirchneriella subcaptata.* This study raises concern about antidepressants in the environment because the concentrations in the environment are frequently around these values. We did not find Brazilian studies about the occurrence of fluoxetine in aquatic systems, but Gonçalves (2012) found a concentration of 40.1 ng L^{-1} of venlafaxine in an effluent of sewage treatment plant in Santa Maria Madalena (Rio de Janeiro), which is in the same concentration range. Clearly, more data are lacking on this specific subject.

Personal care products

Among the class of personal care products, triclosan is used in many consumer products because it has bacteriostatic function (Pusceddu 2009). According to Aranami and Readman (2007), the half-life of triclosan in aquatic ecosystems is approximately 4 to 8 days. Triclosan is capable to inhibit fatty acid synthesis, interact with membrane phospholipids, and affect the mitochondrial function (Canesi et al. 2007). Montagner et al. (2014) found triclosan at 2.2–66 ng L^{-1} in rivers in Sao Paulo state (Table 1). A Brazilian study conducted by Cortez (2011) showed triclosan effects in crustaceans, echinoderms, and mollusks. The results found by Cortez (2011) showed that, in most cases, it is necessary more than the concentration found by Montagner et al. (2014) in the environment to cause ecotoxicological effects in organisms. However, a cell viability technique (neutral red) showed that 12 ng L^{-1} in a 72-h experiment and 120 ng L^{-1} in a 48-h

experiment of this agent was capable of damaging the membranes. These results indicate that we need more studies to evaluate the real extent of environmental pollution, especially cytogenotoxicity tests.

Herbal medicines and heavy metals in the composition of pharmaceuticals

Herbal medicines could be derived from any part of a plant, such as root, stem, and leaf. This class of compounds also needs attention because people used many of these formulations with the perception that they are natural and thus have no collateral effects. Nevertheless, in some cases, natural products can cause irreversible damage on health (Ferreira and Pinto 2010). The largest group of cases, which presents adverse effects, involves herbal sedatives. Generally, these products contain valerian (*Valeriana officinalis*), passionflower (*Passifiora incarnata*), or both (Shaw et al. 1997). Some heavy metals are used in pharmaceutical formulations, especially in oriental medicine with herbal extracts. A Brazilian study investigated some extracts of *Aesculus hippocastanum* (French and German origin) and detected the presence of lead concentrations 440 % above the acceptable levels (Veiga and Pinto 2005). Because of these problems, it is necessary to monitor the composition of natural medicines and its applications.

Consequences of the presence of pharmaceuticals in the environment

In many cases, the consequences of the occurrence of pharmaceuticals in the environment are not yet clear (Huggett et al. 2002), but the concern about drugs is growing every year (Jones et al. 2001; Castiglioni et al. 2006; Caliman and Gavrilescu 2009; Halm-Lemeille and Gomez 2016). Lodeiro et al. (2016) even suggested that we are transforming our sources of drinking water in medicines, literally. Our results indicated that more attention has been given to understanding the presence and impacts of pharmaceuticals in freshwater ecosystems (Hughes et al. 2012) and less attention to investigate the release from sewage collection/treatment/discharge systems that are possible routes for these compounds into coastal environments and their possible impacts in marine ecosystems (Gaw et al. 2014). Beyond that, many of these residues of pharmaceuticals can induce endocrine effects (Caliman and Gavrilescu 2009). The knowledge about the sources, behavior and effects of pharmaceuticals is important to understand environmental risks. Nowadays, there are many uncertainties associated with the environmental risk assessment of pharmaceuticals due to lack of knowledge about their fate in the environment; their uptake, metabolism, and excretion in wildlife; and their target affinity and functional effects in non-target species (Boxall et al. 2012).

Normally, PPCPs are found in low concentrations in the environment and for a long time, they were not considered a concern in environmental monitoring (Pusceddu 2009). However, because of continual release, they behave as "persistent" compounds and could cause long-term ecological effects (Brausch et al. 2012). It is a fact that the concentrations found in the environment are generally low, in the order of ng L^{-1}. However, literature studies are showing effects even in this order; for example, 4 ng L^{-1} of estradiol resulted in feminization of *P. promelas* and the same concentration of 17α-ethinylestradiol also caused feminization of *Rutilus rutilus* (Lange et al. 2001; Lange et al. 2009).

Another important aspect of this question is that drug residues are usually found in the aquatic ecosystems as mixtures, not as single contaminants (Cleuvers 2003). Thereby, the biochemical actions of some compounds can affect the biochemical action of others, producing synergistic or antagonistic effects and turning ecological risk evaluation into a very complicated problem. Cleuvers (2003, 2004) used *Daphnia* as test organism to evaluate the effects of pharmaceutical mixtures. He found, for example, that ibuprofen and diclofenac when presented together can cause higher percentage of immobilized *Daphnia* in the experimental system than when tested isolated, and the same happens when clofibric acid is presented together with carbamazepine. A study conducted by Flaherty and Dodson (2005) shows that mixtures of different compounds in the aquatic environment caused others serious effects on *D. magna*; for example, the mixtures of three to five antibiotics (total concentration of 30–500 μg L^{-1}) elicited changes in the reproduction rate of *Daphnia*. Some studies indicate that the effects of pharmaceuticals in aquatic organisms could be diverse and wide (Rosi-Marshall and Royer 2012), although this subject has not been as extensively studied as required. Pharmaceuticals discharged into water bodies can suppress growth, alter gender, and change behavior and physiology, affecting ecological functions of various organisms such as fish, amphibians, and invertebrates (Doerr-MacEwen and Haight 2006; Bechtold et al. 2013).

According to this review, marine organisms present higher sensitivity to pharmaceuticals than do freshwater organisms, as shown by the few data available on mussels (*Perna perna*) and sea urchins (*Lytechinus variegatus*) in Brazilian studies (supplementary material) that indicated a higher sensitivity by orders of magnitude when compared to freshwater organisms. However, marine organisms are seldom tested, and ecological effects of these compounds in the marine ecosystems remain mostly unknown. Studies reported by Kim et al. 2007 tested different pharmaceuticals, such as acetaminophen, carbamazepine, cimetidine, and diltiazem, in the marine bacterium *Vibrio fischeri* and in two freshwater organisms *Daphnia magna* (crustaceans) and *Oryzias latipe* (fish). Among the tested organisms, *D. magna* was the most sensitive to almost all the pharmaceuticals tested. It is worth emphasizing that

the available literature often report acute toxicity tests and generally in algae, daphnids, and fishes (Cunningham et al. 2006).

In Brazilian studies, the majority of test organisms were cladocerans. These animals are good models because they are sensitive to a wide range of contaminants; they have low genetic variability and are easy to maintain in laboratory (EPA 2002). Studies have tested sublethal endpoints, with the largest number testing growth inhibition, followed by reproduction rate, as these sublethal effects are crucial to be observed (Rand and Petrocelli 1985), because they represent significant damage, which can lead to death of organisms and ecosystem disturbances (Eggen et al. 2004). It is important to study the sublethal effects because the toxicity of substances also depends on time of exposure, and even for small doses, these agents can led to accumulation on the body at levels sufficient to exert a toxic effect (USEPA, 1989). Nevertheless, in a real ecosystem, we find a range of different trophic levels and more attention has been paid to the effects on individual organisms and few studies with systemic approach (Santos et al. 2010). An example that drugs in the environment can cause extensive problems is the development of resistant bacteria, especially for human health. In Brazil, it was found that resistant bacteria are present in river waters (Souza et al. 2000; Falcão et al. 2004), lakes, and ponds (Pontes et al. 2009; Salloto et al. 2012) and even in seawaters (De Oliveira et al. 2010). So, it is necessary to have a better understanding of the causes of resistance and if the discharge of pharmaceuticals residues can contribute to it.

Despite that the concentrations of some pharmaceuticals in the Brazilian environment exhibit relatively higher concentrations than in other countries, such as Germany (Monteiro and Boxall 2010), we did not find many ecotoxicological tests did by Brazilians using hormones. The only tested hormone was estriol that can cause immobility in cladocerans in concentrations of the order of milligrams per liter. Therefore, we do not have many Brazilian studies to compare and predict the consequences of the observed concentrations in Brazilian surface waters. It was possible to observe that ecotoxicological tests using benthic invertebrates and fish as test organisms are lacking, as well as mixture tests. There is a need for further studies focused on the consequences of pharmaceutical exposure for organisms that depend on aquatic organisms for food (e.g., birds, reptiles, mammals), because these compounds can go through biomagnification in trophic webs (Daughton and Brooks 2011; Brausch et al. 2012). In addition, there are many endpoints to test in order to understand better the risks of pharmaceuticals in the environment and apply the principle of prevention. A review about ecotoxicological effects in fish demonstrated the wide range of endpoints that can be evaluated, such as damage in organs, loss of the function of hormone glands, reproductive effects, behavioral effects, etc. (Corcoran et al. 2010).

Toxicity assay assist in risk assessment of substances into the environment (Rand 1995), but with the exception of a few drugs currently available, ecotoxicological data may be unsuitable for technically rigorous risk assessments (Ankley et al. 2007). Because, how can we ensure that toxicity tests developed in laboratories, with different organisms, are representative for ecosystems (Ankley et al. 2010)? For a better understanding about the toxic effects caused by such substances, the ideal would to unite methods such as detection in environment, laboratory experiments testing organisms of different trophic levels and genetic approach, searching for a robust knowledge, and application in real ecosystems.

Many researchers are investigating drug removal in wastewater treatment plants (Castiglioni et al. 2006; Gros et al. 2010; Jelic et al. 2011; Verlicchi et al. 2012), and we have many researches about how it would be possible to enhance their efficiency (Ikehata et al. 2006; Sirés and Brillas 2012; Yao et al. 2016). Some technologies have been quite effective, such as adsorption on activated carbon, techniques with ozone, UV radiation, gamma radiation, and electrooxidation with or without active chlorine generation (Rivera-Utrilla et al. 2013). However, more than that, we need to think about ways to prevent and minimize the problem of sources, such as the proper disposal and reuse or recycling of drugs (Daughton 2007). Finally, we urgently need to establish limits and procedures for safe disposal of these substances.

Review papers are important to help develop new researches, as they present the available knowledge on the subject under discussion and may indicate gaps and further steps required. Furthermore, the synthesis of work presented in the discussion facilitates the discussion of new data. Thus, our results may help fill some gaps in Brazilian research about pollution by drugs, encouraging and demonstrating the need for further research. As far as we could find, this review is the first presenting Brazilian data. It could also be pointed out that these observations from a Brazilian point of view may probably share similar characteristics with that from other developing countries, in which access to modern drugs is available but not a good knowledge on their possible impacts in the environment or the procedures to reducing these.

Finally, the possible effects of environmental exposition to drugs on humans are poorly known; it has been believed that the concentrations of these compounds in the environment are too low to produce risks for human populations. However, recently, this belief is changing, and more researchers believe that pharmaceuticals can represent a risk to human health in the environment (Doerr-MacEwen and Haight 2006; Williams and Brooks 2012). Pomati et al. (2006) studied the effects of a mixture of pharmaceuticals on human embryonic cells in vitro. Results suggested that residues at ng L^{-1} levels could inhibit cell proliferation by affecting their physiology and morphology. Indeed, the effects of this “cocktail” of human

pharmaceuticals has not yet been adequately evaluated (Valcárcel et al. 2011).

There are two main pathways for pharmaceuticals to reach human bodies: ingestion with drinking water and exposure in food tissues. A lot of studies showed that pharmaceuticals can accumulate in aquatic organisms, such as fishes (Daughton and Brooks 2011), so it is important to consider the pathway to humans through fish consumption by recreational or subsistence fisheries (Williams and Brooks 2012). Despite low concentrations of pharmaceuticals, it is necessary to think about this possibility because very little is known about potential hazards of long term, low-dose exposure, and the potential additive or synergistic effects of pharmaceutical mixtures (Monteiro and Boxall 2010; Williams and Brooks 2012).

Summary and future perspectives

Our review has shown that there are more studies with focus on detection of pharmaceuticals in water bodies than ecotoxicological tests in Brazil. In those tests, the more commonly used organisms were cladocerans and the endpoint commonly used was mortality or immobility.

There are more studies about drugs in the southeast of Brazil, and then it is necessary to conduct more research in other areas, investing in corrective and preventive measures if necessary. When comparing the concentrations found in Brazilian water bodies with other countries, Brazil has some compounds with high concentrations: 17β-estradiol, 17α-ethinylestradiol, and caffeine.

Papers about these questions in Brazil are very scarce, while many dissertations and theses were not published for the scientific community. Further studies are needed to understand whether the biotic and abiotic processes can act in removing drugs in the environment or simply by transferring them between environmental compartments. There is a need for monitoring not only the compounds in its original form but also the degradation or transformation products and assess whether they retain pharmacological activity or become significant from a toxicological point of view.

With the increased use of drugs, it is also extremely important to educate the public about their use and correct disposal. Brazilian environmental authorities should urgently review the laws and provide also a control on the proper disposal of medications. It is also important to raise the investment in new and more effective technologies for the treatment and removal of these compounds in water bodies. These same observations would apply to many other countries now facing the same questions.

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A global trend of caffeine consumption over time and related-environmental impacts☆

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ABSTRACT

Caffeine is one of the most consumed substances, and it has been largely detected in aquatic ecosystems. We investigated the trends in caffeine consumption over three decades and its relationships with gross domestic product (GDP) and human development index (HDI) to understand global patterns and to identify potential hotspots of contamination. The total caffeine consumption is increasing mainly due to population growth. Moreover, caffeine consumption per capita is also increasing in some countries, such as Brazil, Italy, and Ethiopia. A high positive correlation between caffeine consumption per capita with HDI and GDP was found for coffee-importing countries in Europe, while a high negative correlation was found for coffee-exporting countries in Africa. The literature review showed that the highest caffeine concentrations coincide with countries that present an increasing caffeine consumption per capita. Also, approximately 35% of the caffeine concentrations reported in the literature were above the predicted no-effect concentration in the environment and, again, overlaps with countries with increasing per capita consumption. Despite the high degradation rate, caffeine consumption tends to increase in a near future, which may also increase the overall amount of caffeine that comes into the environment, possibly exceeding the thresholds of several species described as tolerant to the current environmental concentrations. Therefore, it is essential to prevent caffeine from reaching aquatic ecosystems, implementing sewage treatment systems, and improving their efficiency.

1. Introduction

Nowadays, caffeine has become one of the most consumed psychoactive substances in the world (Diogo et al., 2013). Caffeine is part of the methylxanthines – a group of central nervous system stimulants commonly present in the daily life of humans (Diogo et al., 2013). Caffeine consumption mostly occurs through food products, such as tea, coffee, energy drinks, products containing cocoa or chocolate, but can also be found in cold medicines, painkillers, appetite suppressants, and stimulants (Buerge et al., 2003). The caffeine concentration in the products vary greatly, but coffee presents one of the highest amounts of caffeine compared to other beverage categories (Mitchell et al., 2014). Moreover, coffee is highly consumed worldwide. As an example, only in 2014, more than 8 million tons of coffee were consumed around the world (International Coffee Organization, 2015).

A small fraction of the total caffeine consumed is excreted in its original form (2–3%; Tang-Liu et al., 1983). However, a considerable amount can be discarded without being consumed, especially by cafeterias (Montagner et al., 2014a; Tokimoto et al., 2005). According to World Water Assessment Programme (WWAP-World Water Assessment Programme, 2017), around 80% of the total volume of wastewater is discharged without prior treatment in the environment. Thus, significant concentrations of caffeine may be found in sewage and it has been used as a domestic sewage tracer (Strauch et al., 2008; Tokimoto et al., 2005). Once in the sewers, caffeine can reach water bodies, and spread in surface waters, groundwater, and also in drinking waters around the world (Bruton et al., 2010; Machado et al., 2016). Wastewater treatment plants

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(WWTPs) have been shown to be able to remove up to 95% of the caffeine from the water (Bruton et al., 2010), but the percentage varies according to the WWTPs type. WWTPs using the activated sludge process, for example, were able to remove up to 98% of caffeine, while through other methods, the average removal can drop down to 70% (Camacho-Muñoz et al., 2012).

Caffeine follows several routes to reach the aquatic environment, and untreated sewage is among the most important ones. Caffeine concentration in sewage varies according to several aspects, such as ingestion patterns, temperature, time of the year, the number of consumers, the extent and the sewage network (Montagner et al., 2014a). Even with effective removal rates, the high concentration of caffeine in the sewage reflects the broad consumption patterns and lack of adequate sanitation (Montagner et al., 2014a). Caffeine may eventually be present in the sewage sludge, and this solid fraction has been used for agricultural fertilization of soils worldwide. Once in the soils, the substance can reach the aquatic ecosystems through surface runoff or leaching (Montagner et al., 2014a). Groundwater can be pumped and used for consumption or undergoes treatment, and as in WWTPs, drinking water treatment plants do not remove the caffeine completely (Montagner et al., 2014a).

Therefore, caffeine is acknowledged as an emerging contaminant and, although it is considered a safe compound, high caffeine concentrations can be toxic to aquatic and terrestrial organisms and even to humans (Hollingsworth et al., 2003; Price and Fligner, 1990). Here we aim to explore patterns of caffeine consumption worldwide in order to: (1) investigate the global trends of caffeine consumption over the years; (2) identify possible relationships between caffeine consumption and human development index (HDI) and the gross domestic product (GDP); (3) detect hotspots of contamination and possible environmental impacts.

2. Methods

We used coffee consumption as a proxy to estimate caffeine consumption globally since coffee contains a high amount of caffeine among caffeine-based products (Mitchell et al., 2014). Moreover, coffee consumption has been monitored for decades in many countries by the International Coffee Organization and the data is available online. Thus, data on coffee domestic consumption and importation were obtained from the International Coffee Organization (International Coffee Organization, 2018). Population size, as well as global HDI and GDP, were obtained from the World Bank database (The World Bank, 2018). We estimate caffeine consumption per capita dividing the coffee consumption by the population size of each country per year. All the data were compiled from 1990 to 2016 for 87 different countries. In general, 61.5% of the countries had 27 years of data, 26% had 24 years, and 12.5% of the countries had less than that. For some countries (*e.g.* Chile, Argentina, Australia, China, Canada) the database was not available or it was incomplete and, for that reason, they were not included in the analyses. All data compiled and used in this study are available in Table S1, while the number of data available for each country can be found in Table S2.

The caffeine consumption per capita was tested for correlation along the years, HDI and GDP. Data were previously tested for normal distribution and homoscedasticity. When data met the assumptions, it was applied the Pearson correlation test, for those that did not meet the assumptions it was applied the Spearman's correlation test. All correlation values and their associated p values are available as supplementary material (Table S3). For all statistical analyses, it was assumed $p = 0.05$ as the significance threshold. Figures and statistical analyses were performed using JMP (version 14.0.0).

Maps of the current global caffeine consumption per capita and the Pearson correlations between caffeine consumption per capita along the years with HDI and GDP were created in ArcGIS (ESRI, v10.3.1) using the Jenks Natural Breaks classification, a data clustering tool designed to determine the best arrangement of values into different classes. A meta-analytic framework (z-score) was used to summarize the effect size of caffeine consumption over time (from 1990 to 2016). The Z-score graph was created in SigmaPlot v.12.0. Literature data on caffeine concentrations were compiled for different aquatic matrices (e.g. wastewater, surface water, groundwater, drinking water, and sediment) worldwide to support discussion (Table S4). A graph summarizing the literature data was created in JMP v.14.1.0.

3. Results and discussion

Coffee consumption is increasing in the world, possibly due to global population growth (Fig. 1). Caffeine has been detected in aquatic matrices worldwide and, consequently, it is reasonable to relate the coffee consumption over time with increasing environmental concentrations of caffeine. In general, the caffeine load in the aquatic environment is pretty much the same during seasons, which means that the consumption is linear over time, with a higher spatial variation, i.e., between regions (Senta et al., 2015). Culture is important when it comes to regional caffeine consumption and as expected, we observe different patterns and hotspots over the world. High positive correlations between caffeine consumption per capita and time were found in 41 countries (47%), while high negative correlations were found in 31 countries (36%)

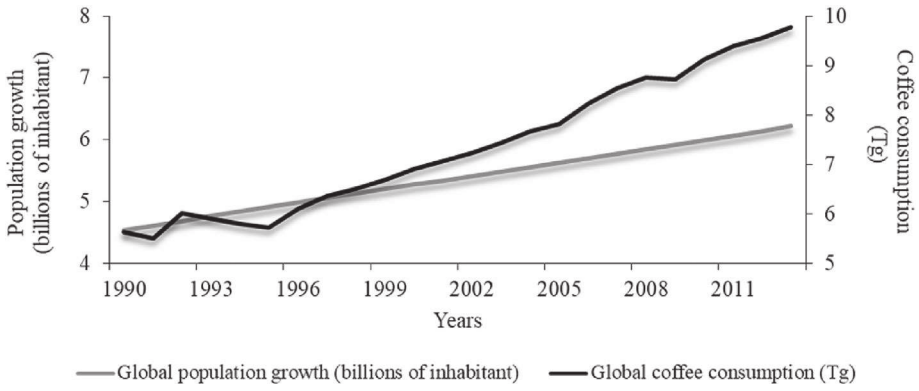

Fig. 1. Global population growth (billions of inhabitant) and global coffee consumption (Tg) from 1990 to 2013.

among the 87 countries evaluated in this study (Fig. 2). In general, the increase in caffeine consumption over time was mainly observed for the importing countries in the European continent, while the decrease was observed mainly by coffee exporting countries on the African continent (Fig. 2).

When considering the HDI and GDP, a similar trend was observed (Fig. 2). For HDI, it was found high positive correlations in 43 countries (49%), where most of which were coffee-importing countries located in the European continent, while a high negative correlation was found in 29 countries, most of them located in the African continent (33%; Fig. 2). Similarly, for GDP it was found high positive correlations in 49 countries (56%), again, the majority of them from Europe while a high negative correlation was found in 26 countries, mostly located in Africa (30%; Fig. 2). Both for HDI and GDP, the negative correlations were mostly found in coffee exporters countries.

The z-score data supports these assessments since the European continent stands out from the others with the highest ratio of caffeine consumption per capita over the years (Fig. 3). Also, the consumption maps show that Europe has the highest general mean of caffeine consumption per capita, and Africa the lowest one (Fig. 4). When analyzing per country, the strongest positive correlation between caffeine consumption over time was found for Vietnam (1.00), Indonesia (0.99) and Brazil (0.98), and the strongest negative for Malawi (-1.00), Zimbabwe (-1.00) and Ecuador (-1.00) (Table S3).

We believe that developing countries with higher per capita consumption over the years may be hotspots for contamination, since usually, they share a lack of sanitation and technologies in their WWTPs, such as Brazil, Ethiopia, Indonesia, Vietnam, Turkey, and Tunisia. The literature review shows that the caffeine concentrations in the aquatic environment are wide-ranging, with relatively high values on wastewater and surface water (Table S2, Fig. 5). The highest caffeine concentration reported in the surface water was found in Costa Rica (1.1 mg.L^{-1}; Spongberg et al., 2011) and in wastewater in Singapore (3.6 mg.L^{-1}; Tran et al., 2014) (Table S2, Fig. 5). Although the pattern for caffeine consumption over the years in Costa Rica was negative, the high caffeine concentration in surface water may be related to coffee production in the surrounded areas (Spongberg et al., 2011). Indeed, other sources may contribute to caffeine loads in the environment, such as coffee grounds disposed of in the sink or toilet without being consumed (Gracia-Lor et al., 2017). This behavior represents an issue, since the residues of coffee can induce mutagenicity effects, cause DNA damages, and pose toxicity effects in aquatic organisms (Fernandes et al., 2017).

In Brazil – one of the strongest positive correlation between caffeine consumption per capita over time – caffeine concentrations in surface waters were high in comparison to other countries (mean value of 129,910 ng.L^{-1}) (Table S2, Fig. 5). These observations agree with previous literature (Montagner et al., 2014a; Quadra et al., 2017; Rodríguez-Gil et al., 2018). In Brazil, it was showed a

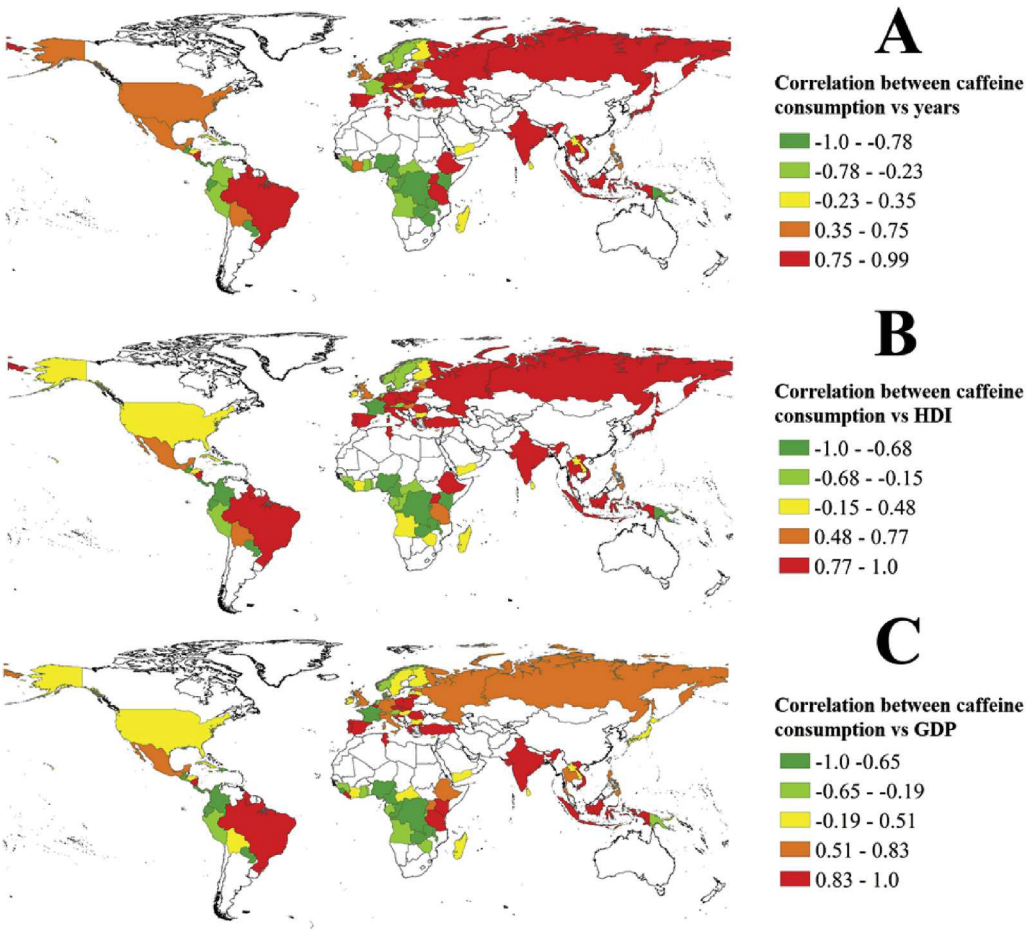

Fig. 2. Correlations of caffeine consumption per capita per: (A) years, (B) human development index (HDI), and (C) gross domestic product (GDP) between countries from 1990 to 2016. When data was not available, countries were not assigned with a color. Red colors show positive correlations, while green represents negative correlations. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

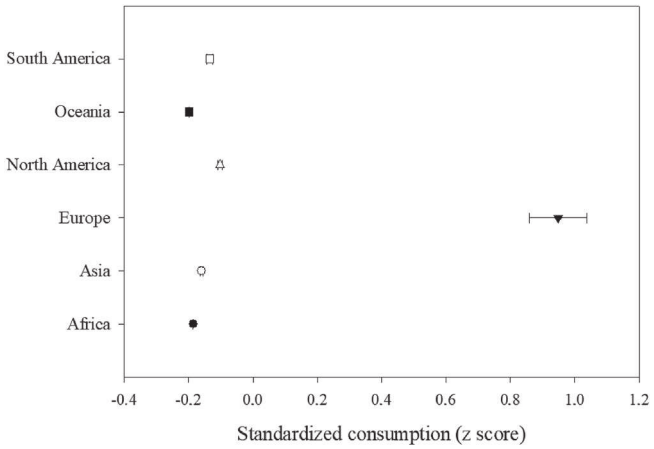

Fig. 3. Caffeine consumption per year per continent. The graph shows standardized consumption (x-axis) and continents (y-axis) with their confidence interval. Data are from 1990 to 2016.

caffeine detection frequency of 93% in water samples (Montagner et al., 2014a), higher than the ones found in China (Leung et al., 2013) and Spain (Boleda et al., 2010), where the detection frequency did not exceed 88%. For other countries with also strong positive correlation of caffeine consumption over time, we also found high concentration of caffeine in surface water and wastewater, such as Vietnam, Turkey and Tunisia (Aydin and Talinli, 2013; Ayman and Işık, 2015; Chau et al., 2018; Kuroda et al., 2015; Moslah et al., 2018) (Table S2, Fig. 5). Then, these countries may be hotspots of caffeine contamination, where potential risks to aquatic biota may occur.

However, countries in Europe and North America, such as Switzerland, Norway, and United States, did not show a high positive correlation between caffeine consumption over time but showed high concentrations in aquatic ecosystems (Figs. 2 and 5). Although these countries present high sanitation and technology in WWTPs, North America and Europe are big consumers of coffee (International Coffee Organization, 2019). On the other hand, African countries are not big consumers of coffee (International Coffee Organization, 2019) and the trends of caffeine consumption over time are decreasing even more (Fig. 2). However, there is a lack of caffeine quantification data in aquatic environments of this continent. Although the caffeine consumption is not increasing over time in the African continent, the concentrations in the aquatic ecosystems may reach high values due to lack of adequate sanitation as well as due to coffee production. In conclusion, developing countries may be hotspots of caffeine contamination and, the patterns of consumption need to be taken into account for the other countries as well.

Here we use coffee consumption as a proxy for caffeine consumption, but there are many other uses of caffeine for human welfare, including medicines. Many of the caffeine-based drugs are sold without prescriptions (Afolabi, 2012; Rahman et al., 2010). Additionally, industrial production and the incorrect disposal of drugs may also act as a potential source for environmental pollution (Kinrys et al., 2018; Klatte et al., 2017; Quadra et al., 2019). However, the countries with the highest correlation between coffee

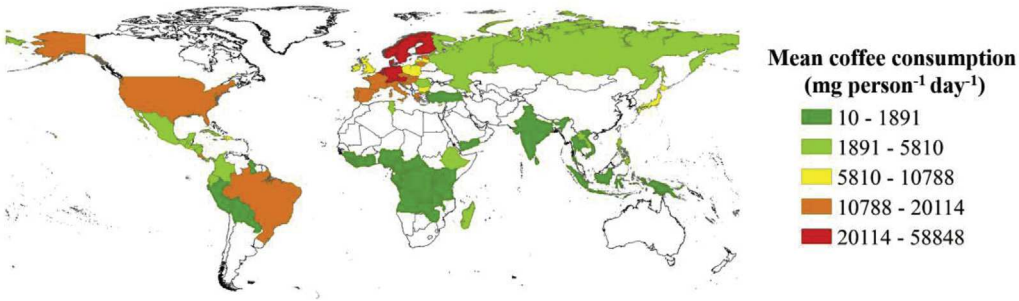

Fig. 4. Average coffee consumption from 1990 to 2016 by country. When data was not available countries were not assigned with a color. Red colors show high consumption over time and green low consumption over time. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

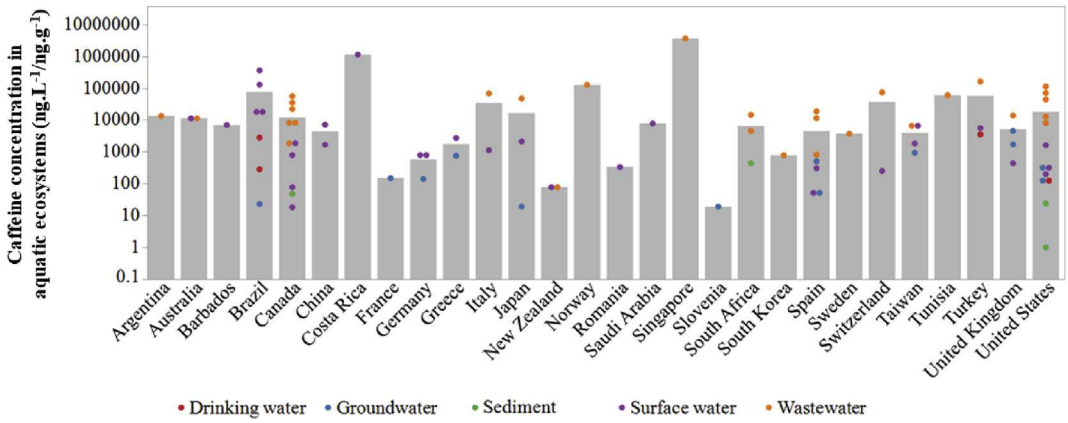

Fig. 5. Mean value of caffeine concentration in aquatic matrices worldwide. The points represent values for drinking water (red), groundwater (blue), sediment (green), surface water (purple) and wastewater (orange). The values for liquid matrices are represented in $ng.L^{-1}$ and sediments in $ng.g^{-1}$. The y-axis is represented in logarithmic scale. All the sources are presented in Table S4. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

consumption over time are not the most frequent medicines consumers (IMS Health, 2012). Brazil is as an exception for that list, occupying the sixth position as the largest medicine consumer in 2012, with analgesics being the most selling drugs, which usually includes caffeine in their composition (IMS Health, 2012). Therefore, medicines consumption may also be another source of caffeine into the environment and should be considered.

Moderate caffeine consumption poses no risk to human health (up to 200 $mg.d^{-1}$; European Food Safety Authority, 2015). However, risk groups, such as women in reproductive age and children should consume caffeine with moderation (Nawrot et al., 2003). A review showed that women in reproductive age should consume less than 300 $mg.d^{-1}$ and children less than 2.5 $mg.kg^{-1}$ body weight (Nawrot et al., 2003). Despite being considered a safe substance for humans, little is known about the ecotoxicological thresholds in the environment. Although caffeine degradation rate is high, the levels in aquatic ecosystems are constantly replenished due to its continuous input (Thomas and Foster, 2005). Then, chronic effects are more expected to occur than acute effects. The ecotoxicological data of caffeine available is wide-ranging, varying from $ng.L^{-1}$ to $mg.L^{-1}$. *Danio rerio* (fish) embryos exposed to caffeine cause angiogenesis and decrease movement activity at 250 − 350 and 17.5 − 150 $mg.L^{-1}$, respectively (Chen et al., 2008; Yeh et al., 2012). Caffeine impaired *Ceriodaphnia dubia* (cladocerans) reproduction at 44 $mg.L^{-1}$ and *Pimephales promelas* (fish) growth inhibition at 71 $mg.L^{-1}$ (Moore et al., 2008). These values are higher than environmental concentrations compiled in the current study.

However, if we consider more sensitive endpoints, such as at the cellular level, several impacts could be registered in lower caffeine concentrations. For example, caffeine at 18 $\mu g.L^{-1}$ − environmental concentration similar to many studies reported here (Table S2, Fig. 5) − was able to cause oxidative stress and cellular damage to the clam *Ruditapes philippinarum* (bivalve, Cruz et al., 2016). In the same species, another study reported that 2.4 $\mu g.L^{-1}$ of caffeine was able to affect lysosomal membrane stability, which means cellular stress (Aguirre-Martínez et al., 2013). Polychaetes were even more sensitive where caffeine at 0.5 $\mu g.L^{-1}$ induced oxidative stress and lipid peroxidation (Pires et al., 2016). Moreover, caffeine at 0.05 and 0.2 $\mu g.L^{-1}$ was also able to cause cellular stress in gill tissue of *Mytilus californianus* (bivalve, Del Rey et al., 2011). Bunch and Bernot (2011) showed that caffeine concentrations at a range of 40 $ng.L^{-1}$ to 3,000 $ng.L^{-1}$ affected microbial activity (Bunch and Bernot, 2011). Microbial respiration rate increased until reaching the saturation threshold and decreased again, while the nitrate and ammonium uptake were affected in an exponential and linear way, respectively (Bunch and Bernot, 2011). Adverse effects on the nitrogen cycle can result in changes in ecosystem services, such as the purification process.

Rodríguez-Gil et al. (2018) suggested a predicted no-effect concentration (PNEC) of 15 $\mu g.L^{-1}$ of caffeine for acute effects and 4 $\mu g.L^{-1}$ of caffeine for chronic effects considering aquatic organisms from three representative trophic levels (algae, *Daphnia* and fish). Using these values, caffeine concentrations might be causing chronic risks on aquatic organisms in wastewater (28% of the cases), surface water (7%) and estuary water (5%) around the world (Rodríguez-Gil et al., 2018). Indeed, our review agrees with Rodríguez-Gil et al. (2018), with higher concentrations of caffeine in wastewater and surface water (Table S2, Fig. 5), although many countries did not present data regarding caffeine in groundwater, sediment and drinking water. In a total of 87 studies evaluated, 35% exceed the threshold considering chronic effects and 18% for acute effects, most of them on wastewater matrix. A recent study found a no observed effect concentration (NOEC) of 39 $\mu g.L^{-1}$ of caffeine on Zebrafish behavior (Steele et al. 2018), which is a more sensitive endpoint. Then, considering this result and calculating the $PNEC_{aquatic}$ according to the European Comission (2003), a value of 390 $ng.L^{-1}$ may be adequate as a threshold. Thus, dividing the measured environmental concentrations by the PNEC, almost all the literature data regarding wastewater and surface water will be above 1, which means a high potential risk.

The risk assessment based on single compounds and species may be inadequate (Lawrence et al., 2012). Although a pool of pollutants is found in the aquatic environment, mixtures effects are understudied. Lawrence et al. (2012) showed that algal and bacterial biomass decreased with a mixture of caffeine, acetaminophen, and diclofenac at 5 $\mu g.L^{-1}$ (Lawrence et al., 2012). The authors also showed that the same mixture decreases protozoan populations and increase grazing by nematodes and rotifers. Another study by Di Lorenzo et al. (2019) also showed that the mixture of caffeine and propranolol did not present antagonistic effects considering immobilization on *Dapnhia magna*. These authors performed environmental risk assessment and they found that caffeine posed environmental risks to all aquatic ecosystems studied in Spain. In the study, they have suggested that mitigation measures should also be applied when caffeine is found above 1 $ng.L^{-1}$ in the aquatic systems. By considering the caffeine threshold suggested by them as a reference, all the values reported in our study are above the limit. Further, we need to take into account that long-term exposures may cause alterations on the physiology and the behavior of aquatic organisms (Di Lorenzo et al., 2019) and that mixtures may also result in ecological unbalances with still unknown consequences for ecosystem services. Consequently, the risk assessments need to take into account both more sensitive endpoints and mixture effects.

4. Conclusions

The World Health Organization has pointed out the emerging contaminants as a real issue, demanding immediate action, such as research on emission sources and environmental controls (Montagner et al., 2014b). It is important to highlight that when caffeine is detected in aquatic ecosystems, there is a high probability of finding other compounds, such as illicit and licit drugs, personal care products, hormones (Montagner et al., 2014b). We observed that caffeine consumption was correlated with HDI and GDP. Developing countries may be hotspots of caffeine contamination. However, the concern extends to countries with better sanitation since the concentrations in the environment may already represent a risk to aquatic ecosystems. Therefore, it is essential to prevent caffeine from reaching aquatic ecosystems, implementing sewage treatment systems, and improving their efficiency.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2019.113343.

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Short Communication

Investigation of medicines consumption and disposal in Brazil: A study case in a developing country

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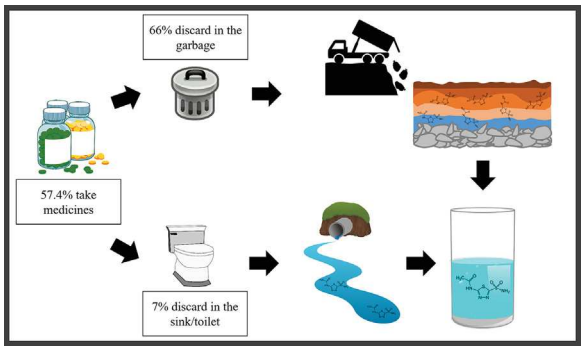
HIGHLIGHTS

- The incorrect disposal of medicines may represent a risk to the environment.
- Investigate how people are disposing unused medicines is crucial.
- Online questionnaires were spread out in Brazil.
- 66% of the respondents discard unused or expired medicines in common garbage.
- Environmental education may help to mitigate pharmaceuticals pollution.

GRAPHICAL ABSTRACT

The most important pathways for pharmaceuticals to the environment considering human disposal in the present study case.



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ABSTRACT

The incorrect disposal of medicines can be harmful to the environment. Here, we aim to understand the consumption and disposal of medicines in Brazil using online forms. 64% of the respondents have the habit to self-medicate. 66% of respondents dispose the disused or expired medicines in the garbage. 71.9% of respondents never receive any information about correct disposal of medicines. 95.2% of respondents believe that residues of medicines can be harmful to the environment. Environmental education can provide information to the population and help to mitigate pharmaceuticals pollution.

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1. Introduction

The pharmaceutical industry produces thousands of different compounds and its importance to the world economy and health is unquestionable. However, the increase in production, prescription and use of pharmaceuticals have an environmental cost. The entire range of synthetic compounds produced by the pharmaceutical industry has the potential to enter and contaminate the ecosystems. Then, pharmaceutical waste has been part of ecosystems, especially in environments close to urbanized regions. Therefore, the environmental concern regarding pharmaceutical pollution has been increasing.

Many factors push the pharmaceutical industry, such as the increase of world population, self-medication and the inversion of the population pyramid (An and Jeon, 2006; Daughton and Ruhoy, 2013; Quadra et al., 2017). There are many pathways of medicines to reach the environment, especially through incorrect disposal and excretion by human and veterinary uses and also untreated industrial waste (Bila and Dezotti, 2003). When pharmaceuticals – active principles from medicines – reach the water and sewage treatment plants, these compounds are not completely removed (Petrović et al., 2005; Suárez et al., 2008; Tambosi et al., 2010). In this way, pharmaceuticals reach the water bodies and drinking water (Halling-Sørensen et al., 1998; Loos et al., 2013; Liu and Wong, 2013; Kostich et al., 2014). In Germany, for example, 156 pharmaceuticals were detected in surface water, groundwater and drinking water (Küster and Adler, 2014).

Currently, the concern has been raised regarding the occurrence of pharmaceuticals on the environment since the discovery of adverse effects on organisms, ranging from acute intoxication to endocrine and ecological disruption (Rosi-Marshall and Royer, 2012; Rosi-Marshall et al., 2013). Environmental variables added to the natural degradation processes modulate effects in these pharmaceutical compounds, generating metabolites with ecotoxicological potential (Pfluger and Dietrich, 2001; Ferrari et al., 2003). Moreover, the complexity of pharmaceuticals in the environment can lead to poorly know mixtures effects (Cleuvers, 2003, 2004; WHO-UNEP, 2012).

The incorrect disposal of medicines by the population is an essential pathway for pharmaceuticals to reach the environment and many countries still lack effective regulation. Brazilian laws, for example, regulate the industrial production of medicines, however, do not include adequate disposal by the final consumer (Ueda et al., 2009). Therefore, bringing information about the consequences of incorrect disposal of medicines to the population is crucial. Then, this research aim was to investigate the habits of consumption and disposal of medicines by citizens in Brazil. Moreover, this study also aims to bring knowledge to the population, as well as generate awareness about the consumption and disposal of medicines.

2. Methods

Data collection was performed through wide dissemination of questionnaires, via Google Forms (online and free platform). The exploratory study was carried out with a varied population in Brazil, and the distribution was through electronic media, such as social media, e-mail, and websites. Therefore, anyone with internet access was able to answer the questionnaire. There was no direct interference in the population. In the questionnaire, general questions about residence localization, age and scholarly were made. Moreover, specific questions about self-medication, classes of medicines most consumed and way of disposal were included (Table 1). Furthermore, all the questions had the option of preference for not responding.

Questions were elaborated following some related studies (Bound and Voulvoulis, 2005; Seehusen and Edwards, 2006; Vellinga et al., 2014). Any person with internet access and over 18 years were used as inclusion criteria, without restriction regarding gender, geographic location, ethnicity, schooling or social class. The only exclusion criteria was not answering all questions.

Table 1
Intention of the questions in the questionnaire and type of response for each question.

Intention of the question	Response type
Living place	Short answer
Age group	Multiple choice
Scholarly	Multiple choice
Currently taking any medication	Yes or No
Number of medicines consumed currently	Short answer
Self-medication	Yes or No
Most consumed medicine class	Multiple choice
Side effects	Yes or No
Action after feeling side effects	Multiple choice
Place of disposal of medicines	Multiple choice
Existence of medicines collectors in the city	Yes or No
Knowledge about the correct disposal of medicines	Yes or No
Knowledge about the environmental impact of incorrect disposal of medicines	Yes or No

The sampling was based on the snowball method (Dörnyei and Taguchi, 2009), in which participants receive a questionnaire and are encouraged to disseminate it after answering. This method allows the obtaining of a higher amount of participants and moves out the academic network, in order to increase diversity and improve representativeness. An online tool was used to calculate the minimum sample size that represents the Brazilian population over 18 years old, in which it is based on the following equation (SM, 2019):

$$MSS = \frac{\frac{z^2\, p\,(1-p)}{e^2}}{1+\frac{z^2\, p\,(1-p)}{e^2\, N}} \quad (1)$$

where *MMS* is the minimum sample size; *N* is the total population number (1.47×10^8); *e* is the margin of error (percentage in decimal format); *p* is the population proportion; and *z* is a score based on the confidence level. A confidence level of 90% was considered, which results in a *z* score = 1.65; a *p* value of 0.5 was considered, which is the most conservative assumption.

To estimate the margin of error, we used the following equation:

$$MOE = z\,\frac{\sigma}{\sqrt{n}} \quad (2)$$

where *MOE* is the margin of error; *n* is the sample size; σ is the standard deviation of the population (*N*); and *z* is a score based on the confidence level, as above mentioned (1.65).

We obtained a license by the research ethics committee of the Federal University of Juiz de Fora (CAAE: 88169518.6.0000.5147, approval: 2.761.846). A period of six months was established for the questionnaire to continue online. As a descriptive study, graphs were produced using the software Excel, and the results were presented in percentages and pie charts.

3. Results and discussion

In 2018, approximately 70% of the Brazilian population was composed of individuals over 18 years old (IBGE, 2018). Therefore, based on Eq. (2), a 4% margin of error was estimated under such criteria. According to Eq. (1), a minimum sample size of 421 respondents was then calculated and would be representative of the Brazilian population.

In total, 540 forms were answered, and the majority was in the Southeastern region (88.3%), followed by Central-West (6.1%), South (3%), Northeast (1.5%), North (1.1%). A high number of respondents from the Southeastern region was expected since this region holds more than 40% of the Brazilian population (IBGE, 2018). Among the 26

states and one district of the Brazilian political division, 19 states and the district were represented. Espirito Santo (ES), Maranhão (MA), Mato Grosso (MT), Pará (PA), Piauí (PI), Rondônia (RO), Roraima (RR), did not have representatives, most of them are located in northern region of Brazil. 47.4% of the respondents have 26 to 40 years, and 45.4% are post-graduate (Fig. 1). Although the questionnaires were spread out by different electronic media, the academic network of the authors may have influenced the number of responses with undergraduate schooling. This fact may imply conservative results since it is expected that educational background may influence the consumption and disposal of medicines.

Within the participants taking medicines currently (57.4%), most take one to two medicines per day (41.7%). Seehusen and Edwards (2006) interviewed 301 respondents in a pharmacy waiting room at Madigan and found similar results regarding participants taking medicines currently. These authors found that 68.9% of patients were taking one to five medicines in the United States. Our findings also indicate that 64% of the respondents have the habit to self-medicate, and 40.2% have already felt some side effects. Among those that claimed to feel side effects, 15% of them changed the treatment. The change of treatment ends up increasing the environmental impact, as it results in leftover from the old medicine and purchase of a new one, which in turn, can also cause some side effect. Analgesics were the class of medicines more mentioned by the participants (30%, Fig. 1). Analgesics are commonly sold without a prescription in Brazil and abroad, and consequently, this class of medicines is usually found in natural waters worldwide (Heberer, 2002; Quadra et al., 2017).

A total of 66% of respondents discard their disused or expired medicines in common garbage (Fig. 1). This data demonstrate that despite the higher participants' academic background, the number of answers regarding the discard medicines in the garbage was substantially high. This result is in accordance with Seehusen and Edwards (2006), which 77.1–86% of patients do not return the unwanted medicine to a pharmacy or health care service, and 53.8% disposed it in the toilet. Another similar study interviewed 398 respondents in Galway and Cork cities, representing Ireland (Vellinga et al., 2014). The authors also found similar results, which 72% of the respondents disposed medicines in the garbage (51%), sink (29%) or toilet (14%) in Ireland. Bound and Voulvoulis (2005) interviewed 392 respondents of households in southeastern England, representing the United Kingdom. The authors also found similar numbers, which 63.2% of respondents disposing unwanted medicines in the garbage, 11.5% in sink or toilet and 21.8% return to pharmacies in the UK. Then, it is possible to infer that the academic background probably had little influence on the habits related to the disposal of medicines.

A total of 54.4% of respondents do not know if their cities have specific collectors of medicines. Although the National Solid Waste Policy, published in 2010 in Brazil, predicted that the waste products would be returned to their original producers (Brazil, 2010), a large respondent percentage (71.9%) never receive any information about correct

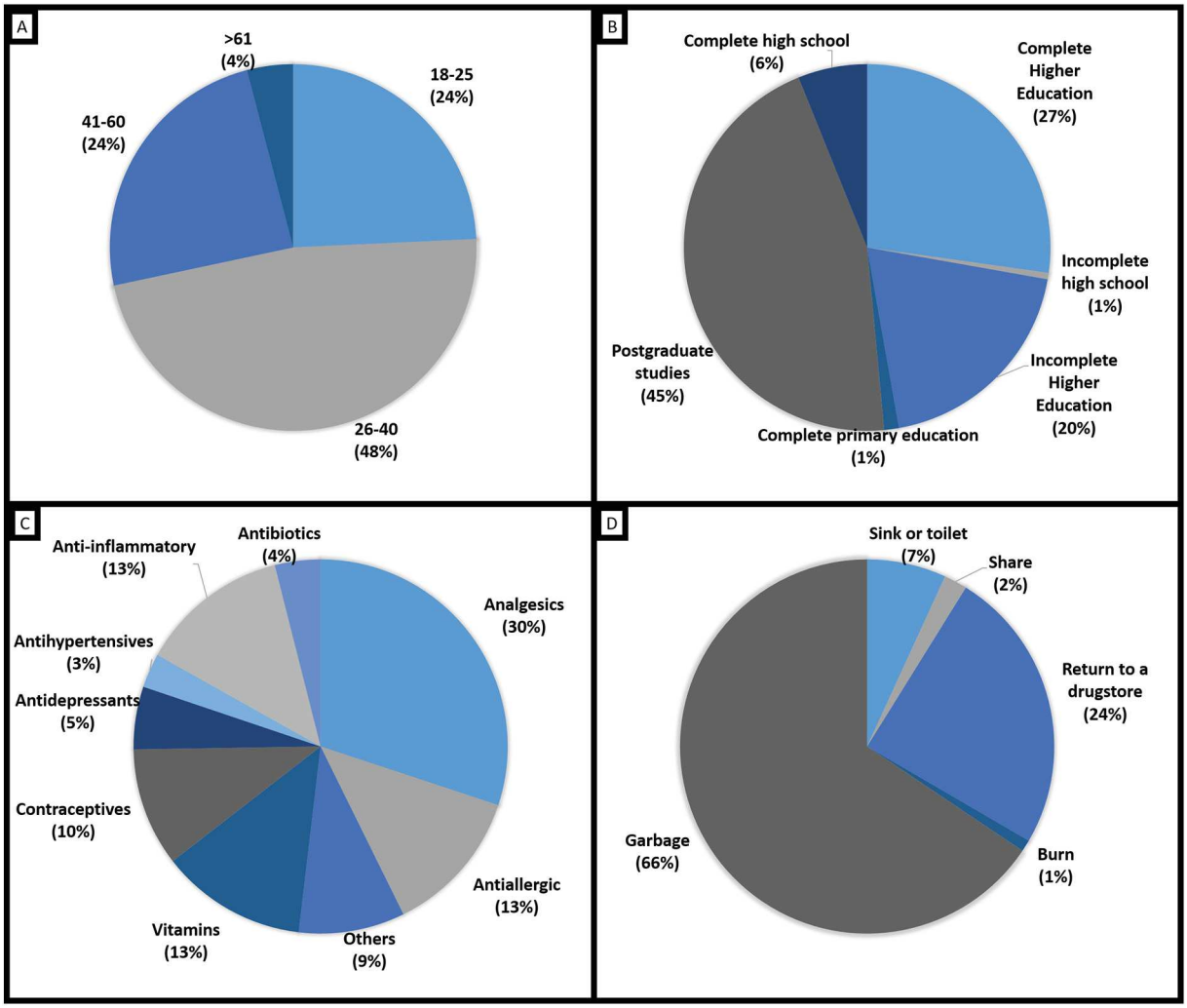

Fig. 1. Results in percentage from Brazilian forms about (A) age (years), (B) scholarly, (C) classes consumed of medicines, (D) disposal way of expired or unused medicines.

disposal of medicines. These numbers are mainly due to the absence of a Brazilian reverse logistics system added to the low investment in environmental education to inform the population. Similar results were found by Seehusen and Edwards (2006), in which 80.3% of patients were never advised about medication disposal by the health sector (Madigan, United States). Vellinga et al. (2014) also found a similar number of 81% of respondents that never receive advice from the health sector (Galway and Cork, Ireland). The previous study in Massachusetts showed that even a brief educational intervention is effective at changing pharmacists' attitudes and knowledge of inappropriate and environmentally unsafe medication disposal practices. Pharmacists receiving the educational intervention were more likely to report that they would recommend appropriate methods of medication disposal (Jarvis et al., 2009).

The respondent majority (95.2%) believe that residues of medicines can be harmful to the environment. The pattern was similar to those found by Seehusen and Edwards (2006) in the United States, in which the majority of patients think that is not acceptable to dispose of medication in a sink or toilet. However, probably many respondents began to reflect on it after this type of questionnaire. Bound et al. (2006) interviewed 400 householders from the South-East of England, and they found that half of the respondents believe that medicines can be harmful to plants and fish. However, a high number did not answer the question, which means that this result is conservative.

Tong et al. (2011) reviewed some studies about the disposal of expired or unused medicines around the world, and similar results were found. Among the studied countries, the United States seems to have a higher percentage of population disposing of unwanted medicines in toilet or sink (Seehusen and Edwards, 2006), while Kuwait seems to have the higher percentage of population disposing of unwanted medication in the garbage (97%) (Abahussain et al., 2007). In the other hand, Sweden seems to have a higher percentage of population returning unwanted medicines to the pharmacy (43%) (Persson et al., 2009). In general, comparing the results with other similar studies, it is possible to observe that the sample studied in our Brazilian survey seems to present similar patterns to those previously observed for other countries regarding the medicines disposal habits. Although these results are conservative, they are already worrying and need to be more discussed.

Many conferences have already mentioned the need for environmental education since it is the base for environmental health and management (Palmer, 2002; De Kumar and De Kumar, 2004). Tong et al. (2011) concluded that the lack of knowledge about the correct way to discard unwanted medicines and how it can affect the environment is still great. Therefore, efforts to raise environmental awareness will affect medicines disposal practices in a beneficial way (Kotchen et al., 2009).

Our findings present a meaningful contribution to knowledge regarding pharmaceuticals pollution in Brazil, since this is, to our knowledge, the first national survey about the disposal of medicines in the country. Although a high-educated population background was considered in this study, most of the respondents do not know about the proper way of disposing medicines, even though environmental issues were likely to be known by them. This demonstrates the need for environmental education activities to instruct the public about pharmaceuticals pollution.

Considering the developing countries, such as Brazil, medicine disposal procedures need to be further investigated since the collection and treatment of Brazilian sewage is still lower than 50% (ITB, 2018). Moreover, the regulation and surveillance of residues disposal and the population environmental education is not a priority by the Brazilian government. Then, we truly believe that our findings are important for decision makers, not only for Brazilian ones but also to other countries where this type of information is either not available or not regulated by their legislation.

4. Conclusion

Although many countries still do not have adequate protocols for unused medicines disposal, it is essential that the population is aware of the incorrect forms and consequences for the environment. This study emphasizes the need for greater incentive in environmental education and public policies related to pharmaceuticals use and disposal. Furthermore, we believe that the conscious consumption of medicines, the medical treatments correct accomplishment, the reduction of self-medication, and the proper destination of these compounds are significant for the mitigation of environmental impacts caused by pharmaceutical pollution.

CRediT authorship contribution statement

Gabrielle R. Quadra: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft. **Pâmela S.A. Silva:** Conceptualization, Methodology, Validation, Investigation, Resources, Supervision, Writing - review & editing. **José R. Paranaíba:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing - review & editing. **Iollanda I.P. Josué:** Conceptualization, Methodology, Investigation, Writing - review & editing. **Helena Souza:** Conceptualization, Methodology, Investigation, Writing - review & editing. **Rafaela Costa:** Conceptualization, Methodology, Investigation, Writing - review & editing. **Marcos Fernandez:** Conceptualization, Methodology, Investigation, Supervision, Writing - review & editing. **Jéssica Vilas-Boas:** Conceptualization, Methodology, Investigation, Writing - review & editing. **Fábio Roland:** Conceptualization, Methodology, Investigation, Supervision, Project administration, Writing - review & editing.

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