Pharmaceuticals and personal care products as emerging micropollutants in Brazilian surface waters: a preliminary snapshot on environmental contamination and risks

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Abstract: This work aimed to present a preliminary snapshot on the contamination and risks of Brazilian surface waters concerning the presence of hormones, pharmaceuticals and personal care products. Data gathered in the literature for Measured Environmental Concentrations (MEC) in Brazilian surface waters were compared with the most restrictive Predicted No-Effect Concentration (PNEC) available in the literature. A risk assessment was performed revealing that hormones, antibiotics drugs and triclosan should be prioritized to subsidize the generation of water quality standards to protect aquatic life.

1. Introduction

Emerging environmental micropollutants, such as pharmaceuticals and personal care products, are potentially toxic substances of recent interest to academics, regulatory agencies, and sectors of society. Information on the occurrence and effects of such micropollutants in environmental compartments is critical to assess their risks under natural conditions. Although there are some isolated requirements for surface water monitoring in Brazil, as a result of the first studies published in the country during the last decade, there are still no quality standards that guarantee the safe use of water for different purposes. Among the many uses of water is the protection of aquatic life, probably one of the most noble since it aims to guarantee the integrity and survival of organisms from different trophic levels. For most micropollutants, legislated or not, restrictive criteria have been reported to protect aquatic life, since the protection targets are organisms extremely sensitive to changes in water quality caused by the input of exogenous substances, even at trace concentrations.

There are many strategies described in the literature to assess environmental risks of chemicals. One of them, as well as the simplest, is based on the comparison of predicted or measured environmental concentrations with predicted no-effect concentration (PNEC) for a given substance. The PNEC can be described as the concentration limit which harmful effects on organisms will most likely not occur. For aquatic systems, a PNEC should be derived that, if not exceeded, ensures an overall protection of the
environment. In the literature, as well as in many reports produced by environmental organizations, several approaches to derive PNEC are described. Most of them are based on a primordial data, mainly obtained from acute or chronic toxicity tests. Standard acute toxicity tests, based on short-term exposure, are commonly expressed as EC$_{50}$ or LC$_{50}$, i.e., the concentration required to cause short-term effects or to kill, respectively, half the organisms of a tested population after a specified exposure time. On the other hand, long-term exposure tests provide toxicity data related to the lowest observable effect concentrations (LOEC) or to no-observable effect concentrations (NOEC).

For some emerging micropollutants, data from both short and long-term toxicity tests can be assessed. However, for other substances, only acute toxicity data may be available. Considering the availability of toxicological data, some extrapolation concerning the aquatic environment has to be done to represent the whole ecosystem sensitivity. Under these circumstances, assessment factors (AF) are used to derive PNEC as follows:

$$PNEC = \frac{Toxicological
data}{AF}$$

(1)

Both acute (EC$_{50}$ or LC$_{50}$) and chronic (LOEC or NOEC) toxicological data, derived from single-species toxicity tests, are used in the literature to calculate PNEC for aquatic systems. In this case, the lowest figures for these tests, representing the worst-case scenario, are commonly used. The use of AF was advocated to establish a concentration below which adverse effects will most likely not occur. The magnitude of AF is inversely proportional to the amount and quality of toxicological data available. For example, according to the European Commission technical guidelines, an AF of 1000 is often used when at least one short-term data is available for one of the three organisms representing different aquatic trophic levels, i.e., a fish, a microcrustacean (generally Daphnia), and an alga. When one long-term NOEC data for either fish or Daphnia is available, an AF of 100 or 50 is used. Assessment factors varying from 1 to 10 are used as more long-term NOECs from two to three trophic levels are available. When species sensitivity distribution (SSD) for multi-species data is available the AF must be reviewed on a case by case basis. The same approach is used when field or model ecosystems data are assessed. For the latter approach, modeling software such as QSAR or ECOSAR, based on structure activity relationships (SAR), generate PNECs assuming a common mode of action (narcosis) and may be useful to identify links between micropollutant groups and environmental toxicity.

In the literature, risk assessment using PNECs are commonly investigated by the risk quotient (RQ) calculated between the predicted environmental concentration (PEC) and PNEC. When available, measured environmental concentrations (MEC) reported in the literature may also be used (Equation 2), but in most cases MEC data are scarce for a meaningful analysis.

$$RQ = \frac{PEC or MEC}{PNEC}$$

(2)

The predicted concentration of a micropollutant in surface waters can be calculated using information such as the amount of the target substance used per year, the removal efficiency in wastewater treatment plants (WWTP), the volume of wastewater entering a WWTP for a given period, a dilution factor in the environment, and toxicity data. Simple PEC calculation may assume that the amount used/consumed is equally distributed over the year, the target substance is used/consumed throughout the region investigated (city, hydrographic basin, country, etc.), it is constantly diluted in the environment without metabolism, transformation, sorption, etc. On the other hand, as pointed out by de Bruijn et al., data on measured levels provides useful information regarding specific steps of the exposure assessment, such as background levels, concentration ranges and distribution. Also, although measured data present uncertainties associated with temporal and spatial variations, the concentration range may reflect different patterns observed during manufacturing or use of the target substances that are not considered in the modelling procedures. In summary, both PEC and MEC data are important for risk assessment complementing each other during the analysis.

In 2009, Souza et al. carried out an environmental risk assessment of antibiotics using PEC estimates for 21 substances in Brazil. Consumption data was assessed from reports of an intensive care unit and from hospital pharmacies of the city of Curitiba. One can consider that the most challenging aspect in order to calculate PEC values for pharmaceuticals and personal care...
products in Brazil is the assessment of consumption data. Baldoni et al. reviewed 620 pharmacoepidemiologic studies produced in Brazil and observed that forms and interviews were frequently used as the main source instead of secondary sources such as prescription data and electronic databases. Locatelli et al. investigated environmental concentrations for the eight most consumed antibiotics in Brazil according to data obtained from the National Health Surveillance Agency (ANVISA). However, as pointed out by the authors, there is a large number of pharmacies and drugstores selling controlled drugs without prescription throughout the country making the available data uncertain.

In the face of the problems surrounding data gathering for PEC calculations, this work aimed to provide a snapshot on the environmental contamination and risks of pharmaceuticals and personal care products in Brazil, based on the few data available for MEC in surface waters throughout the country. Therefore, our intention is not to perform a complete risk assessment of emerging micropolllutants, but rather to provide a scenario consistent with the contamination of Brazilian waters considering the concentration ranges of the most investigated substances as well as their possible risks to the aquatic life.

2. Experimental

The most restrictive PNEC values reported in the literature, at the best of our knowledge were selected. In some cases, PNECs were estimated in this work using assessment factors suggested by the European Commission as well as toxicological data available elsewhere. Table 1 shows a list of the most commonly investigated emergent micropolllutants in Brazil and PNEC values obtained in the literature or estimated in the present work.

| Main group   | Substance       | PNEC (ng/L) | PNEC Calculation | Reference   |
|--------------|-----------------|-------------|------------------|-------------|
| Hormone      | Estrone         | 3           | NOEC and LOEC; AF=5 | 25          |
|              | 17β-estradiol   | 1           | LOEC; AF=10      | 25          |
|              | Estriol         | 60          | Vitellogenin assay; AF=10 | 26          |
|              | 17α-ethinylestradiol | 0.1  | NOEC e LOEC; AF=5 | 25          |
| Antibiotic   | Amoxicillin     | 100000      | NOEC; AF=10      | 14          |
|              | Azithromycin    | 19          | Derived from EC50; AF=1000 | This work |
|              | Cephalexin      | 100000      | NOEC; AF=10      | 14          |
|              | Ciprofloxacin   | 50          | Derived from NOEC; AF=100 | This work |
|              | Erythromycin    | 27530       | Derived from NOEC; AF=100 | This work |
|              | Norfloxacin     | 20          | Derived from NOEC; AF=100 | This work |
|              | Sulfamethoxazole| 10          | Derived from NOEC; AF=100 | This work |
|              | Oxytetracycline | 230         | Derived from NOEC; AF=100 | This work |
|              | Tetracycline    | 5           | Derived from NOEC; AF=100 | This work |
|              | Trimethoprim    | 16          | Derived from NOEC; AF=100 | This work |
| Anti-inflammatory | Acetylsalicylic acid | 61000 | Derived from EC50; AF=100 | 16          |
|              | Diclofenac      | 1000        | Derived from NOEC; AF=100 | This work |
|              | Ibuprofen       | 2300        | Derived from EC50; AF=100 | This work |
|              | Naproxen        | 2000        | Derived from NOEC; AF=100 | This work |
|              | Acetaminophen   | 1000        | Derived from NOEC; AF=100 | This work |
| Antidepressant | Carbamazepine   | 250         | NOEC; AF=10      | 28          |
|              | Citalopram      | 360         | ECOSAR Database   | 10, 29      |
|              | Sertraline      | 43          | Derived from EC50; AF=1000 | 30          |
| Anthelmintic | Mebendazole     | 98000       | Derived from LC50; AF=1000 | This work |
| Anxiolytic   | Diazepam        | 14100       | EC50; AF=1000.   | 16          |
| Beta blocker | Atenolol        | 77700       | ECOSAR Database   | 15          |
|              | Metoprolol      | 7900        | EC50; AF=1000.   | 31          |
|              | Propranolol     | 10          | NOEC; AF=50      | 22          |
|              | Losartan        | 78000       | NOEC; AF=10      | 32          |
| Stimulant    | Caffeine        | 5200        | NOEC; AF=100     | 28          |
| Personal care product | Triclosan | 12          | Derived from EC50; AF=1000 | This work |
|              | Galaxolide      | 310         | ECOSAR Database   | 33          |
|              | Tonalide        | 4000        | NOEC; AF=100     | 34          |
Details on the toxicological assays used to estimate the PNEC values portrayed in Table 1 can be obtained from the respective references. Table 2 shows a compendium of results generated in Brazil from 1999 to 2018 on the presence of emerging micropollutants in surface waters, notably hormones, pharmaceuticals and personal care products. The total number of samples and the concentrations reported above limits of quantification (LOQ) is shown. Table 2 also shows the concentration range and the classification of the samples in the three different ranges referring to the risk quotients calculated according Equation 2.

### Table 2. Concentration and risks of emerging micropollutants frequently investigated in Brazilian Surface waters.

| Main group       | Substance                  | Total Samples<sup>a</sup> | Positive results<sup>b</sup> | Min<sup>c</sup> | Max<sup>c</sup> | Median<sup>c</sup> | RQ<sup>d</sup> ≥ 1 | 1 > RQ<sup>d</sup> ≥ 0.1 | RQ<sup>d</sup> < 1 |
|------------------|-----------------------------|-----------------------------|-----------------------------|-----------------|-----------------|-------------------|-------------------|------------------|------------------|
| Hormone          | Estrone                     | 278                         | 57                          | 0.21            | 1800            | 7.7               | 49                | 7                | 1                |
|                  | 17β-estradiol               | 324                         | 81                          | 0.21            | 13450           | 51                | 68                | 13               | 0                |
|                  | Estradiol                   | 30                          | 9                           | 1.5             | 182             | 7.7               | 1                 | 4                | 4                |
|                  | 17α-ethinylestradiol        | 190                         | 44                          | 3.0             | 5900            | 305               | 44                | 0                | 0                |
| Antibiotic       | Amoxicillin                 | 10                          | 5                           | 1.3             | 1284            | 8.9               | 0                 | 0                | 5                |
|                  | Azithromycin                | 8                           | 8                           | 10              | 313             | 26.2              | 5                 | 3                | 0                |
|                  | Cephalexin                  | 19                          | 11                          | 2.4             | 2422            | 150               | 0                 | 0                | 11               |
|                  | Ciprofloxacin               | 18                          | 12                          | 0.6             | 350             | 208               | 9                 | 0                | 3                |
|                  | Erythromycin                | 8                           | 4                           | 35.3            | 1586            | 66                | 0                 | 0                | 4                |
|                  | Norfloxacin                 | 18                          | 13                          | 0.5             | 276             | 114               | 9                 | 1                | 3                |
|                  | Sulfamethoxazole            | 42                          | 13                          | 1.1             | 1529            | 106               | 10                | 3                | 0                |
|                  | Oxytetracycline             | 24                          | 1                           | 44              | 44              | 44                | 0                 | 1                | 0                |
|                  | Tetracycline                | 18                          | 7                           | 11              | 153             | 104               | 7                 | 0                | 0                |
|                  | Trimethoprim                | 18                          | 14                          | 2.3             | 6376            | 150               | 9                 | 5                | 0                |
| Anti-inflammatory| Acetylsalicylic acid        | 89                          | 15                          | 12.2            | 20960           | 2096              | 0                 | 3                | 12               |
|                  | Diclofenac                  | 196                         | 54                          | 0.02            | 8250            | 118               | 5                 | 24               | 25               |
|                  | Ibuprofen                   | 28                          | 10                          | 326             | 2094            | 1659              | 0                 | 10               | 0                |
|                  | Naproxen                    | 80                          | 28                          | 0.02            | 21285           | 174               | 1                 | 12               | 15               |
|                  | Acetaminophen               | 99                          | 17                          | 13.4            | 13440           | 35                | 1                 | 5                | 11               |
| Antidepressant   | Carbamazepine               | 33                          | 17                          | 0.12            | 652             | 58                | 3                 | 6                | 8                |
|                  | Citalopram                  | 16                          | 5                           | 48              | 79              | 55                | 0                 | 5                | 0                |
|                  | Sertraline                  | 16                          | 8                           | 30              | 164             | 62                | 6                 | 2                | 0                |
| Anthelmintic     | Mebendazole                 | 10                          | 1                           | 1.4             | 14              | 14                | 0                 | 0                | 0                |
|                  | Diazepam                    | 17                          | 12                          | 0.38            | 0.71            | 0.32              | 0                 | 0                | 12               |
| Beta blocker     | Atenolol                    | 28                          | 25                          | 0.48            | 90              | 7.1               | 0                 | 0                | 25               |
|                  | Metoprolol                  | 19                          | 7                           | 1.3             | 28              | 14                | 0                 | 0                | 7                |
|                  | Propranolol                 | 3                           | 1                           | 0.56            | 0.56            | 0.56              | 0                 | 0                | 1                |
|                  | Losartan                    | 10                          | 3                           | 12              | 32              | 16                | 0                 | 3                | 0                |
| Stimulant        | Caffeine                    | 175                         | 162                         | 0.02            | 4150            | 3.1               | 6                 | 13               | 143              |
| Personal care product | Triclosan             | 151                         | 85                          | 2.2             | 415             | 77                | 72                | 13               | 0                |
|                  | Galaxolide                  | 17                          | 17                          | 2.4             | 53              | 5.6               | 0                 | 1                | 16               |
|                  | Tonalide                    | 17                          | 17                          | 2.8             | 28              | 6.3               | 0                 | 0                | 17               |

<sup>a</sup>Total of samples investigated. <sup>b</sup>Number of samples with concentrations reported above method LOQ. <sup>c</sup>Reported data considering only positive results. <sup>d</sup>Risk quotient = MEC/PNEC.

### 3. Results and discussion

Figure 1 portrays the most frequently quantified emerging micropollutants reported in studies carried out in Brazilian surface waters between 1999 and 2018. The personal care products galaxolide and tonalide, together with the antimicrobial azithromycin, were in the top of the list. However, is important to point out that the number of samples investigated for the abovementioned substances is relatively low in comparison with data available for substances such as...
caffeine and triclosan. Also, in the present work, the characteristics of the different sampling points, such as land use and potential pollution sources were not explored. Thus, aquatic systems with different degrees of anthropic impact were selected without distinction. Consequently, it is possible that the most frequently quantified substances were investigated only in a few samples as well as in more polluted aquatic systems.

In Figure 1, it is also noticed that caffeine was the most frequently quantified substance (92.6%) among the most investigated ones, followed by triclosan (56.3%) and naproxen (35%). The higher frequency of quantification for caffeine is in accordance with the important role of this stimulant drug as an indicator of anthropic activities, notably in Brazilian urban regions.

Another important aspect is the diversity of analytical methods and techniques employed in the studies carried out in Brazil. As a result, different method LOQs are reported, which may imply in a possible underestimation of the contamination degree. For example, Figure 2 shows the evolution of method LOQs reported for the determination of 17α-ethinylestradiol and 17β-estradiol in surface waters from the region of Campinas (São Paulo) using different analytical techniques.
Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) provides higher quantification capacity, i.e., lower LOQ values, when compared to other analytical techniques. Among the 25 studies selected in the present work, 60% used LC-MS/MS systems to assess the concentrations of the target substances. Others employ liquid chromatography with fluorescence (LC-FLU) or diode array detectors (LC-DAD) as well as gas chromatography coupled to mass spectrometry (GC-MS) with or without derivatization steps. Considering the information portrayed in Figure 2, it is expected higher frequencies of quantification when data were produced using only LC-MS/MS systems.

On the other hand, one can consider that the frequency of quantification may also vary if more studies were selected covering different Brazilian regions and aquatic systems with different degrees of pollution.

Finally, it is important to mention that the studies developed in Brazil are not yet equally distributed throughout the country territory. Most of the data generated, about 44%, was obtained in the state of São Paulo, followed by the states of Rio Grande do Sul (15%), Minas Gerais (11%) and Rio de Janeiro (11%). These four states are among the most populous in Brazil, accounting for 45% of the country’s population. The rest of the work was developed in Paraná, Mato Grosso do Sul, Federal District and Amazonas. It is interesting to note that, to the best of our knowledge, no scientific paper has yet been published on the presence of pharmaceuticals and personal care products in surface waters from Northeast Region of Brazil. This region has nine states and accounts for 28% of the Brazilian population, being the second most populous. The Southeast Region, where the states of São Paulo, Minas Gerais, Rio de Janeiro and Espírito Santo are located, is the most densely populated one.

In a recent work, Machado et al.42 aimed to perform a nationwide survey on the presence of emerging micropollutants in drinking and source waters. Although data on the presence of caffeine and atrazine were produced for drinking water samples from almost all Brazilian capitals, only surface waters from São Paulo, Minas Gerais and Rio Grande do Sul were investigated.

Figure 3 portrays the concentrations of pharmaceuticals and personal care products in Brazilian surface waters.

![Figure 3](image-url)
Concentration ranges for the majority of the micropollutants present in Figure 3 had high amplitude, evidencing the diversity of polluted aquatic environments investigated in Brazil so far. For many substances, mean and median values are coincident or close together, whereas for the drugs amoxicillin and caffeine, for example, mean values are up to two orders of magnitude higher than medians. This behavior shows that some of the concentrations reported are exceptionally high, reflecting the influence of more polluted aquatic environments. It is interesting to note that caffeine, investigated in 175 samples and quantified in most of them, presents the highest variability of concentrations, corroborating with its role as an indicator of anthropic activities, since it differentiates aquatic environments with different degrees of pollution.

In general, the levels of pharmaceuticals and personal hygiene products in Brazilian surface waters are higher than those found in other countries, as already reported in recent literature reviews. Higher median concentrations are noticed for acetylsalicylic acid, followed by ibuprofen and 17α-ethinylestradiol. The first two substances have been found at high concentrations not only in Brazilian waters, but also in other countries. The same observation, however, cannot be made for 17α-ethinylestradiol, as well as for other substances investigated in Brazil.

Quadra et al. evidenced that Brazilian surface waters present higher concentrations of 17α-ethinylestradiol, 17β-estradiol, and caffeine in comparison with other locations. In the present study, it should be noted that most of the results involving the occurrence of hormones were obtained by Machado et al. and Montagner et al. in the Upper Iguaçu River Basin (Paraná) and in the region of Campinas (São Paulo), respectively. In both studies, mean concentrations of 17α-ethinylestradiol and 17β-estradiol were 1916 and 3689 ng/L, respectively. These values are also higher than those reported in other Brazilian regions. For example, in Minas Gerais, the average concentration of 17α-ethinylestradiol in waters nearby the capital, Belo Horizonte, is 206 ng/L, considering 15 positive data (34% of the total). In the region of São Carlos (São Paulo), Campanha et al. reported an average value of 2 ng/L for 17β-estradiol in 24 positive data out of a total of 81 (30%). Again, these results demonstrate the great variability of Brazilian surface waters concerning their degree of pollution, certainly influenced by sewage discharges, as pointed out earlier.

Data for MEC portrayed in Figure 3 can be used to perform a preliminary risk assessment on the presence of pharmaceuticals and personal care products in Brazilian surface waters using Equation 2, as well as PNEC data presented in Table 1. As suggested by Komori et al. risk quotients (MEC/PNEC) greater than 1 imply risk, while values lower than 0.1 indicate no-risk. Intermediate values indicate potential risk and, consequently, the need for further studies. Figure 4 shows individual MEC/PNEC ratios for the substances selected in the present work.
Higher risk quotients are noticed in Figure 4 for hormones and antibiotic drugs, evidencing that micropollutants of both classes should be prioritized to ensure the protection of aquatic life. Most of the risk quotients for the hormones 17α-ethinylestradiol, 17β-estradiol and estriol are 1000 to 10000 times greater than the first threshold (MEC/PNEC > 1), due to consequence of their high concentrations as well as to the risk that these substances may pose to aquatic biota. Triclosan should also be prioritized, since all results generated in the country so far evidence risk or possible risk. An extensive investigation on triclosan in Brazilian waters has already put this substance as a strong candidate in a priority list that must be regulated in Brazil to preserve aquatic environments.

Non-prescribed drugs such as acetaminophen, diclofenac and naproxen, as well as the antidepressants carbamazepine and sertraline are not in the top of the rank but may also be candidates to further investigations. Galaxolide and tonalide present the highest frequencies of quantification but are not in the top of rank due to their high PNECs which leads, therefore, to low risk quotients. These substances, however can be used as indicators of anthropic pollution, as pointed out by Glassmeyer et al.57.

Caffeine is also frequently quantified in Brazilian waters but presents low risk to aquatic biota. It is true that some risk quotients for caffeine were above the first threshold, certainly due to extremely high values reported in waters impacted by direct inputs of domestic sewage. Although most MEC/PNEC values indicate low risk for caffeine, it is important to reinforce the role of this substance as an indicator of anthropic pollution. In addition to this use approach, caffeine has recently been used to rank Brazilian surface waters presenting different levels of estrogenic activity61.

Finally, Figure 4 shows positive risk in all samples investigated for tetracycline and 17α-ethinylestradiol. In this case, it is important to mention that the former presented a frequency of quantification of 39 % while the hormone 17α-ethinylestradiol could be quantified in 23 % of the samples. Even so, for both substances, all samples reported with positive values (>LOQ) present risk. Thus, although such substances are obviously of concern in terms of aquatic life protection, representative results may be obtained by improving method LOQs.

4. Conclusions

Data on the occurrence of pharmaceuticals and personal care products in Brazilian surface waters were gathered in order to provide a preliminary snapshot on environmental contamination and risks. Although substances such as tonalide, galaxolide, atenolol and caffeine were frequently quantified, higher risks were accounted for hormones and antibiotics, as well as for triclosan, a biocide present in personal hygiene products. Key aspects including the behavior of micropollutants, as well as the influence of land use and occupation, degree of anthropic pollution, diffuse and point sources, among others, may be considered in future investigations. However, such discussions may be improved as a more uniform and broad database is available. Thus, it is evidenced the need for more studies on the diagnosis of Brazilian surface waters for the presence of several micropollutants of recent interest, legislated or not. It should be mentioned that other emerging micropollutants, such as pesticides, illicit drugs, and industrial-derived substances, were not included in this study, but they can be evaluated in future investigations using the same strategy presented here.

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