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Analysis of the Main Environmental Pollutants Present in Effluents Generated by Pharmaceutical Industries in the West Zone of Rio De Janeiro, Brazil

Análise dos Principais Poluentes Ambientais Presentes em Efluentes Gerados por Indústrias Farmacêuticas na Zona Oeste do Rio de Janeiro, Brasil

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Several pharmaceutical industries are established in the West Zone of the city of Rio de Janeiro, Brazil, which must comply with environmental legislation relevant to their operations. In this work, we present a critical analysis of the measurements of biochemical oxygen demand (BOD), chemical oxygen demand (COD), sedimentable solids (SS), total nitrogen, acute toxicity to fish, phosphorus concentration, presence of anionic surfactants (MBAS), flow, pH and temperature by comparing the monthly averages of these parameters in relation to the limits established in the applicable regulations. The data were obtained from laboratories accredited by Rio de Janeiro State Environmental Agency (INEA). The sampling time varied according to the estimated average flow at the time of the project's licensing. The data of the parameters reported by these laboratories were related to effluents generated by seven pharmaceutical manufacturers. These data were reported according to the control program PROCON-ÁGUA (INEA), in the period of January 2009 to February 2020. We used the monthly average of these parameters. The consolidated data show that the BOD level was exceeded by 100% of the evaluated companies in relation to the limit of the corresponding regulations, while 71% of the evaluated manufacturers exceeded the limit of COD, 57% exceeded the limit of sedimentable solids (SS), 85% surpassed the limit for phosphorus, 75% exceeded the total nitrogen threshold, and 33% exceeded the MBAS limit, according to the relevant regulations. The parameters of acute toxicity to fish, pH, and temperature were not exceeded by any of the factories.

Keywords: Pharmaceutical industry; effluents; pollution; environmental regulations.

1. Introduction

The pharmaceutical industry has contributed greatly to the length and quality of life of people and animals. The discovery of new strains and diseases, most recently the several variants of Corona Virus Disease (SARS-CoV), has motivated the development of new drugs and vaccines and consequently constant expansion of the pharmaceutical industry. Indeed, the pharmaceutical industry is among the top five in the global economy.[1]

Pharmaceutical compounds are typically produced in batch processes.[1] Encapsulation, extraction, processing, purification, and packaging are the main operations carried out in the pharmaceutical industry. Specifically, five processes are carried out: fermentation, chemical synthesis, extraction, formulation, and packaging. Fermentation and chemical synthesis processes are the largest generators of effluents.[2-4] Pharmaceutical wastewaters produced during these chemical-synthetic processes contain high levels of organic pollutants, biotoxicity and salinity.[3]

The production of several pharmaceutical and personal care products can generate pollutants, such as hormones (estriol, mestranol, estrone, 17β estradiol and testosterone, among others), antibiotics (amoxicillin, ampicillin, cefaclor, ciprofloxacin, etc.), lipid regulators (clofibric acid, clofibrate, benzafibrate, etc.), nonsteroidal anti-inflammatory drugs (ibuprofen, diclofenac, acetaminophen, aspirin, etc.), beta-blockers (atenolol, metoprolol, etc.), antidepressants (diazepam, doxepin, etc.), anticonvulsants (carbamazepine, primidone, etc.), antineoplastics (epirubicin, ifosfamide, etc.), diagnostic contrast media (iopromide, iomeprol, diatrizoate acid), fragrances (musk xylene, musk ketone),preservatives (methylparaben, ethyl 4-hydroxybenzoate, etc.), disinfectants (triclosan, 2-phenylphenol, etc.) and sunscreens (octocrylene, ethylhexyl methoxycinnamate, oxybenzone). These contaminants are considered "pseudo persistent organic pollutants".[6]

More specifically, pharmaceutical effluents have high levels of biochemical oxygen demand (BOD), chemical oxygen demand (COD), total suspended solids (TSS), total nitrogen, and surfactants, among others, which when released into water bodies cause a large decrease in dissolved oxygen and at the extreme can cause the death of all biota at the site of the release.[5] These effluents also contain high concentrations of organic and inorganic, degradable, and non-degradable compounds, besides persistent compounds such as benzene, heterocyclic substances, and PAHs, making treatment of these effluents difficult.[1]

Zhou and collaborators (2019),[7] analyzing several works involving analysis of surface waters in Europe between 1988 and 2016, found 475 pollutants (411 drugs and 66 metabolites), of which 284 were above the limit of quantification (LOD) of the analytical methods employed and the other 191 were below the LOD of the method. Among these pollutants were a wide variety of drug residues, such as fungicides, antibiotics, analgesics, anti-inflammatories, anxiolytics, anticonvulsants, antihypertensives, and opioids.[8] Tiwari and collaborators (2020)[5] indicated that the concentrations of these residues varied from ng L^{-1} to µg L^{-1}. The presence of these residues, even in trace quantities, is of environmental concern because they can upset the ecological balance. The presence of antibiotic residues can cause additional damage to human and animal health because of the possible dissemination of genes that are resistant to these drugs.[5] Several drugs, metabolites, personal care products, detergents, and other pollutants related to pharmaceutical manufacturing are considered emergent micropollutants (pollutants found in trace amounts and normally not monitored by regulatory agencies).[8]

There is widespread discussion about the importance of monitoring and treating pharmaceutical substances, but there is still no common practice. However, there are several regulatory initiatives. These initiatives can be classified into levels according to the intensity of the measures taken to regulate pharmaceutical pollutants in the environment.[9]

The monitoring of environmental pollutants is of fundamental importance for the creation of public control policies, because through the testing of pollutants at release sites it is possible to identify polluting companies, concentrations of pollutants and delimitation of contaminated areas, serving as the base for the imposition of fines and formulation of monitoring plans, etc.

In Brazil, specifically in the state of Rio de Janeiro, the periodic evaluation of environmental pollutants is specified by environmental regulations such as CONAMA Resolution 430/2011 from Brazil's National Environmental Council, besides state environmental resolutions[10] DZ-942,[11] NT-202,[12] DZ-205,[13] NOP-INEA-008[14] and NOP-INEA-045,[15] which define the tests to be performed, the maximum allowed values and the monitoring frequency.

This work reports data on the parameters BOD, COD, total nitrogen, phosphorus, toxicity, anionic surfactants, pH, and temperature, collected from January 2009 to February 2020 in the effluents of seven pharmaceutical industries with factories in the West Zone of the city of Rio de Janeiro, collected as part of the control program called PROCON-ÁGUA and reported by the Rio de Janeiro State Environmental Agency (INEA). Critical analysis of data obtained from the monitoring of effluents from pharmaceutical industries contributes to generating awareness of the importance of creating appropriate public policies, which can bring consistent benefits to the general population and the environment.

2. Materials and Methods

The West Zone is defined as an area formed by 41 districts, grouped in 10 administrative regions and 4 micro-zones. The municipal government identifies the West Zone as composed of AP-4 to AP-5.[16]

The effluents released by the evaluated pharmaceutical industries flow into the Jacarepaguá lagoon complex in the city. This complex is formed by Jacarepaguá, Marapendi, Tijuca, and Camorim lagoons. This region has an area of about 280 km^2, with several rivers that flow into the lagoons, which connect to the channel from Barra da Tijuca to the sea, allowing the exchange of water (Figure 1) (INEA, 2020).[17,18]

The flow indicates the amount in m^3/d of release into the water body of the liquid effluent generated by each pharmaceutical industry. Effluent flow is usually determined by using flumes, the most common being the Parshall flume, which accelerates the flow through contraction of both the parallel sidewalls and a drop in the floor at the flume throat. Under free-flow conditions, the water depth at a specified location upstream of the flume throat can be converted to a flow rate, in $m^3\ h^{-1}$.[11] The results found in COD tests are obtained through indirect measurement of the organic matter present in the effluent, and the oxygen equivalent of the organic matter that can be oxidized is measured using an oxidizing agent (potassium dichromate) in an acidic medium. The BOD parameter is related to the oxygen content necessary to biodegrade by oxidation of the organic matter present in the effluent by using aerobic microorganisms, commonly considering 5 days of incubation (BOD_5) Settleable solids are determined considering the solids content deposited in an Inhoff cone due to gravity. Phosphorus content is determined spectrophotometrically by using reagents such as ammonium molybdate, potassium antimony tartrate, or ascorbic acid, after acid digestion of the sample to eliminate the organic matter. Total nitrogen is related to the content of nitrogen (in the form of nitrate and nitrite), determined through the Kjeldahl method. MBAS content is determined spectrophotometrically by using a methylene blue solution.[19] Acute toxicity is determined through the exposure of the fish *Danio rerio* to different concentrations

of the sample being analyzed, mainly to identify the lowest concentration of samples that do not cause the death of the organisms. This parameter is used to obtain the Toxicity Factor (TF).[13] pH and temperature tests are carried out in the field during sample collection using a pH meter and thermometer, or a single device with both meters. In Brazil, these devices are subject to certification by an industry that is accredited by the Brazilian Calibration Network (RBC).[10]

The results were obtained from laboratories accredited by Rio de Janeiro State Environmental Agency (INEA). The sampling time varied according to the estimated average flow at the time of the project's licensing. The data of the parameters reported by these laboratories were related to effluents generated by seven pharmaceutical manufacturers. These data were reported according to the control program PROCON-ÁGUA (INEA), in the period of January 2009 to February 2020. We used the monthly average of these parameters. The statistical treatment was conducted on the data provided by the environmental agency. To prepare the graphs, we used Microsoft Windows 10, Office, and Excel 2010®.

The parameters, represented in the form of graphs, follow the specifications of the INEA, in relation to the determination of the limits established in the current regulations. The parameters evaluated in this work were: flow, BOD, COD, sedimentable solids, total phosphorus, total nitrogen, surfactants, acute toxicity to *Danio rerio*, pH, and temperature. The tests were carried out following the Standard Methods, MF 403, ABNT Standards, among others. In addition to the parameters evaluated in this work, the environmental agency also monitors, at some factories, parameters such as animal and vegetable oils and greases, mineral oils and greases, total suspended solids, phenol index, Kjeldhal nitrogen, and ammoniacal nitrogen, with the frequencies defined according to the analyzed environment as specified in DZ-942.[11]

3. Results and Discussion

Data on flow, COD, BOD, sedimentable solids, phosphorous content, nitrogen content, surfactants, acute *Danio rerio* toxicity, pH, and temperature were obtained from the monitoring program of INEA.

The flow indicates the amount in m^3/d of the liquid effluent generated by the pharmaceutical industry released into the water body. This parameter is of fundamental importance because it identifies the amount of effluent released. Figure 2 shows the flows of all pharmaceutical industries evaluated from January 2009 to February 2020.

It may be observed in Figure 2 that company D had three flow rates above the limit in the evaluated period with the highest value being 771 m^3/d in September 2009, the highest value identified for all manufacturers. Pharmaceutical industry C also presented a high result of 710 m^3/d in August 2012. Company F had the highest flow rate of 610 m^3/d in May 2015. The other averages were below the 360 m^3/d range. The decrease in flow over the period evaluated by the pharmaceutical industries can probably be attributed to the implementation of the reuse of effluents after treatment carried out by treatment stations.

To evaluate the discharge flow of effluents from the pharmaceutical industries in relation to the period, the trend line, and the coefficient of determination (R^2), which served as the basis for calculating Pearson's correlation coefficient (p), are shown in Table 1. Companies A, B, C, D, and F had weak to moderate correlation (p-value) and showed a decrease in the discharge flow of effluents during the evaluated period. Companies E and G had weak and moderate correlations, respectively, in addition to an increase in the release flow with time. For 72% of the evaluated companies, there was a decrease in the discharge flow, while for 28% there was an increase.

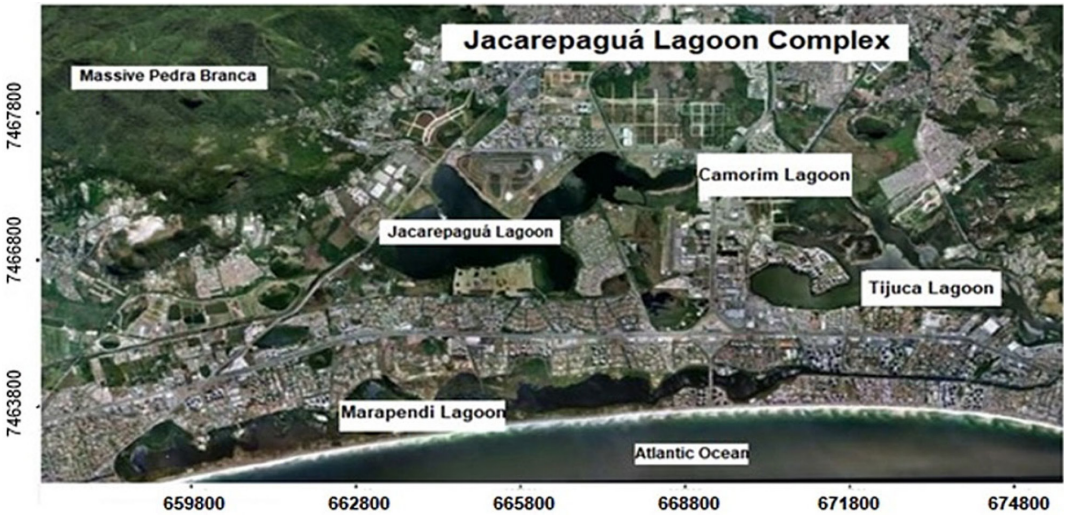

Figure 1. Characterization of the lagoon complex located in Baixada de Jacarepaguá. Based on references 16 and 17

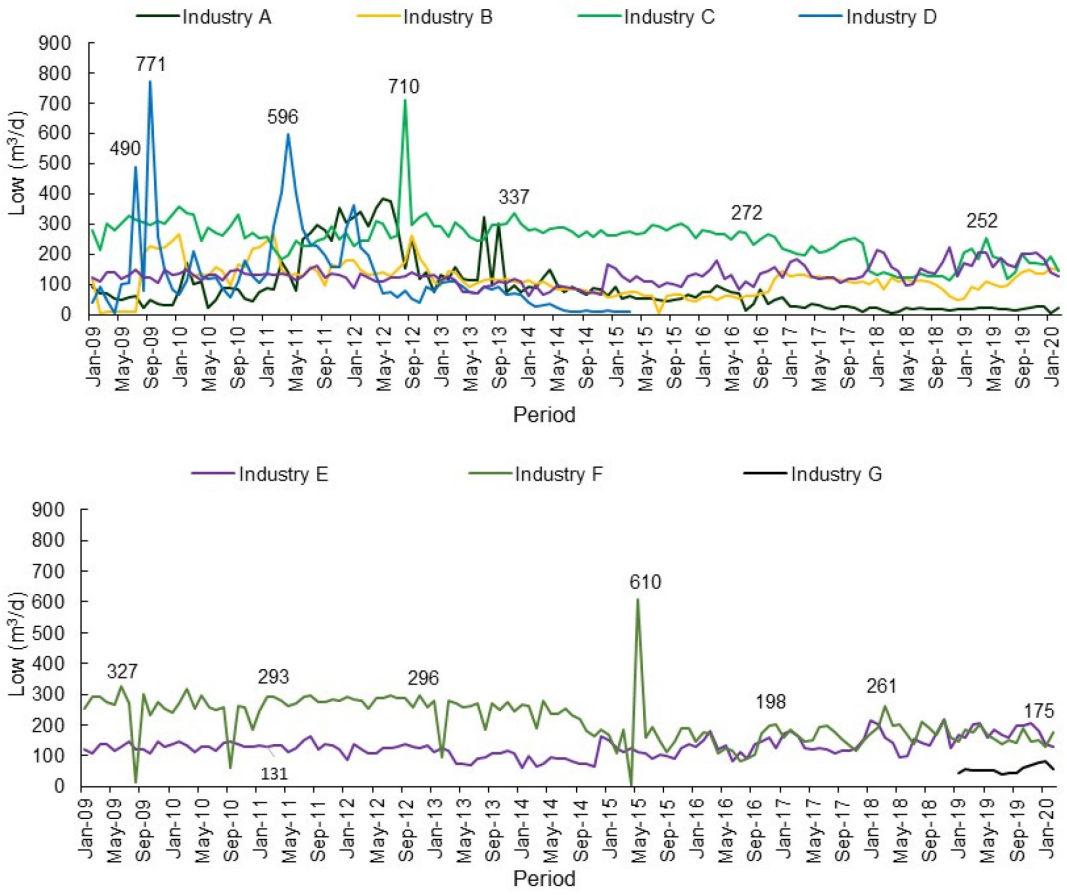

Figure 2. Flow data from pharmaceutical industries A, B, C, D, E, F, and G from January 2009 to February 2020

Table 1. Evaluation of the correlation between period and effluent discharge flow

Pharmaceutical industry	R^2	*P*	Trendline indication	*p*
A	0.2187	0.4676	Decrease	Moderate
B	0.0452	0.2126	Decrease	Weak
C	0.3441	0.5866	Decrease	Moderate
D	0.1391	0.3729	Decrease	Weak
E	0.1169	0.3419	Increase	Weak
F	0.2903	0.5388	Decrease	Moderate
G	0.3444	0.5868	Increase	Moderate

Figure 3 shows the results of the COD tests, which were performed on data from indirect measurement of the organic matter present in the effluent, where the equivalent oxygen of the organic matter that can be oxidized is measured using an oxidizing agent (potassium dichromate) in sulfuric acid. One of the possible environmental consequences of a high COD is the consumption of oxygen present in the aquatic environment in the process of degrading organic compounds, leading to a decrease in the concentration of available oxygen and the death of aquatic organisms.[4]

Figure 3 shows that pharmaceutical industry A had COD data above the regulatory limit in 3.0% of the cases evaluated; for company B, this was 7.3%; for company D it was 1.4%; for company E it was 0.7%; for company F it was 0.7%, and companies C and G did not present any monthly averages above the regulatory limit during the evaluated period. Effluents from 71% of the evaluated manufacturers contained COD above the established limit, while 29% of these companies managed to meet the regulatory limit referring to the monthly average release.

Moraes (2019)[20] indicated that only eight Brazilian states have maximum values allowed for the COD, and these limits are highly diverse. Rio de Janeiro is one of the few Brazilian states with effluent discharge limits for COD by type of industrial activity (according to Directive DZ-205 R,[13] the maximum limit for COD from pharmaceutical industrial waste is 150 mg L^{-1}).

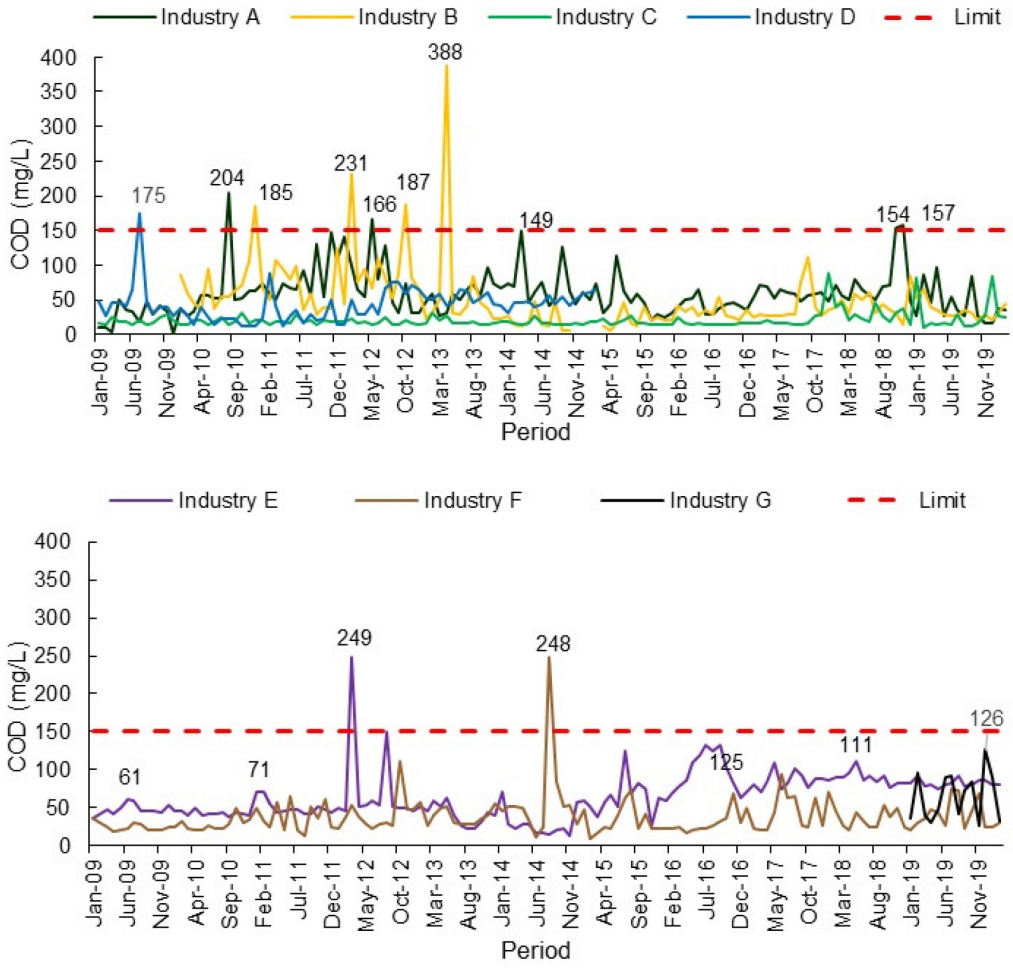

Figure 3. COD data from pharmaceutical industries A, B, C, D, E, F, and G from January 2019 to February 2020

Resolution 430/2011[10] from CONAMA, the federal environmental agency, does not specify a limit for the COD parameter, either for release in general or for specific manufacturers. States can legislate without having a federal reference as a ceiling value to be followed, *i.e.*, are able to define standards that are more adequate to their environmental and economic contexts, or even not define a limit. For instance, the states of São Paulo, Santa Catarina, and Goiás do not adopt limits for the COD parameter, which is a parameter present in the most recent regulations on effluent discharge.[20]

Leonel (2016)[21] reported that the average COD removal found due to sewage treatment in activated ponds was 119 mg L^{-1}, lower than the value indicated by Morais and Fonseca (2008),[22] but around 6 times greater than the COD reduction values achieved by the industries evaluated in this work. In the study carried out by Ambrósio (2018)[23] related to the implementation of a pharmaceutical effluent treatment system by employing ultrafiltration membranes, the COD value achieved was 8 mg L^{-1}. The highest value found by Ambrósio was 378 mg L^{-1}, about 2.5 times greater than the limit established in DZ-205 R.06[13] (Rio de Janeiro, Brazil), which is 150 mg L^{-1}. According to Cubas (2011),[24] the COD values found for effluent treated by activated sludge were 142.0, 10.0, and 48.0 mg L^{-1}, for the months of February, March, and April 2011, with removal rates of 85.6, 98.9 and 93.6%. During the period evaluated, there was no release of effluents with values above the limits of DZ-205 R.06.[13]

Table 2 shows the highest values achieved for the BOD parameter, in mg L^{-1}, for the seven pharmaceutical industries evaluated. It can be observed that 57% of the companies had BOD values equal to or greater than the limit of 120 mg L^{-1} established in CONAMA Resolution 430/2011,[10] and a 47% reduction would be able to meet the regulatory limit for BOD.

CONAMA Resolution 430/2011[10] establishes that the minimum removal for any polluting activity is 60% BOD, and this limit can only be reduced in cases where there is "self-debugging", which can prove compliance with the goals established for the receiving body.

The Rio de Janeiro State Environmental Agency in DZ-205 R.06[13] stipulates limits that are directly linked to the total organic load released by polluting activity. This removal limit can vary from 70 to 90%, but for the companies studied, the minimum limit established by the Agency is 90% due to its strong polluting potential.

Figure 4 demonstrates the results found in the BOD tests, which were evaluated to quantify the oxygen needed to carry

Table 2. Maximum BOD values, in mg L^{-1}, reported by the pharmaceutical industries evaluated during the period from January 2009 to February 2020

Pharmaceutical industry	BOD (mg L^{-1})
A	104
B	152
C	134
D	120
E	56
F	158
G	30

out the oxidation of the biodegradable organic matter present in the effluent using aerobic microorganisms to consume the organic matter. One of the possible environmental consequences of high BOD is the faster consumption of oxygen present in the aquatic environment in the process of degradation of organic compounds, leading to a decrease in the concentration of available oxygen and the death of aquatic organisms.[4]

Pharmaceutical industry G was the only one that presented BOD above the limit of 120 mg L^{-1}, specified in CONAMA Resolution 430/2011, with the highest value presented being 126 mg L^{-1} during the period evaluated. Pharmaceutical industries B, C, D, E, and F did not show results above this limit. All told, 14% of the evaluated companies were above the regulatory parameter for BOD, and 86% managed to meet the limit of average monthly release.

Figure 5 demonstrates the results found in the sedimentable solids (SS) tests, which determined the amount of solids that can settle in 1 hour in an Inhoff cone. This determination aims to control the amount of solids released into water bodies that can be deposited in their beds.[4]

Pharmaceutical manufacturers A, B, F, and G presented SS results above the regulatory limit, which is 1 mL/L, with the highest value being 5.5 mg L^{-1}, for two consecutive times by industry B. Company A was above the average monthly values of the regulatory limit in 3.0% of the readings, while for industry B this percentage was 11.3%;

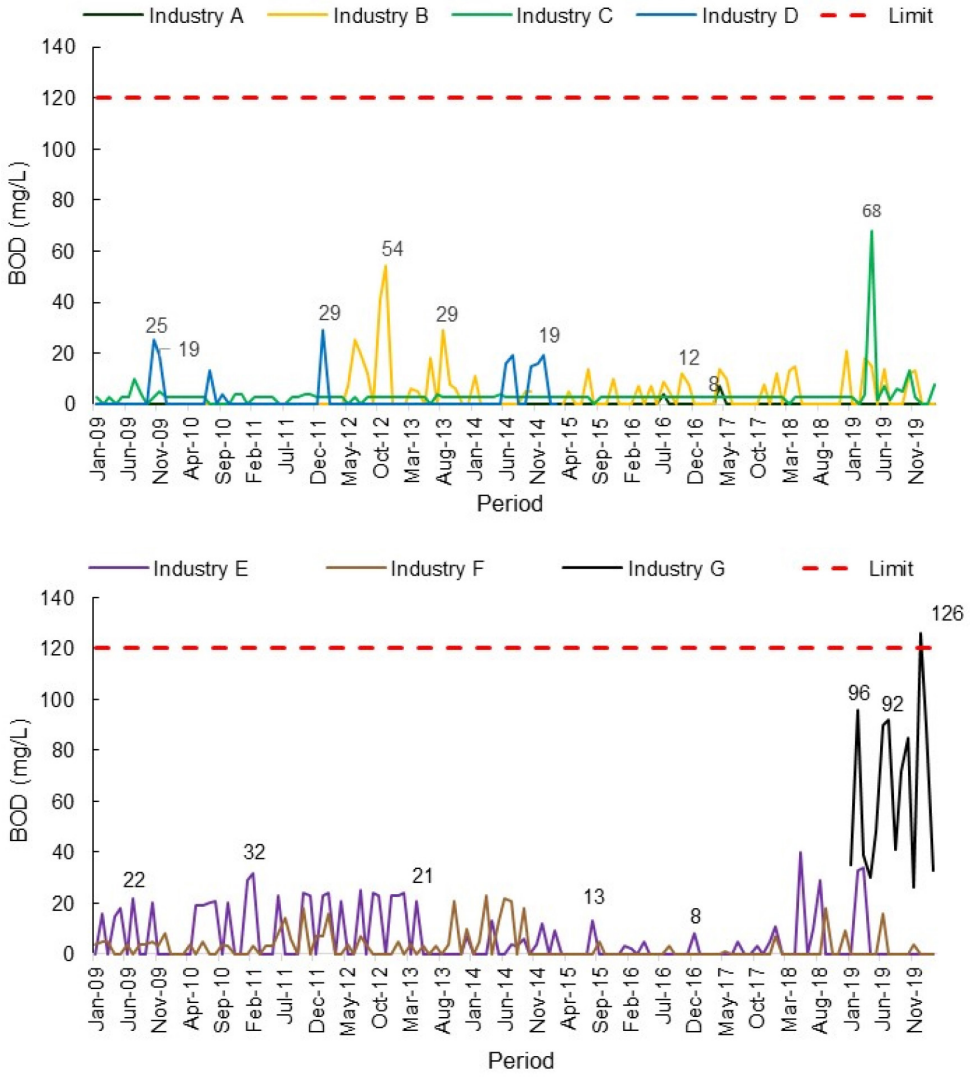

Figure 4. BOD data from pharmaceutical industries A, B, C, D, E, F, G from January 2019 to February 2020

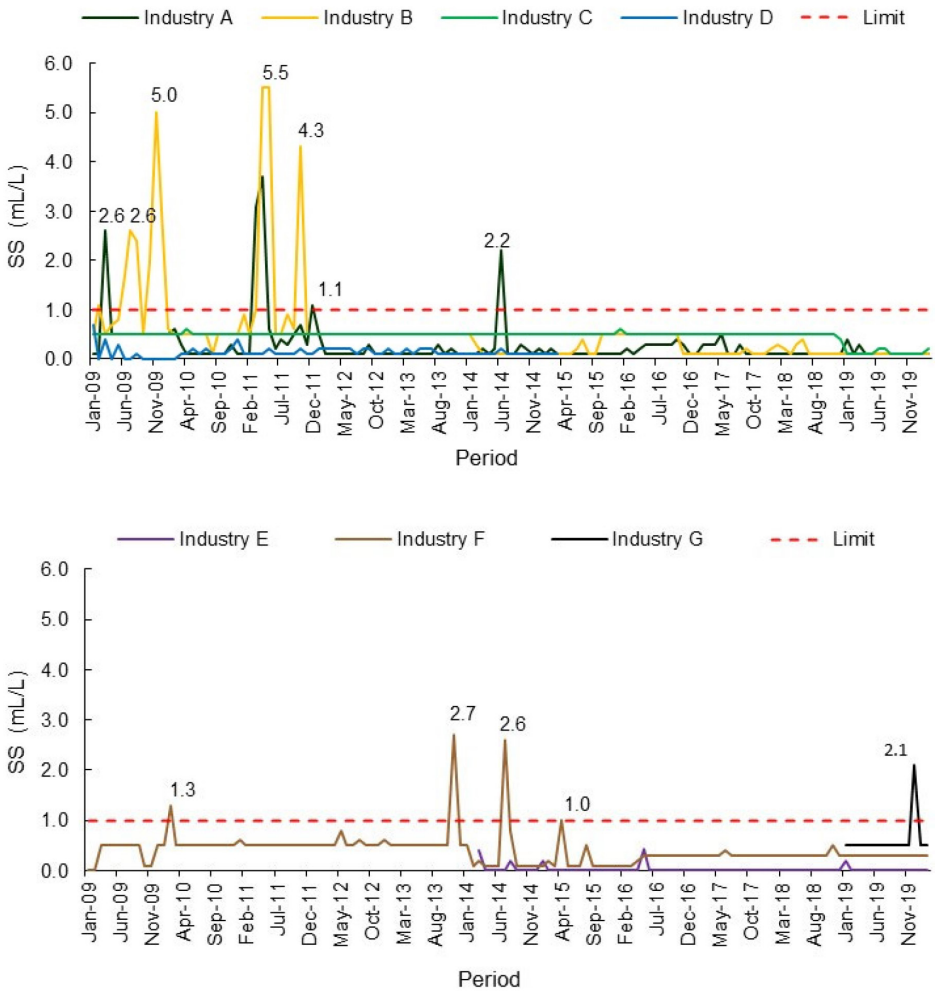

Figure 5. SS data from pharmaceutical industries A, B, C, D, E, F, G from January 2019 to February 2020

for industry F it was 1.5%; for industry G it was 7.1%; and for manufacturers, C, D, and E did not have monthly averages above the legal limit during the period evaluated. In other words, 57% of the evaluated companies discharged industrial effluent with SS content above the regulatory limit and 43% of the companies complied with the limit regarding the monthly average discharge.

The average for sedimentable solids found in this work was 0.4 mL L^{-1}. Leonel (2016)[21] reported an evaluation of sewage treatment plants employing stabilization ponds and found SS content less than 0.5 mL L^{-1}. This result indicates that SS content obtained by those sewage treatment plants was close to the results obtained by the companies evaluated here.

Phosphorus is one of the most important nutrients for the growth and reproduction of microorganisms that promote the stabilization of organic matter present in sanitary sewage and biodegradable industrial waste. The level of phosphorus in wastewater analyses refers to the amount of the element present in the sample.[23] According to Braile (1979),[19] eutrophication caused by the release of phosphorus above the limit is one of the main problems faced by pharmaceutical companies. This phosphorus is usually due mainly to detergents used for equipment cleaning, but also comes from sanitary sewage. Two possibilities for removing this pollutant from effluents are chemical coagulation and electrocoagulation.

In NT-202 R.10,[12] for control of industrial liquid effluents, the maximum phosphorus limit for the release of waste is 1 mg L^{-1}. According to item 4.8 of the mentioned technical standard, the phosphorus and total nitrogen parameters must be evaluated in stretches of watercourses that contribute to lakes.

Rebelo (2016),[25] studying the water quality of the Jacarepaguá lagoon complex, which receives a large part of the effluents discharged by the pharmaceutical industries in the region, reported that from 2001 to 2015 monthly average levels of phosphorus were at least five times the established limit, which is 0.186 mg L^{-1} according to CONAMA Resolution 357/2005[25] for class 2 water (brackish water). The results reported by Rebelo (2016)[25] showed a need for stricter control by the relevant authorities in relation to phosphorus. The reported values were very high, and a high concentration of phosphorus has a relationship with other parameters, such as turbidity, Kjeldhal nitrogen, and thermotolerant coliforms.

Figure 6 shows data on phosphorus content present in the effluents of the companies studied. Large amounts of phosphorus tend to increase algal growth, which can cause eutrophication. This is often associated with the large application of fertilizers in agriculture.[4]

The consolidated data referring to pharmaceutical industries for the phosphorus parameter (Figure 6) showed that the monthly average effluent of industry A was above the regulatory limit in 8.9% of the readings, while this figure for industry C was 4.0%; for industry D it was 2.9%; for industry F it was 25.9%; for industry G it was 7.1%, and industry E did not exceed the monthly average regulatory limit during the period evaluated. Pharmaceutical industry B does not carry out self-control for the phosphorus parameter. Thus, it was possible to conclude that 85% of the evaluated pharmaceutical manufacturers, which must monitor the phosphorus parameter, discharged more than the regulatory limit at least once, while only 15% of the companies managed to meet the limit in all cases.

The presence of nitrogen compounds in aquatic systems is of great interest in monitoring water bodies. Ammoniacal nitrogen is also one of the parameters evaluated for the classification of natural water bodies and the release of effluents according to CONAMA Resolution 357.[26] Ammonia is considered toxic mainly if present in aquatic environments, and the balance between NH_3 and NH_4OH can be transposed due to changes in temperature and pH. At low temperatures and acidic pH, ammonia is solubilized, leading to the production of NH^{4+} and OH^- ions that do not cause problems for the biota, but when there is an increase in pH above 9 and high temperatures, gaseous ammonia is released, and can accumulate in organisms, causing a toxic effect.[4,19]

CONAMA Resolution 430/2011[10] does not establish a specific limit for the release of total nitrogen. In NT-202 R.10,[12] the maximum limit for total nitrogen from the release of waste is 10 mg L^{-1}. According to item 4.8 of the mentioned technical standard, the phosphorus and total nitrogen parameters must be evaluated in stretches of watercourses that contribute to lakes.

One of the main causes of high nitrogen in wastewater is the high concentration of nitrogen compounds in sanitary

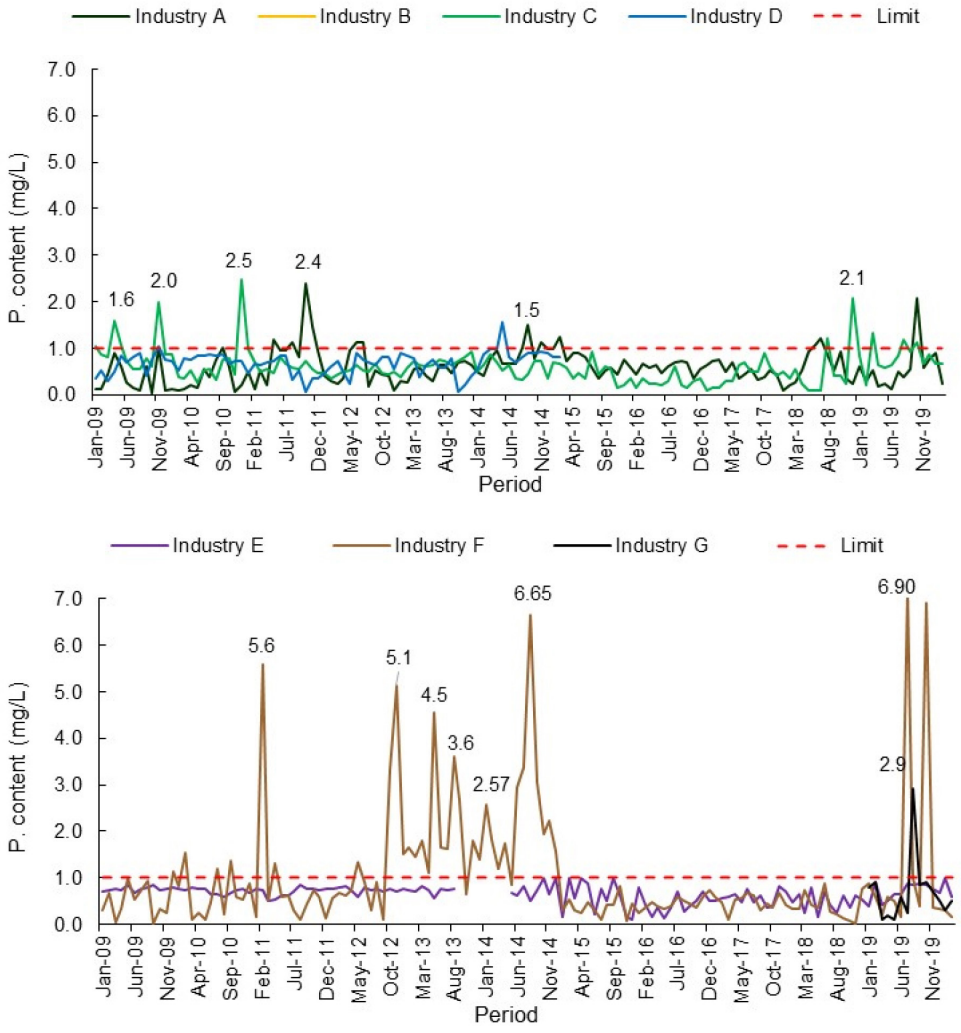

Figure 6. Phosphorous content from effluents of the pharmaceutical industries A, B, C, D, E, F, and G were obtained from January 2019 to February 2020

effluents, which are rich in different forms of nitrogen, such as ammonium carbonate, ammonium hydroxide, nitrites, nitrates, and organic nitrogen. Ammonium carbonate is formed in effluents due to the hydrolysis of urea present in urine. Proteins or amino acids have nitrogen in their molecules and significantly increase the concentration of organic nitrogen. Nitrogen is important in the treatment of effluents since it is essential for the proliferation and development of the biological environment, but treatment systems must be able to properly treat this nutrient to prevent its release into the environment at high concentrations.[19]

Figure 7 demonstrates the results found in the tests of N content, which were evaluated to determine the amount of total nitrogen present in the effluents. This nitrogen can generate nitrogenous compounds, increasing the growth of algae, and causing eutrophication. Also, ammonia above 5.0 mg L^{-1} is lethal to fish and high concentrations of nitrates can cause childhood methemoglobinemia.[4]

The consolidated data for the parameter nitrogen content (Figure 7) indicated that for industry D, 41.4% of the monthly averages were above the regulatory limit; while the figure for industry F was 29.9%; for industry G it was 14.3%, and industry E did not present monthly averages above the regulatory limit during the period evaluated. Pharmaceutical industry A did not carry out self-control of the total nitrogen parameter, but monitored ammonia, with 6.7% of the results being above the monthly average limit. Pharmaceutical industry B did not evaluate any kind of nitrogen in its effluents, and industry C performed monitoring of Kjeldahl nitrogen, which does not have limits in the reference regulations. It was possible to conclude that for 75% of the evaluated companies, there was a discharge of industrial effluent above the legal limit in some readings, while 25% of the companies managed to meet the limit regarding monthly average discharge in all cases.

In comparison with the results obtained in this work regarding the general average of total nitrogen, which was 5.88 mg L^{-1}, Leonel (2016),[21] analyzing sewage treatment plants employing stabilization ponds, found that the general average of ammoniacal nitrogen (which is only a part of the total nitrogen) was 30.1 mg L^{-1}. Thus, the sewage treatment stations presented results about 5.1 times higher than those reported by the manufacturers evaluated, confirming that sanitary effluents have a large amount of nitrogen in their composition. Nitrogen must be periodically evaluated since it is one of the major causes of eutrophication of receptor bodies.

Surfactants are an important environmental pollutant, mainly due to their wide use in various industrial sectors, as detergents, wetting agents, emulsifiers, and foaming agents. Anionic surfactants are the oldest and most widely used in household and personal cleaning products, pharmaceuticals, and cosmetics.[27] These contaminants harm all aquatic life, destroying microbial populations and causing damage to fish. CONAMA Resolution 357/2005[26] establishes a maximum concentration of 0.5 mg L^{-1} for surfactants in effluents to protect aquatic habitats.

The consolidated data referring to companies for the anionic surfactants parameter (Figure 8) identified that industry C presented readings above of the monthly averages evaluated above the regulatory limit in 1.0% of cases; while for industry D this indicator was 2.9%; and manufacturers B, E, F, and G did not show any monthly averages above the regulatory limit during the period evaluated. Industry A did not monitor anionic surfactants. In other words, for 33% of the evaluated manufacturers, which must monitor the parameter, there was the discharge of industrial effluents above the regulatory limit in some cases, while 67% of the manufacturers managed to meet the limit in all cases. CONAMA Resolution 430/2011[10] does not establish a specific limit for the release of anionic surfactants (MBAS). In NT-202 R.10,[12] the upper limit for anionic surfactants is 2.0 mg L^{-1}. The lowest discharge value of MBAS was 0.03 mm L^{-1} and the highest reported value was 1.82 mg L^{-1},

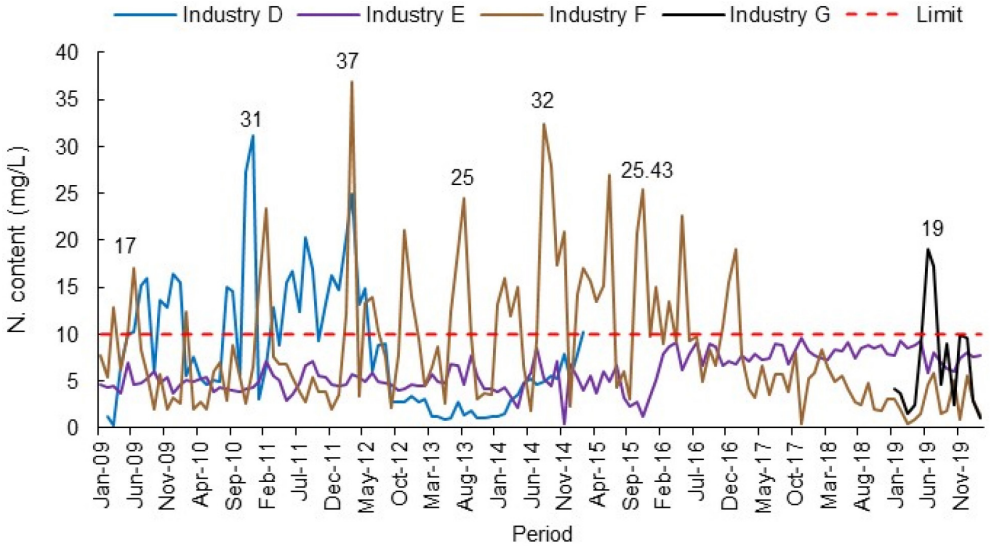

Figure 7. N content data from pharmaceutical industries D, E, F, G from January 2019 to February 2020.

so there were no cases of effluent discharge above the limit defined in NT-202 R.10,[12] which is 2.0 mg L^{-1}.

Harter (2007),[28] evaluating a river in the Brazilian state of Minas Gerais, found average MBAS content of 0.21 mg L^{-1}. However, he reported a very high presence of MBAS in the months of November 2005 and July 2006 in the district of Martinésia in the municipality of Uberlândia (0.66 and 1.2 mg L^{-1}), The effluents generated by companies evaluated here, in general, presented MBAS content of 0.30 mg L^{-1}.

The acute toxicity parameter is measured mainly as a complement to physicochemical analyses, which assess the effects of substances in the biological environment. The results obtained are mainly used in monitoring ecosystems and managing pollution control plans. The toxicity assessment is an important complementary tool to assess the quality of water and effluents, since several physicochemical analyses are usually carried out, such as measurement of BOD, COD, SS, organic compounds, and several other substances. However, these parameters are not able to distinguish between the substances evaluated, which affect biological systems and are innocuous to the environment, in addition to not being sufficient to express the potential environmental risk of contaminants.[4]

Acute toxicity is primarily evaluated to identify the damage that can be caused to aquatic organisms. In the test, standard organisms are used, which are established by INEA in NOP-INEA-008 R.00[14] according to the salinity and conductivity of the samples. Only in December 2020 did the analysis of pollution start using two organisms with different trophic levels.

CONAMA Resolution 430/2011[10] provides that, if not established by the competent environmental agency, the following criteria must be adopted for the toxicity parameter: in effluents that are released into receiving bodies classified in Class 1 and 2 (saline and brackish waters), according to CONAMA Resolution 357/2005,[26] the effluent concentration in the receiving body (CECR) must be less than or equal to the concentration with unobserved effect (CENO) of at least two trophic levels. In other words, the CECR must be lower than or equal to the CENO when the chronic toxicity tests are performed, or the CECE must be less than or equal to the median lethal concentration (LC_{50}), divided by 10, or less than or equal to the toxicity factor divided by 30 when performed to measure the acute effect.

In effluents that are discharged into class 3 freshwater and saline water and class 2 brackish water bodies, the

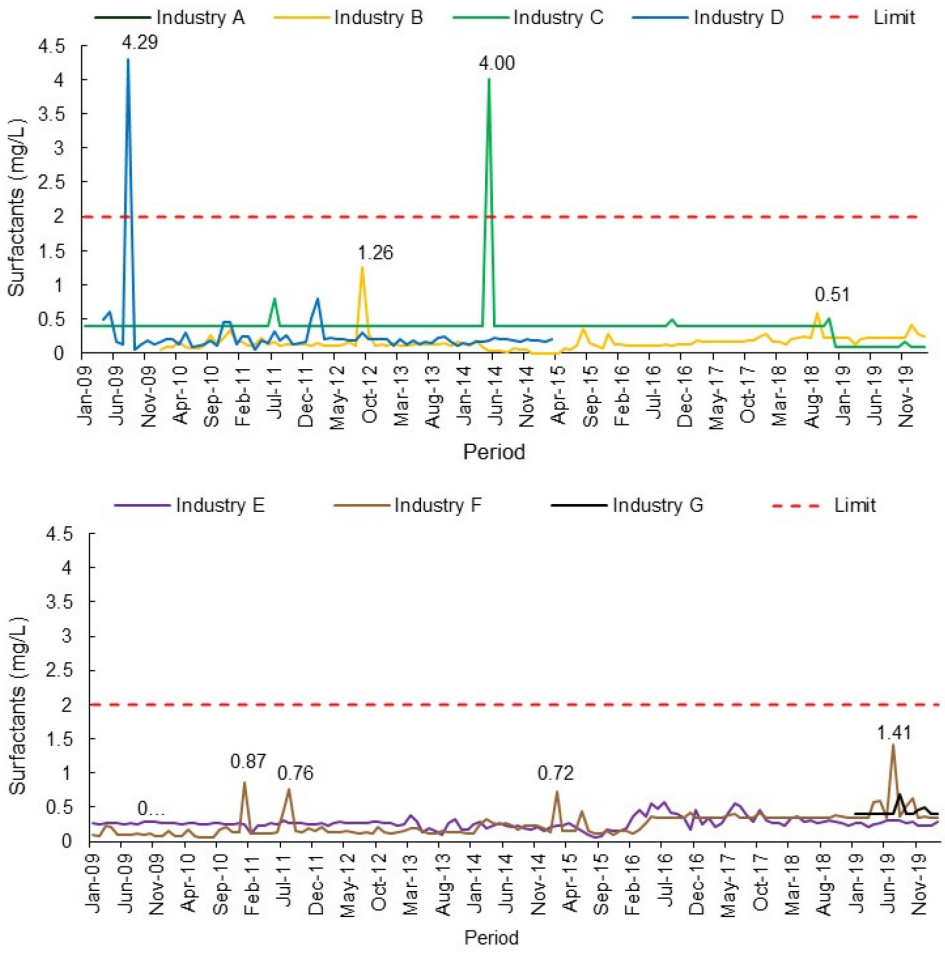

Figure 8. Data on surfactants from pharmaceutical industries A, B, C, D, E, F, and G from January 2019 to February 2020

CECR must be less than or equal to the CENO in aquatic organisms in at least two trophic levels, that is, the CECR must be less than or equal to the LC_{50} value divided by 3, or less than or equal to toxicity factor divided by 100 when performing acute toxicity tests.[10]

CONAMA Resolution 430/2011[10] also determines that environmental agencies can reduce the number of trophic levels to be evaluated based on the evaluation of the historical series for the purpose of monitoring the toxicity of the discharged effluent and determines that the environmental agency must establish for which projects and activities it is necessary to carry out toxicity tests according to the characteristics of the generated effluents and the receiving body.

In NOP-INEA-008 R.00,[14] the upper limit for acute toxicity in fish for the release of waste is 8 TF. Cubas (2011)[24] analyzed the treatment of industrial effluent with activated sludge, applying tests of acute toxicity with *Daphnia magna*. The results found were 2 TF, 4 TF, and 4 TF respectively for the months of February 2011, March 2011, and April 2011, indicating that the values found met the applicable regulations in the state of Rio de Janeiro and met the limit established by the Paraná State Environmental Council.

Figure 9 demonstrates the results found in the acute toxicity tests with *Danio rerio*. pharmaceutical industries B, C and E did not present results of toxicity above the regulatory limit, which is 8 TF, and manufacturers A, D, F and G did not perform the test.

Castro (2008)[29] reported average acute toxicity (*Danio rerio*) of 4.3 TF for industrial effluents from a textile factory subject to physicochemical treatment. However, in this work, the average overall toxicity was 1.16 TF. This result indicates that the effluent from the companies, despite containing several dissolved substances, showed acute toxicity lower than the effluents evaluated by Castro (2008).[29]

pH is an important quality parameter for industrial waste that causes changes in the solubility of various nutrients.[3] CONAMA Resolution 430/2011[10] establishes a lower pH limit of 5 and an upper limit of 9 for the discharge of liquid effluents into receiving bodies. The range established in NT-202 R.10[11] for the pH parameter is also from 5.0 to 9.0.

Testing the pH parameter is considered fundamental in the different phases of effluent treatment and needs to be periodically evaluated with process quality control. The release of effluents into water bodies with pH values outside the established standards causes strong environmental impacts, the two main ones being an alteration of the solubility of nutrients in water and alteration of the physiology of species in aquatic ecosystems.[19] Figure 10 demonstrates the results found for the pH parameter.

Pharmaceutical industries A, B, C, D, E, F, and G did not present pH data outside the regulatory limits (Figure 10), which has a limit range of 5 to 9. In other words, for 100% of the companies that perform the test, there was no release of industrial effluents above the limits of the regulations.

Wastewater temperature is a very important parameter due to its effects on aquatic life. This parameter is considered of fundamental importance for the survival of the microbiota since it can alter the solubility of oxygen in the water and hamper fish reproduction.[3] CONAMA Resolution 430/2011[10] establishes the limit of 40 °C and NT-202 R.10[12] also adopts the same limit for the temperature of discharge into receiving bodies. Pharmaceutical industries A, B, C, D, E, F, and G did not release effluents at a temperature above the regulatory limit, which is 40 °C. In other words, for 100% of the companies that conduct the test, there was no release of industrial effluent above the regulatory limit established in CONAMA Resolution 430/2011[10] and NT-202 R.10.[12] The temperature parameter should be monitored regularly since it can cause a strong impact and is subject to variations due to many causes.

Rebelo (2016),[25] in a study of rivers located in the West Zone of Rio de Janeiro, reported that the lowest temperature found was 16 °C and the highest temperature found was 32 °C. This broad range was likely due to factors such as the time of sampling, weather conditions, seasons of the year or whether the measurement station was under some cover, but it was not possible to rule out that the temperature

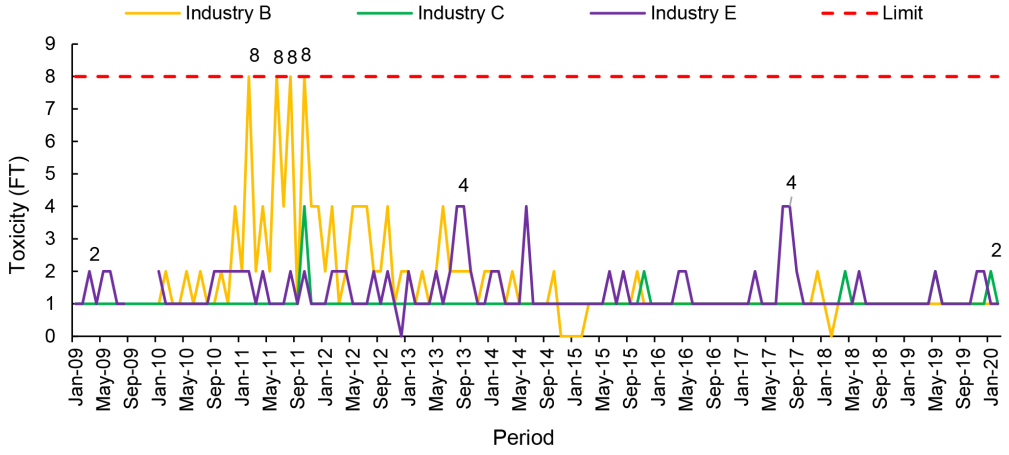

Figure 9. Toxicity data from pharmaceutical industries B, C, E from January 2019 to February 2020

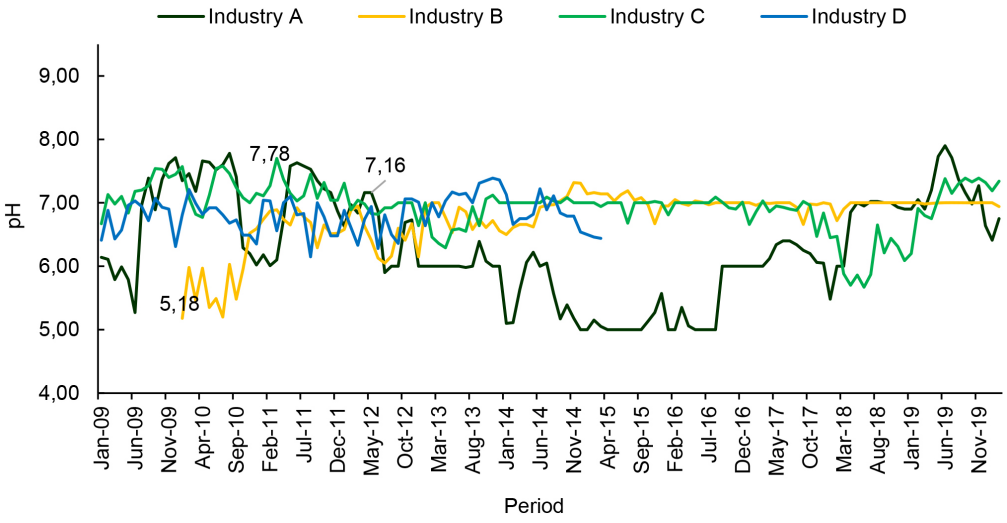

Figure 10. pH data from pharmaceutical industries D, E, F, G from January 2019 to February 2020

change was due to the release of hot effluents by companies. According to the author, these data were within the estimated range for growth of organisms (also with a broad range from 10 to 45 °C) and were also close to the range normally considered as optimal temperature for fish growth in Brazil, which is from 26 to 32 °C.

To carry out the BOD test, the incubation time and temperature must be controlled, according to APHA (2017).[30] Thus, the temperature can also influence the final result of BOD_5. Table 6 shows very low correlations between temperature and BOD parameters, indicating no significant influence between the two parameters.

Table 3. The correlation between the monthly averages of the temperature and BOD parameters of the pharmaceutical industries was evaluated

Pharmaceutical industry	R^2	P	Interpretation p
A	0.0165	0.1285	Very weak
B	0.0387	0.1967	Very weak
C	0.0352	0.1876	Very weak
D	0.0115	0.1072	Very weak
E	0.0012	0.0346	Very weak
F	0.00005	0.0071	Very weak
G	0.0246	0.1568	Very weak

The average data of COD, BOD, COD/BOD, P content, and pH obtained in this work were compared with other results of the literature (Table 4). The COD data found in this work were similar to the COD data described by Chakrabortty *et al.* (2020) (other pharmaceutical effluents), Soriano-Molina *et al.* (2019) (municipal wastewater), and lower than the limit established in state legislation (DZ R205),[13] but lower than COD data of pharmaceutical effluent treatment plants. The BOD data found in this work were lower than several results reported by Farhari *et al.* (2012)[36] and Liu *et al.* (2022) (pharmaceutical effluents), Khatamian *et al.* (2020)[31] (industrial effluents), and Soriano-Molina *et al.* (2019)[34] (municipal wastewater), indicating a higher content of refractory organic matter. BOD data shown in this work were also lower than reported by El-Rehaili *et al.* (1995)[33] related to effluent after passing through the primary treatment stage. Higher COD/BOD ratio also indicates that the effluent reported in this work probably has a higher content of refractory organic matter than other effluents reported in Table 4. Refractory materials cannot be treated by conventional processes, and these pollutants can cause carcinogenic and mutagenic impacts on flora, fauna, and human beings.[40] The phosphorus content reported in this work was higher than the P content reported by Tardy *et al.* (2021),[35] but lower than the limit established in NT 202.R-10.[12] According to Marcondes,[41] eutrophication caused by the release of P above the limit is one of the main problems of pharmaceutical manufacturers. The high content of P in these effluents is usually related to the detergents used in the cleaning processes of equipment. The pH levels of the effluents analyzed in this work were similar to the pH of the different effluents reported in Table 4.

4. Conclusions

Based on the aspects discussed in this work, it can be concluded that the effluents generated by the companies presented high levels of all the parameters. All the evaluated pharmaceutical industries violated the BOD limit established in the standard DZ 205 R.06 and released 71% effluents with COD above the limit (150 mg L^{-1}) established by DZ 205 R.06. Regarding the correlation between the tests of COD and BOD, 71% of the evaluated companies showed a moderate correlation between these parameters, while 29% of them showed weak correlation. According to the test of sedimentable solids, 57% of the evaluated companies discharged effluents with this parameter above the limit (1.0 mL/L) of NT-202 R. 10. For the phosphorus parameter, which is monitored by only part of the evaluated manufacturers, the monthly averages were above the limit of NT-202 R.10

Table 4. Comparison of the data on flow, COD, BOD, SS, P and N content, surfactants, toxicity, pH, and temperature obtained in this work and results reported in the literature

Effluent	COD(%)	BOD(%)	COD/BOD	P(mg L^{-1})	pH	Ref.
Pharmaceutical effluent	64.16	9.53	6.73	0.70	6.36	This work
Industrial effluent	210	60	3.5	-	-	31
Pharmaceutical effluent	78.5	< QL	-	-	6.6	32
Secondary effluents under varied concentrations of chlorine	170	130	1.30	-		33
Municipal wastewater	58.3	19.7	2.96		7.4	34
Pharmaceutical plant wastewater	-	-	-	0.03	7.68	35
Pharmaceutical plant wastewater	-	102	-	-	-	36
Hospital and urban wastewater	-	-	-	-	-	37
Pharmaceutical plant effluent	132.7	-	-		8.2	38
Pharmaceutical effluent	4000-16,500	1330-4800	3.00-3.44		3.06-5.35	39

in 85% of the evaluated companies (1.0 mg L^{-1}). A total of 75% of the companies discharged effluents containing total nitrogen above the limit of the NT-202 R.10 (10.0 mg L^{-1}). In contrast, 33% of the evaluated companies released effluents with MBAS above the limit of NT-202 R.10 (1.0 mg L^{-1}). According to the monthly means obtained, it can be concluded that the parameters of acute toxicity (to *Danio rerio*), pH, and temperature were not above the limits. In other words, 100% of the pharmaceutical industries did not release effluents with these parameters above the limits of the relevant regulations. The scientific references used as a basis for the preparation of this work brought to light several results that should be considered objectively by all stakeholders, namely environmental agencies at the federal, state, and municipal levels, pharmaceutical manufacturers, nonprofit organizations, and representatives of society in general. The data collected show that the concentrations of several pharmacological substances are very high. This finding should be used to foster discussions on the environmental sustainability of these industrial operations.

The data on COD, BOD, COD/BOD ratio, P, and N reported here show that pharmaceutical effluents generated in the ten years studied had high polluting potential. Comparing the data reported in this work with other results described in the literature it was possible to observe that in general the pharmaceutical effluents analyzed here contained a higher content of refractory material, indicating a more complex composition and more difficult treatment. The Jacarepaguá lagoon complex was the environment that received these pharmaceutical effluents. Thus, the environmental impact related to these effluents on this region should be prioritized in future research, as well as public projects related to mitigation of these contaminants.

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