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Pharmaceuticals and environmental risk assessment in municipal wastewater treatment plants and rivers from Peru

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ABSTRACT

This is the first study dealing with removal of the pharmaceutical substances in municipal wastewater treatment plants (MWWTPs) from Peru and the impact of these compounds in surface waters receiving treated wastewater. To this aim, samples from MWWTP of Lima (Peruvian Coast), MWWTP of Cusco, Puno and Juliaca (Peruvian Highlands), as well surface water (confluence of Torococha and Coata rivers in Juliaca) were analyzed. A total of 38 target pharmaceuticals were included in this study and were determined by Liquid Chromatography coupled to tandem Mass Spectrometry (LC-MS/MS). Around 60% and 75% of the target pharmaceuticals could be quantified in surface water and MWWTPs, respectively. Acetaminophen was the drug found at the highest concentration, and it was present in all the treated wastewater samples reaching average values above 100 μg/L in the department of Puno. The gabapentin anti-epileptic drug (up to 11.85 μg/L in MWWTP Lima) and the antibiotics clarithromycin, trimethoprim, ciprofloxacin, sulfamethoxazole and azithromycin (1.86 to 4.47 μg/L in MWWTP Lima) were also found at moderate concentrations in the treated wastewater. In surface water, the highest concentration corresponded also to acetaminophen (28.70 μg/L) followed by sulfamethoxazole (4.36 μg/L). As regards the pharmaceuticals removal, data of this work showed that the MWWTP Cusco (aerobic biologic process by synthetic trickling filters as secondary treatment) was more efficient than the MWWTP Lima (a preliminary treatment that combines grilles, sand trap, degreaser-aerated and sieved of 1.0 mm). However, many pharmaceuticals (around 50% of the compounds investigated) presented concentrations in treated wastewater similar or even higher than in influent wastewater. The environmental ecological risk of pharmaceuticals was assessed based on calculated Risk Quotient (RQ) in the treated wastewater and surface water from the concentration data found in the samples. According to our data, three antibiotics (clarithromycin, ciprofloxacin, clindamycin) and the analgesic acetaminophen posed high environmental risk (RQ $\geq$ 1) on the aquatic environment. In the river, all antibiotics (except norfloxacin) as well as the analgesic-anti-inflammatory compounds acetaminophen, diclofenac posed a high environmental risk (RQ $\geq$ 1). Based on data reported in this work for the first time in water samples from Peru, it can be deduced that the treatment processes applied in important cities from Peru are not enough efficient to remove pharmaceuticals in wastewater. As a consequence, severe environmental risks associated to the presence of pharmaceuticals in treated wastewater and surface water are expected; so complementary treatment processes should be implemented in the MWWTPs for a more efficient elimination of these compounds.

1. Introduction

Nowadays, the presence of pharmaceutical compounds and their metabolites, considered as emerging organic micropollutants, in the aquatic environment is a major concern worldwide (Couto et al., 2019; Valdez-Carrillo et al., 2020; Pereira et al., 2020a; Pereira et al., 2020b). The main reason to explain the occurrence of pharmaceuticals in waters is found in their wide consumption and the incomplete removal in the

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municipal wastewater treatment plants (MWWTP); therefore, drug residues come into surface waters (SW) (Couto et al., 2019; Peña-Guzmán et al., 2019), groundwater and seawater (Hernández et al., 2019a; Alygizakis et al., 2016) with the consequent impact on their quality. Within the wide group of pharmaceutical compounds, antibiotics are those of most concern due to the negative impacts that they can generate on aquatic ecosystem and human health, e.g., the development of antimicrobial resistance strains caused through the discharge of wastewater to water bodies (Kairigo et al., 2020; Ben et al., 2019). Illustrative of this concern is the inclusion of several pharmaceuticals in the Watch List of European Union (EU), recently updated (EU, 2020). Nine pharmaceuticals and one metabolite are included in this list, of which four are antibiotics (Amoxicillin, Ciprofloxacin, Sulfamethoxazole, Trimethoprim).

Investigating the presence of pharmaceuticals in wastewater as well as the environmental risk associated to treated wastewater and water bodies receiving the effluents, has become a field of special interest because of the risks for human health and aquatic ecosystems (Crane et al., 2006; Desbiolles et al., 2018). To this aim, advanced analytical techniques are required, such as Liquid Chromatography coupled to Tandem Mass Spectrometry (LC-MS/MS), able to accurately quantify pharmaceuticals and their metabolites at sub-ppb levels (Hernández et al., 2019b; Gracia-Lor et al., 2014).

In Latin America, only a few studies are available on occurrence of pharmaceuticals in water in comparison to more industrialized countries (Peña-Guzmán et al., 2019; Tran et al., 2018; Couto et al., 2019). Additional information can be found in recent reviews that report data on pharmaceuticals in different water environments (de Oliveira et al., 2020; Peña-Guzmán et al., 2019; Reichert et al., 2019; Valdez-Carrillo et al., 2020). Some examples are the works performed in Argentina, reporting the presence of ibuprofen (0.4 to 13.0 μg/L), carbamazepine (0.2 to 2.3 μg/L), atenolol (0.2 to 1.7 μg/L) and diclofenac (0.03 to 1.2 μg/L) in municipal wastewater and surface water (0.50 to 13.32 μg/L) (Elorriaga et al., 2013a,b); in Colombia, where the occurrence of pharmaceutical substances was studied in hospital and municipal treated wastewater, finding acetaminophen at high concentrations (up to 50 μg/L), followed by antibiotics, such as azithromycin, ciprofloxacin and norfloxacin (0.47 to 3.99 μg/L), and the antihypertensive drugs losartan and valsartan (0.13 to 2.18 μg/L) (Botero-Coy et al., 2018); or in Brazil, where several pharmaceuticals of different therapeutic groups were found, from 0.023 to 138 μg/L in influent wastewater (the highest levels were for paracetamol (acetaminophen)) and from 0.023 to 1.4 μg/L in the effluent wastewater (the highest levels were for sulfamethoxazole) (Bisognin et al., 2019). However, up to our knowledge, in Peru, the presence of the pharmaceuticals in water matrices has not been reported yet.

The toxic threat caused by pharmaceuticals into the aquatic ecosystems and the ecotoxicological risks can be estimated by the Risk Quotient (RQ), a parameter that relates the potential exposure to a substance with the level at which no adverse effects are expected. RQ is calculated as the ratio between PEC (predicted environmental concentration) or MEC (measured environmental concentration) and PNEC (predicted-no-effect concentration). Based on this estimation, several studies reported that the concentrations found for non-steroidal anti-inflammatories, antibiotics and beta-blockers may represent high toxicity risk in water bodies (Rivera-Jaimes et al., 2018; Aydin et al., 2019; Desbiolles et al., 2018; Godoy et al., 2015; Guruge et al., 2019; Kosma et al., 2014; Mijangos et al., 2018; Wang et al., 2017), whereas other studies pointed out no high environmental risk to aquatic biota in water resources (French, Spain) and ocean waters (Spain) (Biel-Maeso et al., 2018; Bouissou-Schurtz et al., 2014; Gómez-Canela et al., 2019). However, these studies did not include the dilution factor in the environmental risk assessment, which is a critical component in estimating concentrations of so-called "down-the-drain" chemicals (e.g., pharmaceuticals) in rivers according to Keller et al. (2014). The estimation of the RQ values, therefore, depends on the concentration of pharmaceuticals in the wastewater discharged into water bodies, and on the dilution associated, which must be measured and monitored in order to develop and incorporate a regulatory framework for the improvement of the water quality and public health.

The absence of data in Peru, leads to a gap of information on occurrence and risks of pharmaceuticals in the water bodies and in sewage, mainly because of the lack of specialized instrumentation and trained personnel to implement the advanced analytical techniques required for their reliable determination. In addition, the non-regulation of the pharmaceutical compounds makes that most efforts are directed towards other types of contaminants in water.

In this work, we selected several sites belonging to the department of Lima (Peruvian Coast), Cusco and Puno (Peruvian Highlands). They were selected because of the environmental, cultural, and socio-economic impact that treated wastewater may have on the aquatic ecosystems and on public health in these populated areas, and also because the MWWTPs apply different treatment processes to municipal wastewater. The overall goal of this study was to investigate the occurrence and removal of pharmaceuticals in selected MWWTPs based on quantitative analysis by LC-MS/MS with triple quadrupole. A total of 38 substances from different pharmaceutical classes, such as antibiotics, analgesic-anti-inflammatories, anti-epileptics, anti-hypertensives, anxiolytics, lipid regulating drugs, anti-depressants, anti-protozoal drugs, beta-blockers, beta-agonists, contrast agents and proton-pump inhibitors, were quantified in influent and effluent wastewaters. The environmental risk in the effluent wastewater and surface water receiving the wastes was also evaluated. The results presented in this paper are the first data reported on Peru, and constitute the initial contribution for a better knowledge on pharmaceutical compounds present in effluent wastewaters, and on the ecotoxicological risk in aquatic ecosystems. Hopefully, this and other future works will help to the development of future environmental regulations in Peru and other Latin-American countries.

2. Materials and methods

2.1. Characteristics of the wastewater treatment plants and studied areas

The wastewater samples were collected in MWWTPs of the Peruvian Coast (Department of Lima) and Highlands (Department of Cusco and Puno). These MWWTPs treat municipal wastewaters which comprise domestic, service, hospital, veterinary, industrial by-product water, and storm water collected in the municipal network.

Fig. 1 shows the location of the MWWTPs studied. MWWTPs were sampled and labeled as MWWTP Lima, MWWTP Cusco, MWWTP Puno and MWWTP Juliaca. In the Department of Lima, there are 19 MWWTPs of which the MWWTP Lima was selected for this work because of the relevance of the domestic wastewater from the capital city in Peru and because the wastewater from the main hospitals of Lima is discharged directly to the sewer system. MWWTP Lima treats around 70% of the wastewater of Lima and Callao, which corresponds to approximately 4.5 million inhabitants, equivalent to 50% of the population of these cities. The treatment system includes only a preliminary process (grilles, sand trap, degreaser-aerated and sieved of 1.0 mm). After the preliminary treatment, the effluent wastewater (EWW) is discharged to the sea (Bay Callao) by an underwater emissary (3.5 km length and 15 m depth). The average daily flow rate of the treatment plant is 14 m^3/s, with a maximum of 20.3 m^3/s (Fig. 1a).

The MWWTP Cusco was selected in the Department of Cusco. The MWWTP Cusco is located at an average altitude of 3245 m above sea level (masl) and treats 85% of the wastewater of the city corresponding to around 428,450 inhabitants. The treatment system entails an aerobic biological treatment through synthetic trickling filters and the sludge treatment by anaerobic process. The average daily flow rate is 446 L/s with a maximum of 802 L/s. The effluent is finally discharged to the Huatanay River (Fig. 1b), which water is used for crop irrigation. It is a

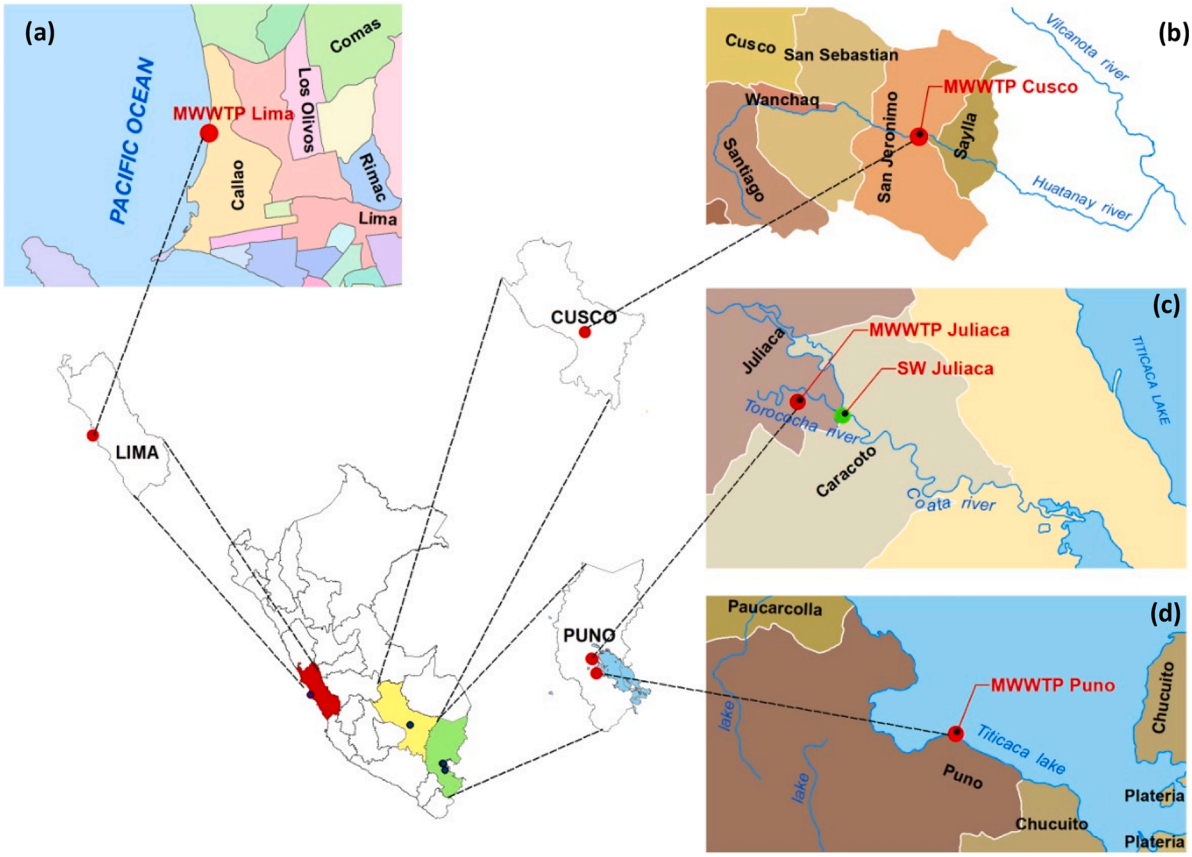

Fig. 1. Location of wastewater samples from MWWTP collected in three Departments of Peru (Lima, Cusco and Puno) labeled as MWWTP Lima (a), MWWTP Cusco (b), MWWTP Juliaca (c) and MWWTP Puno (d), and of the surface water (confluence River: Torococha and Coata) named as SW Juliaca (c).

tributary crossing the Imperial city and empties into the Vilcanota River (Urubamba, Incas' Sacred Valley and part of the Amazon Basin), as well as in certain rural areas.

In the Department of Puno, two MWWTPs were sampled, labeled as MWWTP Puno and MWWTP Juliaca. These are the main cities of this Department: Puno (capital of the province of Puno) and Juliaca (capital of the province of San Roman) with approximately 135,288 and 278,440 inhabitants, respectively. Around 50% of the wastewater of both plants (MWWTP Puno, 3810 masl; MWWTP Juliaca, 3824 masl) is treated by Oxidation Ponds. After treatment, the effluent is discharged into the inner Bay of the Lake Titicaca in Puno (Fig. 1d) and into the Torococha River flowing (4 km) towards the Coata River, which finally empties into Lake Titicaca in Juliaca (Fig. 1c). The average flow rate of influent wastewater is 0.22 m^3/s and 0.36 m^3/s in MWWTP Puno and MWWTP Juliaca, respectively.

Table S1 in Supplementary Information shows the physicochemical properties of the effluent wastewaters from the MWWTPs under study, as well as the water surface (confluence of Rivers: Torococha and Coata).

2.2. Sample collection

A total of 22 samples were collected from the MWWTPs Lima, Cusco, Puno and Juliaca in May 2019. The samples included influent wastewater (IWW) and effluent wastewater (EWW). In the MWWTP Lima and MWWTP Cusco, composite samples (12 h, from 6 a.m. to 6 p.m., every three hours) were daily collected over five and four consecutive days, respectively, from 23rd to 27th May (10 samples, 5 IWW and 5 EWW) and from 10th to 13th May, (8 samples, 4 IWW and 4 EWW), respectively. In the Department of Puno (Puno and Juliaca cities), grab samples were collected for both treated EWW and surface water. The EWW samples from MWWTP Puno were collected in two consecutive days, 6th and 7th May (2 samples), while in Juliaca one EWW sample and one surface water were collected the same day (7th May). The sampling site for surface water was selected in the confluence of the rivers. This was because the effluent wastewater is discharged to the Torococha River and this flows into the Coata River, which serves as a water source for livestock and agriculture, finally flowing into Titicaca Lake.

In all cases, the samples were collected in high-density polyethylene bottles (1 L) and immediately stored in the dark at 4 °C in a cooler during their transport to the laboratory for the sample treatment. Upon reception in the laboratory, the samples were filtered through 0.45 μm cellulose membrane, and an aliquot (50 mL) was preserved at −20 °C until analysis.

2.3. Target compounds

In total, 38 compounds commonly found in urban wastewater (Botero-Coy et al, 2018) were evaluated for this study: 1 analgesic and 3 non-steroidal anti-inflammatory drugs, 17 antibiotics, 3 anti-epileptic drugs, 4 anti-hypertensive drugs, 2 anxiolytic drugs, 2 proton-pump inhibitors, 1 anti-depressant drug, 1 beta-blocker, 1 anthelmintic drug, 1 lipid-regulating drug, 1 contrast agent and 1 beta-agonist (Table 1).

2.4. LC-MS/MS analysis

The samples were directly analyzed without any pre-concentration step (i.e., SPE was not applied) (Botero-Coy et al, 2018). A high number of isotope-labelled internal standards (ILIS) were used (17 analyte-ILIS out of 38 compounds analyzed) in order to correct for potential matrix effects. The procedure applied was as follows: firstly, a 2-mL aliquot of IWW was centrifuged at 12000 rpm for 3 min. Then, 200 μL of IWW sample was taken and diluted × 5 by adding 750 μL Milli-Q

Table 1
List of target pharmaceutical compounds identified in the wastewater of the WWTP from Peru.

Compounds (Abbreviation)	
Antibiotics	***Analgesic, anti-inflammatories***
• *Azithromycin (AZM)*	• *Acetaminophen (ACE)*
• *Ciprofloxacin (CIP)*	• *Diclofenac (DIC)*
• *Clarithromycin (CLR)*	• *Phenazone (PHZ)*
• *Clindamycin (CLI)*	• *Tramadol (TRA)*
• *Erythromycin (ERY)*	***Anti-epileptics***
• *Flumequine (FLU)*	
• *Furaltadone (FUR)*	• *Carbamazepine (CBZ)*
• *Lincomycin (LCM)*	• *Gabapentin (GBP)*
• *Metronidazole (MTZ)*	• *Primidone (PMD)*
• *Nalidixic acid (NAL)*	***Anti-hypertensives***
• *Norfloxacin (NOR)*	
• *Oxolinic acid (OXA)*	• *Enalapril (ENA)*
• *Roxithromycin (ROX)*	• *Irbesartan (IBS)*
• *Sulfadiazine (SDZ)*	• *Losartan (LST)*
• *Sulfamethoxazole (SMX)*	• *Valsartan (VST)*
• *Tetracycline (TET)*	***Anxiolytics***
• *Trimethoprim (TMP)*	
	• *Alprazolam (APZ)*
	• *Lorazepam (LZP)*
Divers	• *Omeprazole sulphide (OMEP; PPI)*
	• *Pantoprazole (PAN; PPI)*
• *Atorvastatin (AT; lipid regulator)*	• *Salbutamol (SBL; beta-agonist)*
• *Iopromide (IPD; contrast agent)*	• *Venlafaxine (VNX; antidepressant)*
• *Levamisole (LEV; Anthelmintic)*	
• *Metoprolol (MP; beta-blocker)*	

PPI = Proton-Pump Inhibitor.

water and 50 μL ILIS mix of 20 μg/L (final ILIS concentration in samples injected was 1 μg/L). Finally, 100 μL were injected in the LC-MS/MS system. The EWW and surface waters were processed in a similar way, but diluting the samples × 2 (500 μL sample aliquot, adding 450 μL of MilliQ water and 50 μL ILIS mix of 20 μg/L). Calibration curves were prepared with ultrapure water containing the same amount of ILIS than the samples: to 900 μL ultrapure water, 50 μL of mix ILIS at 20 μg/L, and 50 μL of mix standard solution at different concentrations were added to give final analyte concentrations between 0.005 and 20 μg/L. In comparison with the procedure previously applied in wastewaters from Colombia (Botero-Coy et al, 2018), we increased the final concentration of ILIS used, as we observed improvements in recoveries due to a better signal of the ILIS for some compounds under study.

In relation to the limits of quantification (LOQ), a common value was used for all compounds as a function of the matrix sample, and we checked that this value was reached in every samples batch analysed. We took as a reference the lowest calibration level (0.005 μg/L), which considering the dilution factor of the samples (x5 or x2) would be equivalent to 0.025 μg/L and 0.01 μg/L. So, although it was possible to quantify some analytes at lower concentrations (those with higher sensitivity), a default value of 0.025 μg/L was used as LOQ for IWW analysis, and 0.01 μg/L for EWW and SW analysis.

Quality control of analysis was performed by preparing Quality control (QCs) samples for each sample type. QCs consisted on real-world samples (IWW, EWW and SW) that were spiked with the target pharmaceuticals at two levels, 0.1 and 1 μg/L, and were analyzed together with the samples in every sample batch.

Analyses were performed by LC-MS/MS with triple quadrupole (spectrometer Xevo TQS from Waters). Chromatographic separation was performed using an Acquity UPLC BEH C18, 1.7 μm, analytical column, 100 mm × 2.1 mm (Waters). The mobile phase was A = H_2O, B = MeOH, both with 0.01% HCOOH and 1 mM NH_4Ac. Three MS/MS transitions were acquired for each compound, of which one (commonly the most abundant) was used for quantification, and the remaining ones (q1 and q2) for identification of the compound in samples. For those compounds whose analyte-ILIS was available, relative areas were used for quantification, while absolute areas were used for the remaining analytes. More details of analytical methodology can be found elsewhere (Botero-Coy et al, 2018).

2.5. Environmental risk assessment

In order to assess the environmental hazard of the target pharmaceutical compounds on aquatic ecosystems when the treated wastewater is discharged into freshwater bodies, the Risk Quotient (RQ) parameter was evaluated according to European Commission Guidelines (EC, 2003). The basic principle of the environmental risk assessment is the comparison of the predicted environmental concentration (PEC) or measured environmental concentration (MEC) of a given substance with the predicted-no-effect concentration (PNEC) at which no effects on exposed organisms are expected to occur. In this work, RQ was calculated as the ratio between MEC and PNEC, considering MEC as the highest concentration found for each pharmaceutical in the effluent wastewater or surface water, i.e. the worst-case scenario. In the case of the wastewater, a dilution factor (DF) was applied to estimate the MEC. According to Keller et. al. (2014), DF corresponds to the "National annual median dilution factor" that relates the volume of freshwater available and the domestic sewage discharge for each country. In the case of Peru, the DF value is 132.7 (Keller et al., 2014). The PNEC value can be estimated from ecotoxicological data for the three trophic levels (algae, crustacean and fish), taken from the literature, divided by an established security factor according to the EU Technical Guidance Document for Risk Assessment (EC, 2003). This security factor is applied to the lowest chronic or acute toxicity data of the three trophic levels as follow (**Table S6** in Support Information):

(1) If the toxicity endpoints selected (TES) is the short-term toxicity EC50 (or LC50) a security factor of 1000 is applied.
(2) if a single long-term NOEC data is the TES, a security factor of 100 is applied.
(3) In the case of two or three long-term toxicity NOEC data, a factor of 50 and 10 applies, respectively.

3. Results and discussion

3.1. Quality control of analysis

In this work, special attention was paid to quality control of analyses. **Table S2** shows the results obtained in QCs analyses. In total, 10 QC samples were prepared: two QCs (0.1 and 1 μg/L) in surface water from Juliaca samples; two QCs (0.1 and 1 μg/L) in IWW from each MWWTPs Lima and Cusco; two QCs (0.1 and 1 μg/L) for EWW from each the MWWTPs Lima and Cusco. So, in total, recovery data were available for two QCs in surface water, four QCs in IWW and four QCs in EWW. All QCs samples were injected in duplicate.

Most recoveries were between 60 and 140% (SANTE, 2019), and commonly in the range 80–120%, which was surely due to an efficient matrix effects (ME) correction by the use of analyte-ILIS and the absence of complex sample treatments. In fact, the majority of exceptions occurred for those compounds which their own ILIS were not available. This is justified because the analytical procedure did not include any sample treatment step. Therefore, the recovery could be taken as a measurement of the matrix effects. When recovery data were out of the acceptable range, we applied correction factors as a function of the average QC recoveries obtained (**Table S2**). As a summary, there was no need to apply a correction factor for 17 compounds, for which their own analyte ILIS was available, with two exceptions, azithromycin and clarithromycin. For these two compounds, ME was not completely corrected by their ILIS, and showed some QC recoveries out of the range. There was also one sample (IWW from Cusco), which showed anomalous behaviour for roxithromycin, with unexpected high recoveries that might be due to any kind of unknown interference in this specific

sample. In addition, another 14 compounds did not need any kind of correction for reliable quantification, as no relevant ME seemed to occur (all QCs recoveries were in the range 60–140%).

Correction factors (Cf) were calculated for the remaining compounds as a function of the average QCs recoveries in the sample type analysed. These were alprazolam, clindamycin, flumequine, lorazepam, pantoprazole, phenazone and sulfadiazine. In general, the compounds that were most affected by ME and that required higher Cf were alprazolam and lorazepam. A particular case was acetaminophen. For this compound, QCs recoveries could not be calculated at the spiking levels assayed, due to the very high concentrations found in all "blank" samples analysed.

3.2. Removal of pharmaceuticals in municipal wastewater treatment plants

The comparison of the average concentrations between IWW and EWW allowed to roughly estimate the removal efficiency (RE, %) of the pharmaceuticals from MWWTP Lima and Cusco (see **Table S3** and **Table S4** in SI). Although some pharmaceutical compounds of low polarity can be adsorbed onto the solid particles and consequently can remain in the sludge (Göbel et al., 2005; Hyland et al., 2012), the comparison between IWW and EWW is commonly used for the assessment of the removal efficiency of organic micropollutants in MWWTP (Gracia-Lor et al., 2012; Bijlsma et al. 2014). This is a reasonable approach for pharmaceuticals taking into account their medium–high polarity and the low adsorption expected onto solid particles. RE was calculated as:

$$RE(\%) = \left(1 - \frac{C_{EWW}}{C_{IWW}}\right) x100$$

Fig. 2 shows that most of pharmaceuticals were partially-totally removed, while some of them were not removed and/or their concentrations in EWW were even higher than in IWW, leading to a negative removal efficiency, a fact that has been already reported in the literature (Gracia-Lor et al., 2012; Botero-Coy et al., 2018). According to our data, the MWWTP Cusco presented better removal efficiency than MWWTP Lima. In fact, the third part of the studied pharmaceuticals (MP, PHZ, OMEP, SMX, DIC, VEN, GAB, TRA, NOR, TMP, TET) presented high RE (>75%) in the MWWTP Cusco, while in MWWTP Lima, only the atorvastatin seemed to be efficiently removed. Around 30% of pharmaceuticals were partially removed in both MWWTPs. In addition, 13% (IPD, CLI, ACE, MTZ, CLR in Cusco) and 34% (IPD, VST, CLI, OMEP, DIC, ERY, LCM, ENA, SMX, GBP, MTZ, VNX, TMP in Lima) of the pharmaceuticals exhibited no elimination or negative removal efficiency, which highlight their recalcitrant and persistence during the conventional wastewater treatments. Around 20% of the selected pharmaceuticals (APZ, FLU, FUR, LEV, LZP, PAN, PMD, ROX) were not detected either in the IWW or in the EWW of the MWWTPs. The differences observed between the two treatment plants, with better global removal efficiency in Cusco, can be due to the fact that the MWWTP of Cusco utilizes primary and secondary (biological system by synthetic trickling filters) treatment steps, while the MWWTP of Lima employees only a preliminary process (grilles, sand trap, degreaser-aerated and sieved of 1.0 mm). However, our results highlight the need to implement a tertiary treatment step in order to effectively eliminate the pharmaceuticals in both treatment plants.

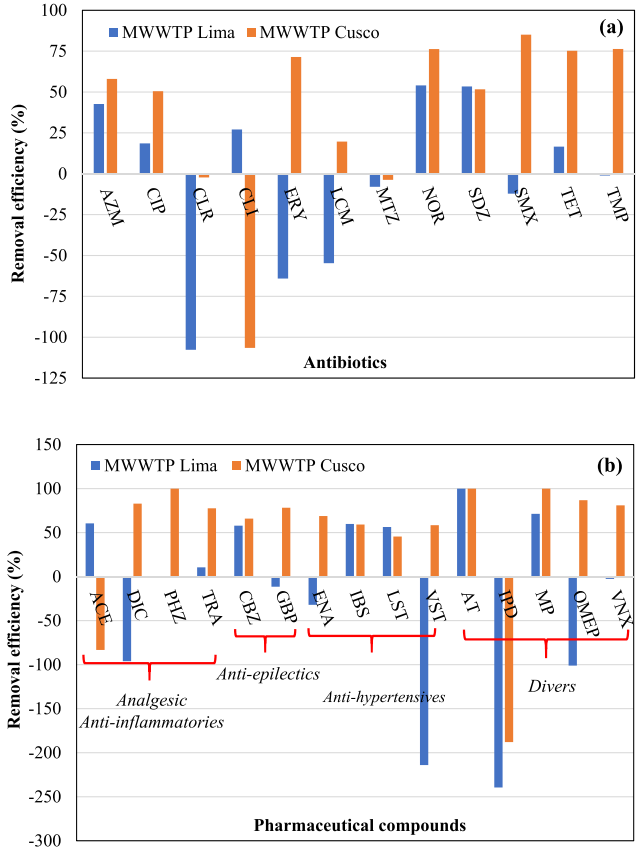

Fig. 2. Estimated removal effciency of (a) antbiotics and (b) drugs such as analgesic, anti-inflammatories, anti-epileptics, anti-hypertensives and divers (antilipemic, contrast agent, proton-pump inhibitor and antidepressant) in both MWWTP from Lima and Cusco.

3.3. Occurrence of pharmaceuticals in effluent wastewater and in river water

The occurrence of pharmaceuticals in EWW was investigated in three Departments of Peru: Lima, Cusco and Puno. In the Department of Puno, EWW was sampled in two MWWTPs, from Puno (Capital of the Province of Puno) and Juliaca (Capital of the Province of San Román). The EWW of the MWWTP Juliaca is discharged to the Torococha River, which flows (4 km) into Coata River (that serves as a water source for agriculture and livestock), to end up into Lake Titicaca (Cultural and Natural Heritage of Peru). For this reason, a surface water sample was also collected at the confluence of the rivers Torococha and Coata (Fig. 1**c**).

The average concentrations of compounds identified and quantified in EWW from Lima, Cusco, Puno and Juliaca, as well as in surface water from Juliaca, are shown in **Tables S3 to S5 (see SI)** and are graphically illustrated in Fig. 3. As can be seen, nearly all the 17 antibiotics included in the analytical method were found in EWW from Lima, Cusco, Puno and Juliaca (except for FUR in Lima and ROX in Lima, Cusco and Juliaca), which reveals their wide presence in wastewater, even after the treatments. The highest antibiotic concentrations in EWW were for SMX (5.18, 2.95, 2.36 μg/L in EWW from Puno, Juliaca and Lima, respectively), followed by CLR (4.4, 2.75 μg/L in Lima and Cusco), TMP (3.65, 2.63, 2.08 μg/L in Lima, Juliaca and Cusco), CIP (3.16, 2.14 μg/L in Lima and Cusco), and AZM (1.87, 1.86, 1.21 μg/L in Cusco, Lima and Puno). The rest of antibiotics presented concentrations below 1 μg/L down to 0.01 μg/L or were just detected but could not be quantified (d < LOQ).

In the surface water sample collected at the confluence of the rivers in Juliaca, a similar trend was observed with nearly all the antibiotics found, with the highest concentrations being found again for SMX (4.36 μg/L) and TMP (1.20 μg/L). It is worth noticing that concentrations of SMX and AZM in SW (4.36 μg/L and 0.29 μg/L, respectively) were around two times higher than in the EWW from Juliaca (2.95 μg/L and 0.16 μg/L, respectively) (see Fig. 3a), revealing the persistence of these pollutants in the water body. Other antibiotics, such as FLU, FUR, NAL, OXA, were detected in SW, but could not be quantified, because their

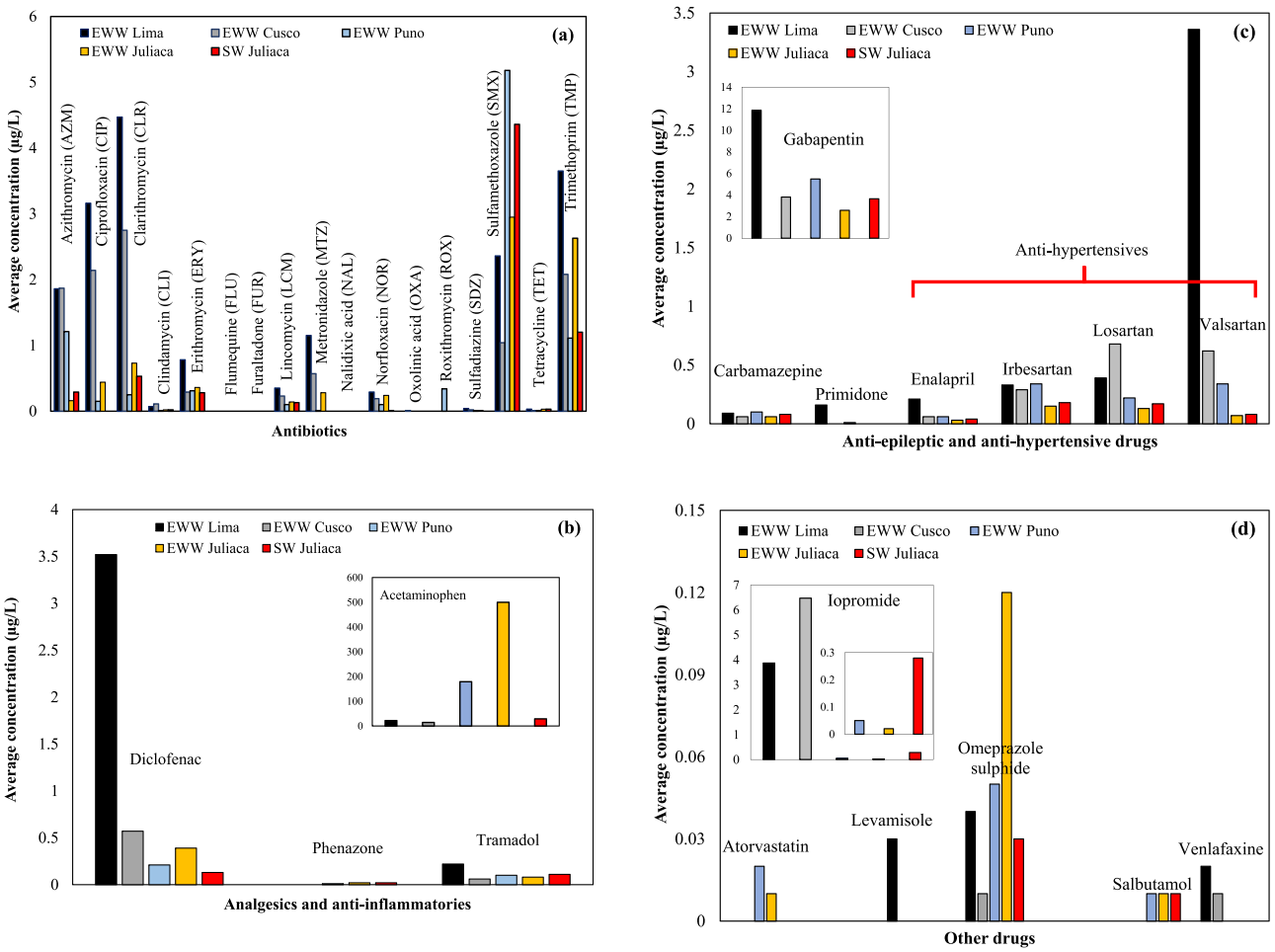

Fig. 3. Average concentration (µg/L) of the effluent wastewater (EWW) from MWWTP Lima, MWWTP Cusco, MWWTP Puno and MWWTP Juliaca, and surface water (SW Juliaca) for (a) antibiotics, (b) analgesics, anti-inflammatories, (c) anti-epileptics and anti-hypertensives, (d) other drugs.

concentrations were lower than the method LOQ. The presence of these antibacterial drugs is common in the water bodies (Al Aukidy et al., 2012; Pedrouzo et al., 2011; Batt et al., 2007), and have been found even in pristine areas such as the Antarctic (Hernández et al., 2019a), which could cause antimicrobial resistance strains and risk to the human health and the aquatic ecosystems (Kairigo et al., 2020; Ben et al., 2019; Posada et al., 2019).

With respect to other pharmaceuticals, the great majority were identified and quantified in EWW (analgesic, anti-inflammatories, anti-epileptics, anti-hypertensives, anxiolytics, anti-depressants, beta-blocker, anthelmintic, lipid-regulating, proton-pump inhibitor, contrast agent and beta-agonist), with few exceptions, such the anxiolytic drug (LZP) (**Tables S3 to S5**). Our data showed that the analgesic acetaminophen (ACE) was the drug found at highest concentrations, reaching > 500 µg/L in EWW from MWWTP Juliaca. In fact, the very high concentration found in this sample impeded the accurate quantification due to saturation of the detector. Therefore, an approximate concentration range could only be reported. Similarly, very high concentrations of ACE were found in EWW from Puno (178.91 µg/L), Lima (21.82 µg/L) and Cusco (14.33 µg/L). As a matter of concern, these treated waters are discharged into water bodies (surface water and seawater). In the case of the MWWTP Juliaca, the EWW (ACE > 500 µg/L) is discharged into the surface water, where the level of ACE significantly decreased by dilution effect or adsorption onto particulate matter, but it was still as high as 28.7 µg/L (Fig. 3b). Although previous studies reported that ACE is readily biodegradable under aerobic environmental conditions (Schaider et al., 2017; Phong et al., 2019), our data show that ACE was found at high concentrations in surface water. The occurrence of the ACE in the MWWTP and SW agrees with the high consumption of this analgesic in Peru, where it is the most popular painkiller, prescribed in human medical but often sold without prescription (Hermoza-Moquillaza et al., 2016). Our data suggest in fact high consumption of this compound in Peru, especially in the Department of Puno, in comparison to Departments of Cusco and Lima.

Another pharmaceutical found at high concentrations in EWW was the psychiatric drug gabapentin (11.85 µg/L, 5.49 µg/L, 3.81 µg/L, 2.58 µg/L, in Lima, Puno, Cusco and Juliaca, respectively). Its level in SW (3.65 µg/L) was a bit higher than in EWW from Juliaca (2.58 µg/L) (see Fig. 3c), suggesting a certain degree of persistence in the environment as described by other authors (Henning et al., 2018). The iopromide contrast agent was also found at high concentrations in MWWTP Cusco and MWWTP Lima (6.47 and 3.87 µg/L, respectively) (see Fig. 3d). Additional, drugs such as flumequine, phenazone, alprazolam, metoprolol, atorvastatin, levamisole, pantoprazole, salbutamol, and venlafaxine were detected in the EWW of the MWWTPs (Fig. 3 and Table S3-S5) at concentrations below the LOQ of the method.

The pharmaceuticals found in effluent wastewater in this work have been also reported in other studies performed in Africa, Latin America, Asia, Europe and U.S.A. (Madikizela et al., 2020; Botero-Coy et al., 2018; Han et al., 2018; Behera et al., 2011; Managaki et al. 2007).

The fact that most of effluent wastewaters are discharged into water bodies (surface water and seawater) in Peru is a matter of concern, as this may cause chronic or acute toxic impacts and may have medium- or long-term effect on aquatic organisms (e.g., effects on growth, ability to reproduce) eventually being a public health risk.

Table 2
Risk Quotients (RQ) estimated for target pharmaceutical substances in effluent wastewater from MWWTPs (Lima, Cusco, Puno and Juliaca) and surface water sample (Juliaca) performed in May 2019.

Antibiotics	**EWW of the MWWTP from**				**Surface Water**
	Lima	**Cusco**	**Puno**	**Juliaca**	**Juliaca**
Azithromycin	0.4	0.5	0.2	0.02	5.6
Ciprofloxacin	1.2	0.9	0.1	0.1	n.d.
Clarithromycin	1.7	1.2	0.1	0.3	24.1
Clindamycin	1.1	1.8	0.3	0.2	29.8
Erythromycin	0.2	0.1	0.1	0.1	5.5
Flumequine	d.	d.	d.	d.	d.
Furaltadone	n.d.	d.	d.	d.	d.
Lincomycin	0.5	0.2	0.1	0.1	16.0
Metronidazole	0.001	0.0003	0.000004	0.0001	d.
Nalidixic acid	d.	d.	d.	d.	d.
Norfloxacin	0.5	0.02	0.005	0.01	0.06
Oxolinic acid	d.	0.00004	d.	d.	d.
Roxithromycin	n.d.	n.d.	0.03	n.d.	n.d.
Sulfadiazine	0.001	0.0004	0.0001	0.0001	n.d.
Sulfamethoxazole	0.04	0.02	0.1	0.04	7.4
Tetracycline	0.02	0.01	0.04	0.01	1.5
Trimethoprim	0.2	0.13	0.1	0.1	7.5
Analgesic, anti-inflammatories					
Acetaminophen	0.14	0.2	0.9	>2.0	14.1
Diclofenac	0.9	0.12	0.03	0.1	2.6
Phenazone	d.	n.d.	0.0001	0.0001	0.02
Tramadol	0.0005	0.0002	0.0002	0.001	0.03

(*continued on next page*)

Table 2 (*continued*)

Anti-epileptic drugs					
Carbamazepine	0.001	0.0002	0.0003	0.0002	0.03
Gabapentin	0.001	0.0004	0.0004	0.0002	0.04
Primidone	0.00003	n.d.	0.000002	n.d.	n.d.
Anti-hypertensive drugs					
Enalapril	0.001	0.0001	0.0001	0.0001	0.01
Irbesartan	0.00001	0.000003	0.000004	0.000002	0.0003
Losartan	0.003	0.01	0.001	0.001	0.1
Valsartan	0.00004	0.00001	0.000003	0.000001	0.0001
Anxiolytic drugs					
Alprazolam	d.	d.	n.d.	n.d.	n.d.
Lorazepam	n.d.	n.d.	n.d.	n.d.	n.d.
Diver drugs					
Atorvastatin (*antilipemic agent)*	n.d.	n.d.	0.00002	0.00001	d.
Iopromide (contrast agent)	0.0004	0.001	0.000003	0.000001	0.002
Levamisole (anthelmintic drug)	d.	d.	n.d.	n.d.	d.
Metoprolol (beta-blocker)	0.01	d.	d.	n.d.	d.
Omeprazole sulphide (PPI)	0.00002	0.00001	0.00002	0.0001	0.001
Pantoprazole (PPI)	d.	d.	n.d.	d.	n.d.
Salbutamol (beta-agonist)	d.	d.	0.00002	0.00002	0.003
Venlafaxine (antidepressant)	0.01	0.004	d.	n.d.	n.d.

d.: detected (not quantified, < LOQ); n.d.: not detected.
Colours: green = low risk; yellow = moderate risk; red = high risk.

3.4. Environmental risk assessment

To assess the environmental hazard caused by the detected pharmaceuticals onto the Peruvian aquatic biota, the approach based on the risk quotient (RQ) was applied according to the commonly used risk ranking criterion. Pharmaceutics with RQ $\leq$ 0.1 are considered of low risk (no adverse effect); while those with 0.1 < RQ < 1.0 are of moderate risk (probable adverse effect); and those with RQ $\geq$ 1 are considered of high risk for the aquatic organisms (adverse effect) (Verlicchi et al. 2012; Rodriguez-Mozaz et al. 2020).

The results of the environmental risk assessment in the tested SW and EWW discharged into surface water are summarized in Table 2. The calculated RQ values are based on the highest concentration found for the pharmaceuticals (MEC; **Table S3-S5** in SI). In the case of the EWW, RQ values were adjusted with a Dilution Factor (DF: 132.7)(Keller et al., 2014). The PNEC of each individual pharmaceutical substance was calculated according to the ecotoxicity data reported in the peer-reviewed literature (**Table S6** in SI). The aquatic organisms, i.e., considered in **Table S6** were algae, crustaceans and fishes.

Concerning the different EWW tested, the highest environmental risk (RQ > 2.0) was found for the analgesic acetaminophen in Juliaca, which represent a risk for crustacean (Table 2; red color). The elevated RQ value could be due to its high concentration (> 500 ppb) in the EWW and its low PNEC value (2.04). In addition, in the EWW the levels of the antibiotics, ciprofloxacin, clarithromycin and clindamycin from Lima and clarithromycin and clindamycin from Cusco, indicated a high risk (RQ values between 1.1 and 1.8). The high risk associated to the presence of ciprofloxacin and clarithromycin is related to the high concentration at the EWW. In fact, ciprofloxacin was detected at concentrations of 4230 ng/L in EWW from Lima and 2980 ng/L in EWW from Cusco, while clarithromycin was found at 5060 ng/L in EWW from Lima and at 3520 ng/L in EWW from Cusco. Despite the relative low concentration of clindamycin (80 ng/L in EWW from Lima and 130 ng/L in EWW from Cusco) in the treated wastewaters, its lower PNEC value (0.00056) is the responsible of the high environmental risk associated to this antibiotic.

Some other antibiotics (azithromycin in the EWW from Lima, Cusco and Puno, erythromycin in the EWW from Lima, lincomycin in the EWW from Lima and Cusco, norfloxacin in the EWW from Lima, trimethoprim in the EWW from Lima and Cusco, clarithromycin in the EWW from Juliaca, clindamycin in the EWW from Puno and Juliaca, ciprofloxacin in the EWW from Cusco), the analgesic acetaminophen (in EWW from Lima, Cusco and Puno) and the anti-inflammatory diclofenac (in EWW from Lima and Cusco) exhibited a moderate risk (RQ values from 0.12 to 0.9) (Table 2; yellow colour), which could cause adverse effects to the algae, crustacean and fish, respectively (see Table S6 in SI). This data reveals that the effluents from MWWTP in Peru need further treatment before being discharged into the aquatic ecosystems.

On the other hand, in the river sample from Juliaca, most of the quantified antibiotics (azithromycin, clarithromycin. clindamycin, erythromycin, lincomycin, sulfamethoxazole, tetracycline and trimethoprim) present a high environmental risk; being clindamycin and clarithromycin the compounds with higher RQ values (29.8 and 24.1, respectively). The presence of these antibiotics in surface water from Peru may influence the emergence of multiple antibiotic resistance genes or strains of bacteria. Furthermore, the analgesic acetaminophen and the anti-inflammatory diclofenac were also detected at concentrations where the risk associated to their presence is of high concern (RQ values of 14.1 and 2.6, respectively).

The above finding agrees with recent data reported in other developing countries around the world. In fact, Rivera-Jaimes et al., 2018 reported that concentrations found for sulfamethoxazole and diclofenac in rivers from Mexico could pose a high toxicity risk on aquatic ecosystems. Recently, Guruge et al. 2019 indicated that several antibiotics (sulfamethoxazole, clarithromycin, ciprofloxacin) and anti-inflammatories (diclofenac, ibuprofen, tramadol) in rivers from Sri Lanka caused medium and high toxicity risk. In contrast, other works reported that several antibiotics (quinolones, macrolides, lincosamides, penicillins, tetracyclines), analgesic/anti-inflammatories, lipid regulators, beta-blocking agents, among others, did not cause toxic effects in natural rivers (Biel-Maeso et al., 2018; Gómez-Canela et al., 2019; Bouissou-Schurtz et al., 2014). Thus, the risks associated to the presence of pharmaceuticals in environmental waters not only depend on their chemical structure and toxicity to aquatic organisms, but also on their concentrations in the tested water.

Finally, in Peru, the over usage of pharmaceuticals is usually practiced and numerous drugs are easily purchased at pharmacies or veterinary stores without prescription. In addition, as stated for other developing countries (Guruge et al. 2019), in Peru, there is an urgent need to implement proper regulations and effective treatment methods for municipal and hospital wastewater in order to improve the water quality and avoid the environmental risk associated to pharmaceutical and illicit drugs (such cocaine) and their metabolites. In this regards, advance oxidation processes arise as promissory alternatives to treat these contaminants (Martínez-Pachón et al. 2021; Prada-Vásquez et al., 2021; Serna-Galvis et al. 2019)

4. Conclusions

Data reported in this work allow to conclude that around 30% of target pharmaceuticals were removed in the Cusco MWWTP, with RE > 75%, while in the Lima MWWTP lower RE were obtained for nearly all compounds tested. However, several pharmaceuticals were present at relative high concentration in treated wastewater in both MWWTPs, as well as in the two treatment plants of the Puno Department (MWWTP Puno and MWWTP Juliaca). Acetaminophen was the drug found at highest concentrations, especially in treated water from Puno, followed by the anti-epileptic drug gabapentin. The antibiotics sulfamethoxazole, trimethoprim, azithromycin, clarithromycin and ciprofloxacin were also frequently found in all wastewater samples collected from Peru. In surface water (confluence of rivers, in Juliaca), the highest concentration was also for acetaminophen, followed by gabapentin, sulfamethoxazole and trimethoprim.

According to the environmental risk assessment in the effluent wastewaters (ciprofloxacin, clarithromycin, clindamycin) and in the tested surface water (based on RQ values), the lincosamides, fluoroquinolone and macrolide antibiotics, and the analgesic-anti-inflammatory acetaminophen and diclofenac were the most hazardous pharmaceuticals, and they could pose a high risk on the aquatic biota.

As confirmed in this work, the treatment processes applied to wastewaters in Peru do not efficiently remove the pharmaceutical compounds, and do not contribute to reduce the environmental risk associated to wastewater discharges into the aquatic environment. So, new and efficient additional treatments are necessary to improve their elimination. Among such additional treatments, advanced oxidation processes are an alternative as reported in recent literature.

CRediT authorship contribution statement

Jessica I. Nieto-Juárez: Conceptualization, Investigation, Resources, Writing - original draft, Funding acquisition. **Ricardo A. Torres-Palma:** Supervision, Writing - review & editing. **A.M. Botero-Coy:** Methodology, Formal analysis, Data curation, Validation. **Félix Hernández:** Methodology, Resources, Writing - review & editing.

Declaration of Competing Interest

None.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106674.

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