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Improving the control of pharmaceutical compounds in activated sludge wastewater treatment plants: Key operating conditions and monitoring parameters

Catarina Silva [a,*], Cristina M.M. Almeida [b,c], João A. Rodrigues [d], Sofia Silva [b,c], Maria do Rosário Coelho [e], António Martins [e], Rita Lourinho [f], Eugénia Cardoso [f], Vítor Vale Cardoso [d], Maria João Benoliel [d], Elsa Mesquita [a], Rita Ribeiro [a], Maria João Rosa [a]

[a] Urban Water Unit, LNEC – National Civil Engineering Laboratory, Av. Brasil 101, 1700-066 Lisboa, Portugal
[b] Laboratory of Bromatology and Water Quality, Faculty of Pharmacy, University of Lisbon, Av. Prof. Gama Pinto, 2, 1649-003 Lisboa, Portugal
[c] iMed.UL (Institute for Medicines and Pharmaceutical Sciences, Portugal), Faculty of Pharmacy, University of Lisboa, Av. Prof. Gama Pinto, 2, 1649-003 Lisboa, Portugal
[d] Empresa Portuguesa das Águas Livres, S.A. – Direção de Controlo de Qualidade da Água, Av. de Berlim, 15, 1800-031 Lisboa, Portugal
[e] Águas do Algarve, S.A. Rua do repouso 10, 8000-302 Faro, Portugal
[f] Águas do Tejo Atlântico, S.A. Fábrica de Água de Alcântara, Av. de Ceuta, 1300-254 Lisboa, Portugal

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ABSTRACT

The control of pharmaceutical compounds (PhCs) in urban wastewater treatment plants (WWTPs) is an issue of health and environmental relevance, expected to become mandatory in the European Union and beyond, but studies at full scale are still scarce. A long-term (2.5-year) full-scale study addressing practical strategies for controlling PhCs was conducted in two activated sludge WWTPs with nitrification (BEI with A2O process; FNW with oxidation ditch). The results showed similar removal patterns in both plants – some of the most abundant influent PhCs were highly removed, others presented intermediate and variable removals, and some were recalcitrant. These behaviours validated a 4-class (A-D) PhC framework (based on biodegradation (k_{bio}) and solid–water distribution (K_d)) for interpreting and predicting PhC removal, particularly sensitive to k_{bio}, with a turning point at 1 L/(gSS.d). A statistical analysis conducted to unveil the key operation variables showed T254 is a good indicator of PhC removal and confirmed that favouring conditions for nitrifiers to grow is an operational strategy to improve PhC control. In BEI, F/M (food to microorganisms ratio) showed the most consistent role (over the sludge retention time), values below 0.08 d^{-1} being associated with effluent PhC concentrations 26–45 % lower. In FNW, the nitrification role was statistically expressed by the alkalinity reduction, values above 40 % (i.e., Nt-removals >80 %) being associated with effluent PhC concentrations 23–61 % lower.

1. Introduction

Pharmaceutical compounds (PhCs) have been frequently reported in the aquatic environment, i.e., in raw urban wastewaters, secondary effluents, surface waters, and groundwaters [1–3], and also at trace levels in drinking waters [4]. Although PhCs are normally present at very low concentrations, their occurrence is a matter of growing concern as they may cause adverse effects to human or freshwater ecosystem health [5–9]. PhCs are introduced in the aquatic environment via several routes (hospital effluents, landfill leachate, surface runoff from agricultural areas where treated wastewater/sludge or manure waste were used) including direct discharge of raw or treated urban wastewaters [1,7,8,10–14]. The PhCs reach the urban wastewaters by humans and animals' excretion (since they may not be completely metabolized) or by being improperly disposed of [15]. PhCs are organic compounds of low/medium molar mass, polar to semi-polar, with a wide variety of chemical structures to deliver different therapeutic effects. Activated sludge (AS) is the most used process in urban wastewater treatment plants (WWTPs) worldwide [16]. The reported removal of PhCs in AS-WWTPs is quite variable, much depending on the PhC properties and WWTP

* Corresponding author.
E-mail address: csilva@lnec.pt (C. Silva).

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operating conditions. A survey with 244 AS-WWTPs referred average percentage removals of 23–94 % for anti-inflammatories, 0–98 % for antibiotics, 23–64 % for lipid regulators, 14–99 % for psychiatric drugs, and 67–80 % for hormones [17].

Biodegradation and sorption onto biomass are the two major PhC elimination mechanisms in AS-WWTPs [18]. The removal by sorption onto biomass can be reasonably predicted by using the solid–water distribution coefficient, K_d, which is defined as the ratio between the concentrations of a substance in the solid and in the aqueous phases at equilibrium conditions [18,19]. According to the literature, in urban WWTPs, the removal by sorption is negligible (below 10 %) for PhCs with K_d values below 0.3 L/gSS [20] and it could be relevant for those with K_d values above 0.5 L/gSS [21]. Regarding biodegradation, the PhCs are present in urban wastewaters in trace levels (ng/L and lower ug/L range) and, for that reason, the energy generated by their biotransformation is not enough to promote significant biomass growth [22]. PhCs are usually transformed by a co-metabolism and the concentration variation rates correspond to a mixed substrate growth [23,24]. Joss et al. [18] observed pseudo first-order degradation kinetics for many organic micropollutants down to ng/L concentrations, indicating that their removal rates can be predicted for reactor configurations typically used for nutrient removal in urban wastewater treatment. According to these authors, it is possible to identify three groups of compounds regarding their biodegradation constant (k_{bio}). Compounds with $k_{bio} < 0.1$ L/(g SS.d) are not removed to a significant extent (< 20 %), compounds with $k_{bio} > 10$ L/(g SS.d) are transformed by >90 %, and a moderate removal is expected for compounds with k_{bio} values in the 0.1–10 L/(g SS.d) range [18]. The most challenging groups of PhCs in wastewater treatment are those having high water solubility, low sorption coefficients, low biodegradability, and high chemical stability [25].

Significant variations in PhC sorption to biomass and in biodegradation rates have been attributed to operating parameters, such as temperature, pH, hydraulic retention time, redox conditions (anoxic and aerobic), organic loading rate, and sludge retention time (SRT, also known as sludge age) [26]. The latter is perhaps the more influential [23], although some different results have been referred and relations are not always straightforward. For instance, it has been widely referred that an increase in SRT could enhance the elimination of some PhCs (e.g., ibuprofen, naproxen, trimethoprim, and erythromycin) due to the build-up of the slowly growing nitrifying bacteria, which can excrete enzymes and, by co-metabolism, may break down some low degradable molecules. According to Clara et al. [23], the effluent concentration of some micropollutants depends on the selected/operated SRT and is independent of the influent concentration, and a minimum value of 10–15 days was proposed. However, it has also been reported that the effect of SRT increase may vary significantly depending on the tested compounds [20,27,28] and that micropollutants can only be degraded above a critical SRT value, which should be determined for different compounds [29]. Regarding redox conditions, some PhCs have been reported to be biodegraded under both aerobic and anoxic conditions (e.g., fluoxetine and the natural estrogens estrone, 17-β-estradiol, and 17α-ethinylestradiol), while others are only significantly biodegraded under aerobic conditions (e.g., naproxen and erythromycin) [17]. Other operating parameters affecting the biodegradation activity and therefore the PhC removal in AS-WWTPs, such as temperature and pH, would require their modification or control using a large amount of energy or reagents, which is hardly economically feasible in urban WWTPs [29]. There is therefore the need to better understand and enhance, at full-scale, the PhC control in urban wastewater treatment. More important than the key operating parameters for such enhanced control are the key easy-to-change/workable operating variables. Furthermore, PhC control requires PhC monitoring and an extensive PhC quantification is complex due to the variety of compounds involved at very low concentrations. In turn, focusing on target PhCs with physical-chemical characteristics related to treatment-specific responses can provide valuable information for the assessment of control strategies without incurring in excessive costs.

Table 1
BEI and FNW unit processes and operations.

	Unit processes and operations of the WWTPs analysed	
	BEI	FNW
Preliminary treatment	Degritting/degreasing	Sieving, degritting/degreasing
Primary settling	2 parallel settlers	–
Biological treatment	Anaerobic/anoxic/aerobic (A2O) reactors, in 2 parallel lines	Anaerobic selector/oxidation ditch (OD) with surface aerators (2 parallel lines, 1 out of service)
Secondary settling	3 parallel settlers	2 parallel settlers
Filtration	3 parallel rapid gravity sand filters	–
Disinfection	UV disinfection for water reuse	UV disinfection of treated water + UV disinfection for water reuse
Thickening	Gravity thickening of primary sludge flotation of secondary sludge	2 rotary drums for secondary sludge with polyelectrolyte (there is no primary sludge)
Stabilization	Anaerobic digestion	–
Dewatering	Centrifuge with polyelectrolyte	Centrifuge with polyelectrolyte

The present study (conducted within research/demo LIFE IMPETUS project) aimed at understanding how far can the PhC control go in current urban AS-WWTPs with nitrification, as well as identifying what are the operational measures for improving the biological treatment performance for PhCs with intermediate and variable removal and what are the recalcitrant PhCs. This is particularly relevant for supporting the expected advances in the urban wastewater treatment regulation in the European Union [30] and beyond. For this purpose, (i) two urban WWTPs of different treatment capacities (one order of magnitude difference) and widely used AS-systems with nitrification (anaerobic/anoxic/aerobic process and oxidation ditch) were selected and characterized towards their operating conditions, (ii) a 2.5-year monitoring of 24 PhCs was conducted in both case-studies, involving 55 sampling campaigns, (iii) the PhC results were processed to investigate if a PhC-class framework k_{bio}-K_d based (from easily removed to recalcitrant) is valid for interpreting and predicting the PhC control in urban AS-WWTPs, (iv) a statistical analysis was conducted for identifying the key operating conditions and bulk parameters and what is/are their turning point(s) determining the ranges of PhC effluent concentrations and related water quality parameters, (v) a monitoring framework was proposed with what parameters, where, when, and how to monitor for enhanced PhC control in this widely used type of urban WWTPs.

2. Materials and methods

2.1. Characterization of the two case-studies

Two urban WWTPs were studied, both located in Portuguese water stressed regions: Beirolas WWTP (BEI), in Great Lisbon area, and Faro-Norwest WWTP (FNW), in the Algarve (south of Portugal). These WWTPs have different AS-systems: anaerobic/anoxic/aerobic (A2O) in BEI for carbon (C), nitrogen (N), and phosphorus (P) control (although the current discharge requirements do not include N or P removal); and extended aeration by oxidation ditch (OD) in FNW for C and N control (treatment schemes in Table 1). The two WWTPs have different processes, but they are both variants of the activated sludge treatment for carbon removal and nitrification, so if properly operated they should provide similar efficiency for these elements and related parameters, as PhCs. The operational variables monitored included the wastewater daily flowrate, the sludge returns, the sludge wasting, and the organic load to the reactor, which allowed computing the following operating conditions – hydraulic retention time (HRT), mixed liquor suspended

Table 2
AS-system, design capacity, and operating conditions of the two AS-WWTPs analysed within September 2016 to January 2019.

WWTP	AS-system (reactor)	Design capacity (10^3 m^3/d)		Treated wastewater (10^3 m^3/d)	HRT in the aerobic reactor (h)	MLSS (mg/L)	SRT (d)	F/M (d^{-1})
BEI	A2O	56.0	Median	40.0	10.6	3900	18.7	0.10
			Min–Max	22.3–64.7	5.0–16.7	2450–5550	7.2–53.9	0.05–0.13
			P5–P95[a]	31.7–53.5	7.1–13.3	2700–4918	13.6–33.1	0.06–0.12
FNW	Oxidation ditch	13.2 (6.6/line[b])	Median	4.4	21.7	2700	12.0	0.14
			Min–Max	3.3–5.5	13.5–29.8	1485–4050	4.5–23.9	0.06–0.24
			P5–P95[a]	3.8–5.1	18.0–25.4	1900–3308	7.0–18.2	0.09–0.21

[a] 5th percentile – 95th percentile.
[b] Only one line was operating.

solids (MLSS), SRT, and food to microorganisms ratio (F/M) – registered during the study, from September 2016 to January 2019 (Table 2).

BEI and FNW differ in the treatment capacity used by approximately one order of magnitude (BEI with 10 times the FNW capacity). BEI operated at 72 % (median) of its design capacity and FNW at 33 % of its full capacity (2 lines) and at 67 % of its capacity in use (only one line was operating). Table 2 further shows BEI was operated at (i) a median HRT in the aerobic reactor above the maximum typical value for A2O (8 h), (ii) a median MLSS within the 2000–4000 mg/L typical range, but with some values above 4000 mg/L, (iii) a median SRT within the typical A2O values (4–27 d) and a 95th percentile (P95) above 27 d, and (iv) a median F/M below the typical ones for A2O (0.15–0.25 kg BOD_5/(kg MLVSS.d)) [31,32]. These high SRT and low F/M ratios are expected to promote nitrifying conditions that favour the PhC removal [23]. FNW was operated at (i) HRT values within the typical range in the OD (18–36 h), (ii) MLSS values within the 2000–4000 mg/L typical range for OD [31,32], (iii) SRT values lower than and F/M ratios higher than those found for BEI, but still typical of oxidation ditches for C and Nt removal in the Algarve (Portugal) region.

2.2. Water quality parameters and analytical methods

Fifty-five sampling campaigns were conducted in each WWTP between September 2016 and January 2019, with a nearly bi-monthly frequency. 24-h composite samples were collected with a 15-min sampling frequency (200 mL/h) and a total volume of 4.8 L, and were analysed for:

- 24 PhCs: caffeine (CAF), acetaminophen (APAP), ibuprofen (IBUP), naproxen (NPX), diclofenac (DCF), carbamazepine (CBZ), fluoxetine (FLX), cortisone (CTS), erythromycin (ERY), sulfamethoxazole (SMX), sulfapyridine (SPD), sulfadiazine (SDZ), bezafibrate (BZF), clofibric acid (CFA), atenolol (ATN), metoprolol (MTPL), propranolol (PPNL), 17α-ethinylestradiol (EE2), diethylstilbestrol (DES), 17-β-estradiol (E2), estrone (E1), estriol (E3), gestodene (GTD), and testosterone (TTE) – non-regular parameters in BEI and FNW, measured in project-dedicated campaigns;
- organic matter (OM), in terms of total organic carbon (TOC) and dissolved organic carbon (DOC), turbidity, UV transmittance at 254 nm (T254), electrical conductivity (EC), and alkalinity – non-regular parameters in BEI and FNW, measured in project-dedicated campaigns;
- total suspended solids (TSS), chemical oxygen demand (COD), 5-day biochemical oxygen demand (BOD_5), total nitrogen (Nt), and total phosphorus (Pt) – regular parameters in BEI and FNW.

For PhC analysis, 500 mL of the collected volume was filtered consecutively through quantitative paper filter, 1.0 μm glass microfilter, and 0.45 μm polytetrafluoroethylene (PTFE) membrane and the filtered samples were stored at 5 ± 3 °C until extraction for PhC analysis, which occurred within 7 days [15]. The samples were pre-concentrated by solid phase extraction (SPE), using an automated AutoTrace 280 SPE workstation Thermo Scientific Dionex (USA), and the concentrated samples were then analysed by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) using a Dionex Ultimate 3000 system. Two chromatographic methods were used, an acidic method and a basic method, both earlier optimised and validated for the analysis of this set of 24 PhCs by LC-MS/MS (as shown in Silva et al. [15]) and adapting the methods described in Gaffney et al. [33]. The analytical limits, method detection limit (MDL), and method quantification limit (MQL) of the global method (SPE-LC-MS/MS) were determined. Samples with PhC concentration higher than MDL were considered positive, whereas samples with concentrations lower than MDL were considered negative. The standards of the 24 target PhCs were provided by Sigma-Aldrich (APAP, ATN, BZF, CBZ, CFA, CTS, DCF, ERY, FLX, IBUP, NPX, PPNL, SPD, and SDZ), by Fluka (CAF, SMX, and TTE), by LGC (GTD and MTPL) and by Dr. Ehrenstorfer GmbH (DES, E1, E2, E3, and EE2). All standards used were of analytical grade (≥ 95 %), suitable for chromatographic analysis. More details are given in Silva et al. [15]. The remaining parameters were analysed using standard methods of analysis (SMEWW 2012) with the equipment and materials described in Campinas et al. [34].

2.3. Data processing methods

For the regular and non-regular parameters, the median, the P5, and the P95 concentrations in the raw and in the treated wastewater were computed. For assessing the overall removal in each WWTP, the median fraction remaining (FR) in the treated water relative to the influent concentration was computed as the effluent median over the influent median ratio. The P25, P50, and P75 of the 55 FR values (one per campaign) were also computed and used for the error bars. The PhC removal efficiency (Er.) is given by 1-FR. The plants' reliability (1 - α) was assessed using the Niku's reliability-based method (a simple and consolidated method), as explained in Silva and Rosa [35].

2.4. Statistical methods and procedures for processing the water quality data and for investigating the key operation variables

Firstly, bivariate scatter plots of each water quality parameter and operation variable were prepared to select the key operation variables for further analysis. Secondly, for the selected variables, the following step-by-step statistical procedure was conducted: (i) standardize the values of each parameter and variable, since their scales were very different; (ii) develop univariate correlations between the operation variables and each parameter to compute the Pearson correlation value (r) and the significance level (*p*-value); (iii) for each operation variable, select the parameters with $r > 0.33$ and p-value <0.05 and conduct a clustering analysis (using the k-means method) with all parameters selected to identify the turning point of the operation variable; (iv) compute the homogeneity of variance of the two clusters of each operation variable using the F-Test Two-Sample for Variances (significance level of 0.05) – F value should be lower than F critical to validate the homogeneity; (v) verify, for every water quality parameter, if a significant difference exists (*p*-values <0.05) between the clusters identified, using the one-way analysis of variance (ANOVA) when the homogeneity

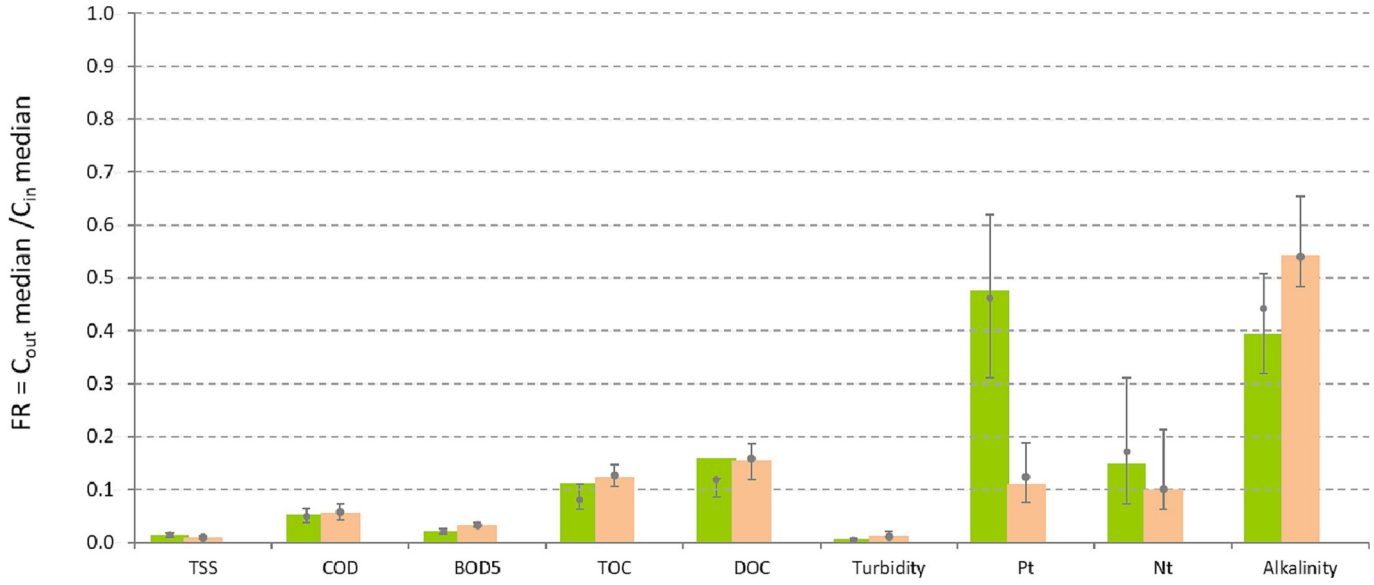

Fig. 1. Fraction remaining in BEI (green bars) and FNW (orange bars) treated waters relative to the influent concentrations of regular and non-regular parameters (the bars represent the overall median fraction; the points with error bars represent P25–P50–P75). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

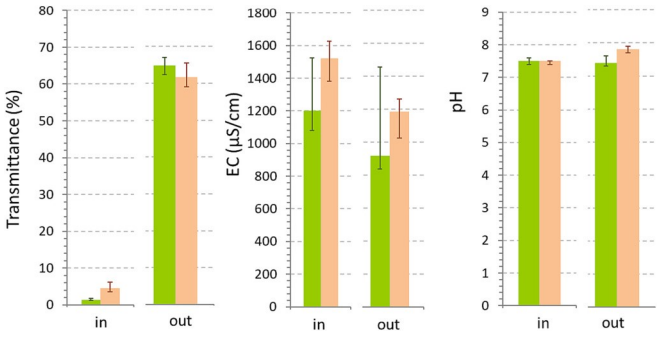

Fig. 2. Influent and effluent values of pH, EC, and T254 in BEI (green bars) and FNW (orange bars) (the bars represent the median, the error bars P25–P75). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of the cluster variance was valid, or the Welch F test otherwise.

3. Results and discussion

3.1. WWTP performance towards bulk parameters of water quality

The WWTP performance towards bulk parameters of water quality was assessed, namely, the fractions remaining in the treated water relative to the influent values of turbidity, TSS, BOD_5, COD, Pt, Nt, alkalinity, TOC, DOC, A254, and A436 (Fig. 1), the influent and effluent values of pH, EC, and transmittance (Fig. 2), and the reliability of BOD_5, COD, and TSS, which represent the parameters of the discharge consents. Table S1 (of supplementary material) shows the data (median, lower quartile - P25, upper quartile - P75) in the influent (in) and effluent (out) of the studied WWTPs, from September 2016 to January 2019. BEI and FNW raw wastewaters are similar and typical of medium-high strength untreated domestic wastewaters [31].

Regarding the parameters in the discharge consents (TSS, COD, BOD_5), the overall median removal efficiencies (1- FR, Fig. 1) were above 95 % (99 % for TSS and 95 % for COD in both plants; 97 % and 98 % for BOD_5 in FNW and BEI, respectively), with low variation (narrow P25-P75 ranges). These removals resulted in full reliability ($1 - \alpha = 1$) for these parameters, in 2016, 2017, and 2018. The water background organic matter, regularly indirectly assessed by the bulk parameters BOD_5 and COD, was herein further characterized in terms of organic carbon content. The median removals of TOC and DOC varied between 89 % and 84 % (Fig. 1), and the effluent median values of TOC and DOC were equal and similar between the two WWTPs (6 mg C/L in BEI and 7 mg C/L in FNW). These results demonstrate a high removal of dissolved (DOC) as well as of particulate and particle-bound OM (TOC), typical of a well-treated and clarified effluent. The turbidity results showed also very high removals (median of 99 % in both plants, Fig. 1), reaching very low values in the treated water (median of 1.3 NTU in BEI and 2.3 NTU in FNW, Table S1). Regarding transmittance at 254 nm (which depends on the suspended solids that scatter the incident radiation and on the presence of dissolved material that can absorb the radiation at that specific wavelength), raw wastewater had very low T254 (median of 1.4 % in BEI and 5 % in FNW), due to high levels of TSS and dissolved matter, whereas the well-treated effluent showed a median T254 of 65 % in BEI and 62 % in FNW (Fig. 2). Pt is not included in BEI and FNW discharge consents, but its removal was 53 % in BEI and 89 % in FNW.

Fig. 1 also shows both plants were (as expected) able to provide nitrifying conditions (important for PhC control) and actually remove nitrogen, namely 85 % Nt median removal in BEI and 90 % in FNW, values not significantly different (Anova *p*-value >0.05). The electrical conductivity (EC) is a general indicator of water quality in ionic species. The EC variation in wastewater treatment is mainly due to changes in pH and in nutrients' concentration, the biological nitrogen removal being the major process for EC decrease, particularly during ammonium-nitrogen removal due to alkalinity or hydroxide ions consumption associated with nitrification [36]. The median pH varied from 7.6 to 7.8 in FNW and kept constant (7.5) in BEI, so the observed EC decrease (Fig. 2) may be attributed to the alkalinity ions consumption (Fig. 1) associated with nitrification, which allowed the observed biological Nt removal.

3.2. PhC control

Table S2 (of supplementary material) presents the concentration of the 24 target PhCs in the dissolved phase of raw (*in*) and treated (*out*) wastewater samples collected at the WWTPs, along with the number of observations (*n* campaigns). It is possible to observe that the concentrations varied significantly, from below MQL to tens of thousands of ng/

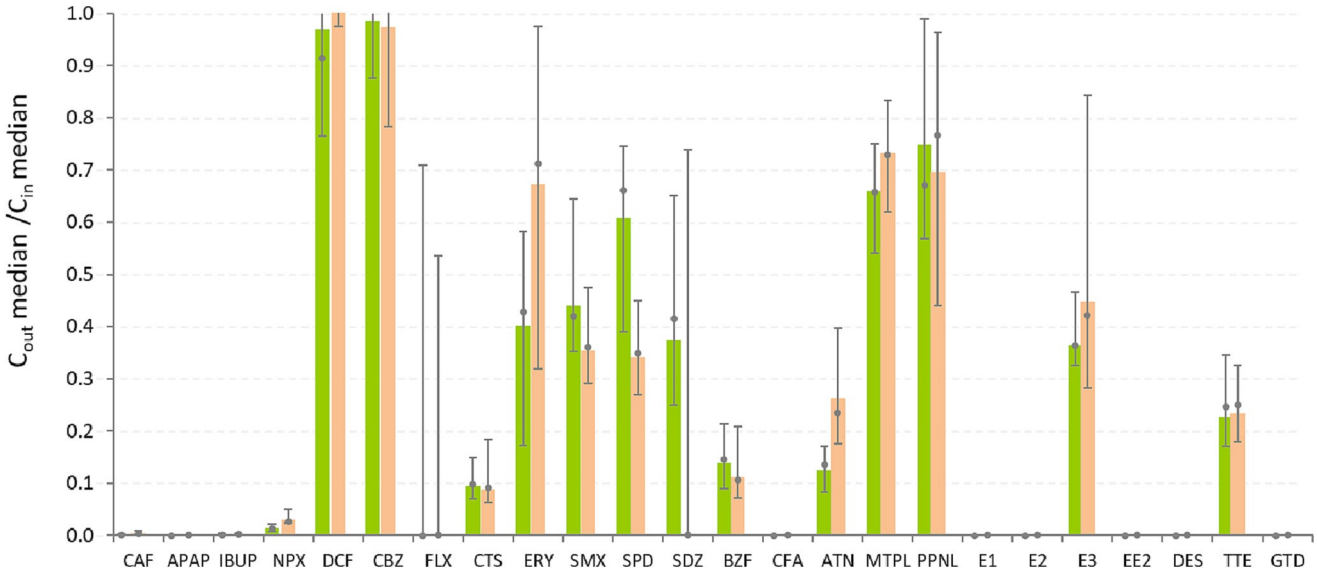

Fig. 3. PhC fraction remaining in BEI (green bars) and FNW (orange bars) treated waters relative to the influent concentrations (the bars represent the overall median fraction; the points with error bars represent P25–P50–P75). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

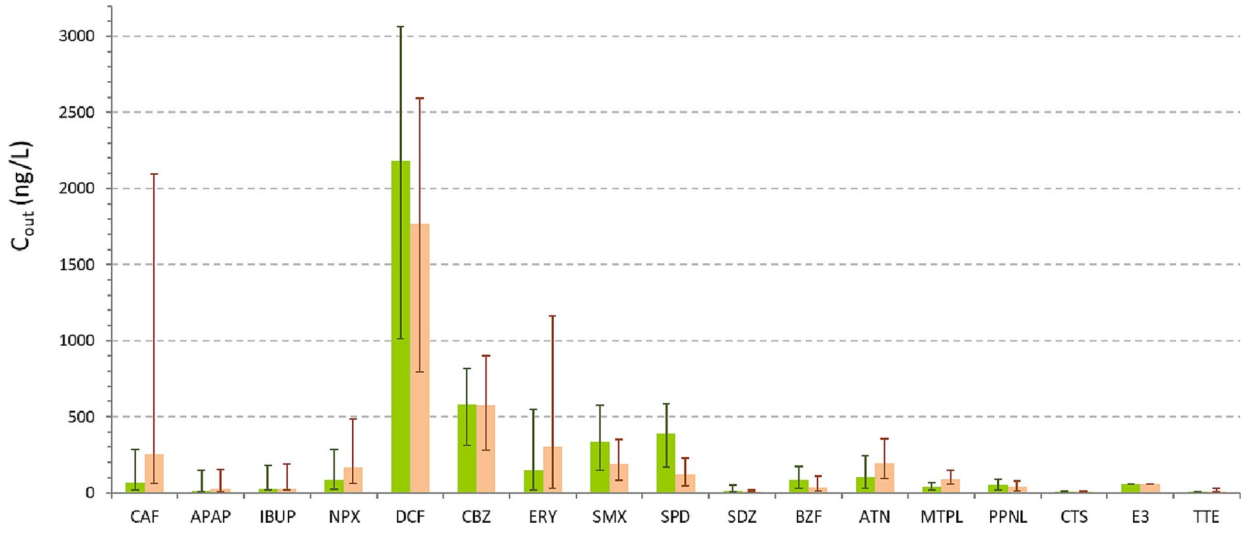

Fig. 4. PhCs in BEI (green bars) and FNW (orange bars) treated waters (the bars represent the median, the error bars P5–P95). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

L, depending on the compound and type of wastewater (raw or treated). Fig. 3 shows, for each of the 24 PhCs monitored, the fraction remaining (FR) in the treated water relative to the influent concentration. Both plants presented similar removals (1-FR), except for sulfapyridine (higher SPD removal in FNW) and erythromycin (higher ERY removal in BEI), both with wide P25-P75. Coherently with literature data [e.g., 17, 37, 38], some of the most abundant PhCs at the WWTP inlet were highly removed during treatment, e.g., caffeine and acetaminophen (P25 > 99 % in BEI and in FNW), and ibuprofen and naproxen (P25 > 95 % in FNW and > 98 % in BEI). The anti-inflammatory cortisone, the beta-blocker atenolol, and the lipid regulator bezafibrate also presented significant removals (for CTS, P25–P75 higher than 84–92 % in BEI and higher than 82–93 % in FNW (some effluent concentration values below MDL); for ATN, P25-P75 of 82–90 % in BEI and 63–85 % in FNW; for BZF, P25-P75 of 78–90 % in BEI and 79–93 % in FNW). Also in agreement with other studies, some compounds were recalcitrant to treatment, as the antiepileptic/anticonvulsant carbamazepine [37,38], and the anti-inflammatory diclofenac. In turn, the antibiotics erythromycin, sulfamethoxazole [37,38], sulfapyridine and sulfadiazine, and the beta-blockers metoprolol and propranolol presented intermediate and variable removals (P25-P75 of 6–72 % in BEI and 0–75 % in FNW). The remaining nine PhCs/hormones exhibited concentrations below the MDL in the treated water (estriol and testosterone) or both in the treated and raw waters (FLX, CFA, E1, E2, EE2, DES, and GTD). For the former two hormones, P25-P75 removal was higher than 53–67 % in BEI and > 18–74 % in FNW for E3, and was higher than 57–81 % in BEI and > 66–81 % in FNW for TTE.

The statistical results of the 17 PhCs detected in BEI and FNW treated waters are illustrated in Fig. 4 (where the bars represent the median concentration and the error bars the P5-P95 range) to easily compare the PhCs with each other. Fig. 5 and Fig. 6 compare the PhC concentrations found in BEI and FNW treated waters with the results found in other Portuguese studies [33,39–41] and in other countries in Europe (Germany, France, Italy, Spain, Netherland, United Kingdom, Switzerland,

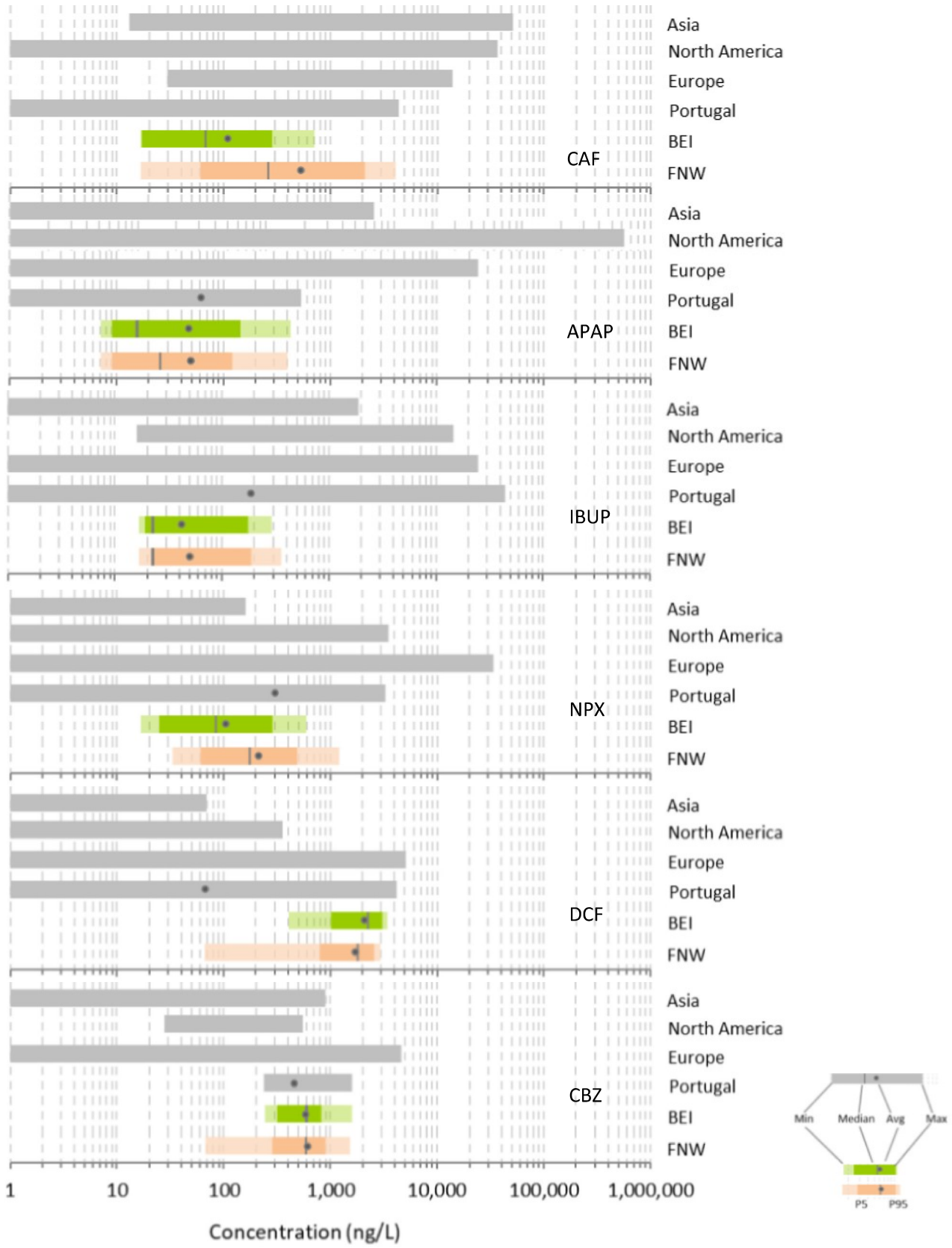

Fig. 5. Comparison of BEI and FNW effluent concentrations for caffeine, acetaminophen, ibuprofen, naproxen, diclofenac, and carbamazepine with those found by others in Portugal (data from [33,39–41]), and in Europe, Asia, and North America (data from [10]).

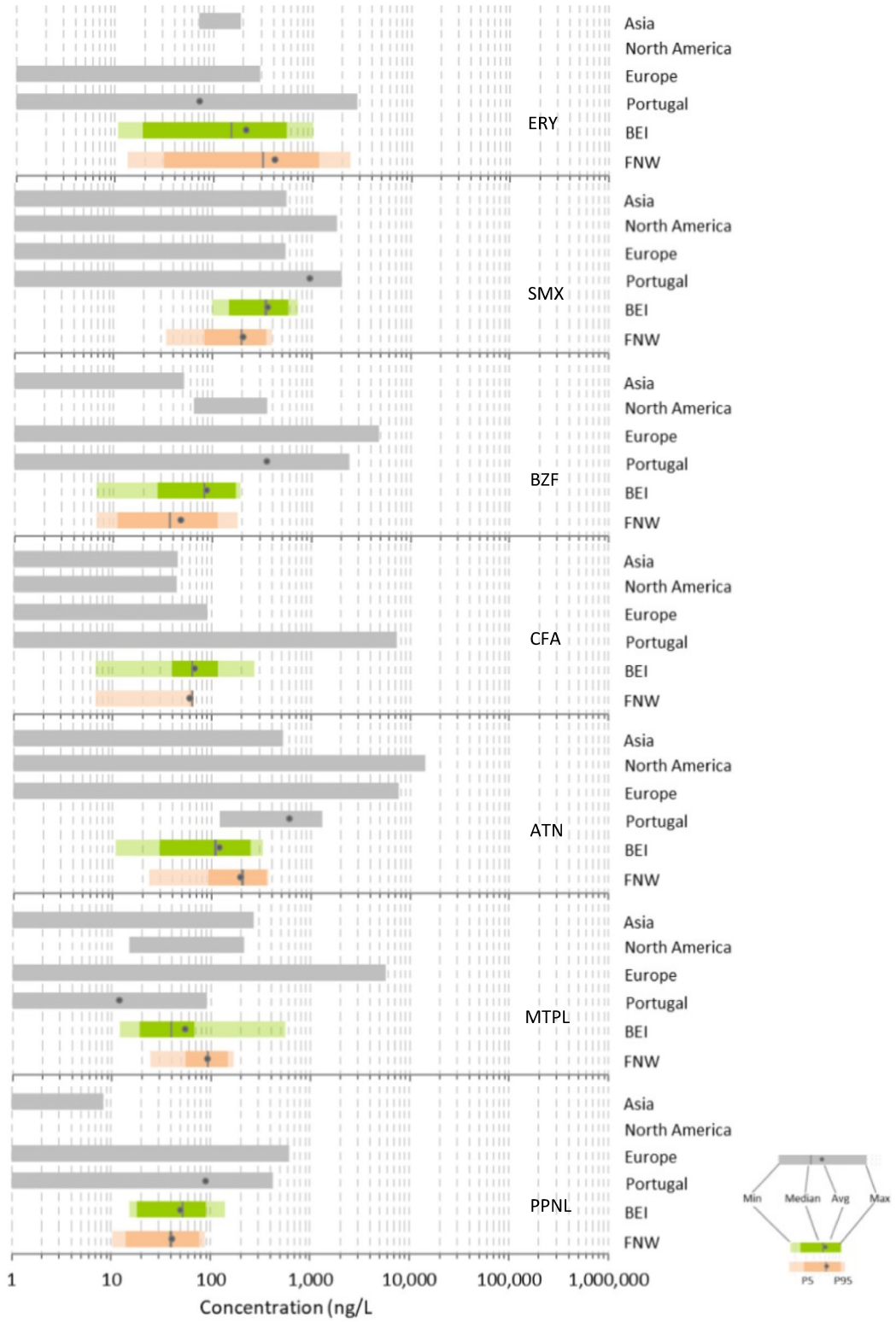

Fig. 6. Comparison of BEI and FNW effluent concentrations for erythromycin, sulfametoxazole, bezafibrate, clofibric acid, atenolol, metoprolol, and propranolol with those found by others in Portugal (data from [33,39–41]), and in Europe, Asia, and North America (data from [10]).

Austria, Greece, Czech Republic, Norway, Belgium, Croatia, and Luxembourg), Asia and North America [10]. The minimum values are often limited by the MDL, so their geographical comparison is not relevant.

As a result of their occurrence at the WWTP inlet and their no (or very low) removal during the biological treatment, diclofenac and carbamazepine were the most abundant PhCs in BEI and FNW treated waters (medians above 500 ng/L in both plants). The second more abundant group (with medians above 100 ng/L) included the antibiotics erythromycin, sulfamethoxazole, and sulfapyridine, the beta-blocker atenolol in both plants, as well as naproxen and caffeine in FNW (Fig. 4).

The most abundant PhCs at the WWTP inlet were highly removed

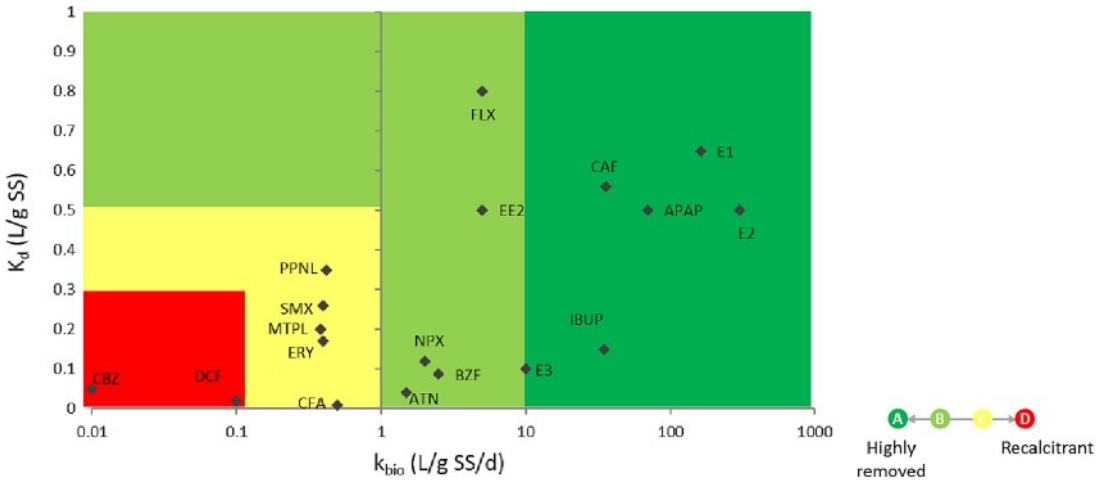

Fig. 7. 4-class (A-D) PhC framework to predict PhC control in urban AS-WWTPs.

during treatment and resulted in median effluent concentrations in BEI and FNW of, respectively, (i) 66 ng/L and 255 ng/L CAF, (ii) 15 ng/L and 25 ng/L APAP, (iii) 22 ng/L IBUP in both plants, (iv) 82 ng/L and 170 ng/L NPX (Table S2 and Fig. 4). Compared to other studies (Fig. 5), the concentration ranges of CAF, APAP, and IBUP are narrower and the maximum values lower than those found in other WWTP effluents in Portugal, Europe, North America, and Asia. The NPX maximum values in BEI and FNW are higher than the maximum value in Asia and lower than the maximum values in North America and in Europe (including in other studies in Portugal (Fig. 5).

Diclofenac was 3 times more abundant in treated water than carbamazepine, with P5–P95 concentration ranges of 1016–3065 ng/L in BEI and 794–2593 ng/L in FNW (median concentration 23 % higher in BEI (2181 ng/L) than in FNW (1768 ng/L)). The carbamazepine results were similar in both treated waters – median concentration 582 ng/L in BEI and 576 ng/L in FNW (Table S2 and Fig. 4). The DCF maximum values in BEI and FNW are similar to those found in Europe and Portugal, which are higher than those observed in Asia and North America (Fig. 5). Regarding CBZ, the concentration ranges are narrower and in the upper range observed in the other studies (Fig. 5). The sulphonamides sulfamethoxazole and sulfapyridine were the antibiotics with the highest median concentrations in BEI treated water (SMX: 337 ng/L in BEI and 191 ng/L in FNW; SPD: 390 ng/L in BEI and 119 ng/L in FNW), whereas erythromycin was the most abundant antibiotic in FNW treated water – median concentration of 304 ng/L in FNW and 147 ng/L in BEI (Fig. 4). Sulfadiazine was the antibiotic with lower concentrations, below the MDL in both plants. The maximum values of erythromycin are lower or similar (in the case of FNW) to those found in other Portuguese studies and higher than in other studies in Europe and Asia (Fig. 6). The SMX concentration ranges are narrower, and the maximum values are similar to those found in Asia and Europe and lower than those observed in North America (Fig. 6).

The lipid regulator bezafibrate showed a median concentration of 81 ng/L in BEI and of 36 ng/L in FNW effluents (Fig. 4). Bezafibrate ranges in BEI and FNW treated waters are narrower than the ranges found in other Portuguese and European studies, and the maximum values are lower than those observed in North America, but are higher than those found in Asia (Fig. 6).

Atenolol was the beta-blocker with the highest removal (Fig. 3). However, since it was also the most abundant in the raw wastewaters (the median concentrations of atenolol were >12 times (in BEI) and 6 times (in FNW) the median concentrations of metoprolol and propranolol), it was the most abundant in the treated wastewaters, with a median concentration of 106 ng/L ATN in BEI and 198 ng/L ATN in FNW (Table S2 and Fig. 4). Metoprolol and propranolol both showed lower concentrations than ATN, in the P5–95 ranges of 19–66 ng/L MTPL in BEI and 55–148 ng/L MTPL in FNW, and 18–89 ng/L PPNL in BEI and 14–76 ng/L PPNL in FNW. The ATN maximum values are lower than those found in earlier national and international studies (Fig. 6). Cortisone, estriol, and testosterone, which occurred in the raw wastewaters, were not detected in most samples analysed of treated wastewater.

PhCs/hormones present very different behaviours towards the treatment and the current number of PhCs is vast and is increasing; therefore, rather than trying to be exhaustive, a smart monitoring program with target compounds per PhC class towards treatability is preferred. Therefore, such PhC classification was investigated based on the two major elimination mechanisms of PhC, i.e., sorption onto biomass and biodegradation, the former related to K_d and the latter with k_{bio}. Based on the limit values of K_d and k_{bio} indicated by Ternes et al. [21] and Joss et al. [18], on a literature review of these constants for each PhC/hormone studied (Table S3), and on the results found for BEI and FNW, a 4-class (A-D) PhC classification for interpreting and predicting PhC control in urban activated sludge WWTPs was proposed (Fig. 7):

- class A: PhCs with $k_{bio} \geq 10$ L/(g SS.d) regardless of the K_d value – highly removed, no effect of the operating conditions;
- class B: PhCs with $1 \leq k_{bio} < 10$ L/(g SS.d) regardless of the K_d value or $k_{bio} < 1$ L/(g SS.d) and $K_d \geq 0.5$ L/g SS – significant/intermediate and variable removals affected by the operating conditions;
- class C: PhCs with $0.1 < k_{bio} < 1$ L/(g SS.d) and $K_d < 0.5$ L/g SS or with
  $k_{bio} < 0.1$ L/(g SS.d) and $0.3 < K_d < 0.5$ L/g SS – intermediate and variable removals affected by the operating conditions;
- class D: PhCs with $k_{bio} \leq 0.1$ L/(g SS.d) and $K_d \leq 0.3$ L/g SS – no relevant PhC removal.

By splitting the 0.1–10 L/(g SS.d) range proposed in the literature into 0.1–1 L/(g SS.d) and 1–10 L/(g SS.d), the classification scheme herein proposed defines 4 ranges of k_{bio}, one more than the schemes proposed by Joss et al. [18].

Fig. 8 exemplifies, for one PhC of each class, the concentration values found in each monitoring point of BEI and FNW for assessing the barriers' performance of the two WWTPs against PhCs. As expected, the PhC removals observed (Fig. 3) occurred essentially in the biological treatment, and they match and validate the PhC (A-D) classification proposed: class A, always high removal in secondary treatment (> 99 %; CAF, APAP, IBUP); class B (NPX, ATN, BZF) and class C (ERY, SMX, MTPL, PPNL) with intermediate and variable removals; class D, no reliable removal (CBZ, DCF).

Fig. 9 shows a strong correlation between the median PhC removals and the k_{bio} values in both plants, with a turning point at 1 L/(g SS.d),

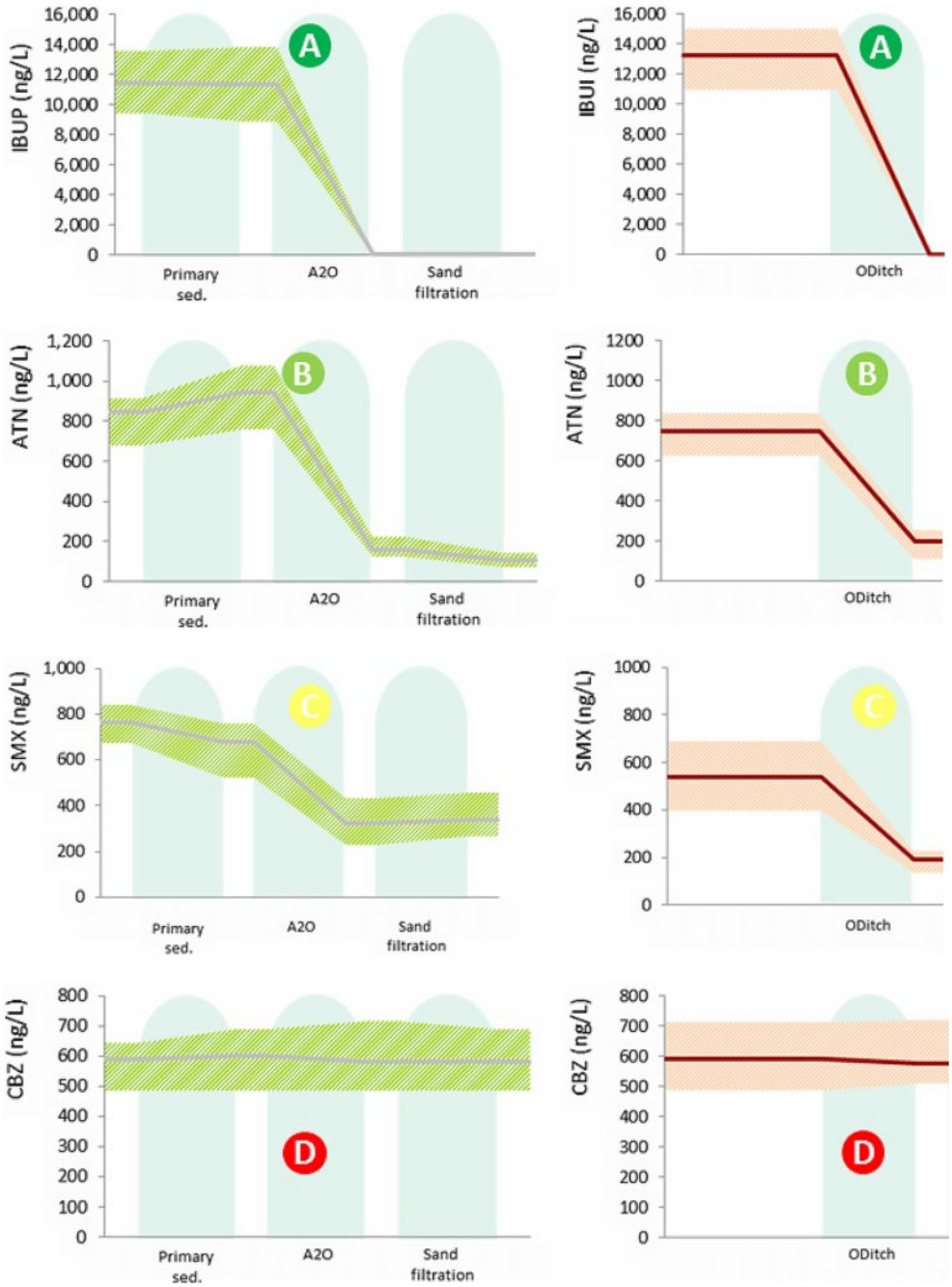

Fig. 8. Illustrative results of PhCs in each monitoring point of BEI (left, in green) and FNW (right, in red) (the line represents the median, the shadowed area the P25-P75). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

above which the median removals were > 86 % in BEI and > 74 % in FNW. PhCs with k_{bio} below 1 L/(g SS.d) and in class C (ERY, SMX, PPNL, MTPL) presented lower median removals (30–60 %). Fig. 9 further shows that MTPL and PPNL removals are closer than expected (similar k_{bio}, higher K_d for PPNL than for MTPL, Fig. 7), which indicates k_{bio} has stronger effect than K_d for these beta-blockers. Class D compounds (with k_{bio} of 0.1 L/(g SS.d) or below) showed negligible removal (< 10 %) as expected. Therefore, the results obtained ultimately show this classification scheme can be used for interpreting and predicting the PhC removal in AS-WWTPs operating under the conditions analysed, as well as to select the target PhCs to be monitored.

3.3. Key operation conditions and monitoring parameters

Operational strategies to enhance PhC removal in urban AS-WWTPs must target the improvement of the PhCs' biodegradation rates. The relations between the effluent concentration of several PhCs and the key easy-to-change operation variables were therefore studied to investigate the operation measures corresponding to better performance towards PhC control, particularly on the effluent concentrations of 11 PhCs and also on two bulk water quality parameters with whom they potentially correlate.

The 11 PhCs targeted included the two recalcitrant DCF and CBZ, the antibiotics ERY, SMX, SDP, and SDZ, and the beta-blockers MTPL and PPNL with intermediate and variable removals, ATN and BZF with significant (though below 93 %) removals, and CAF. Caffeine, although

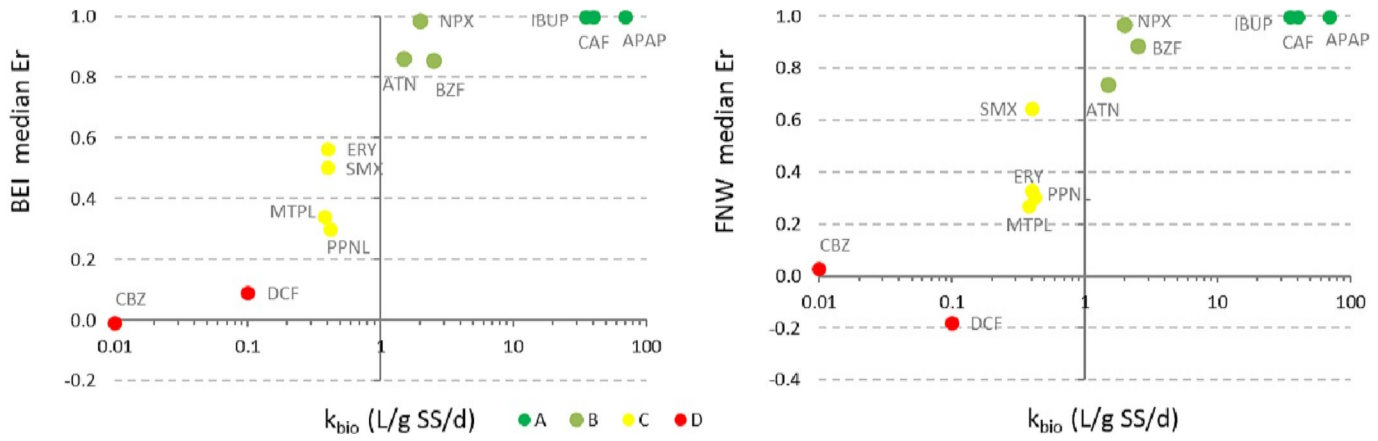

Fig. 9. PhC median removal vs. k_{bio} of each PhC in BEI (left) and in FNW (right) (the colours correspond to the A-D class of the PhC).

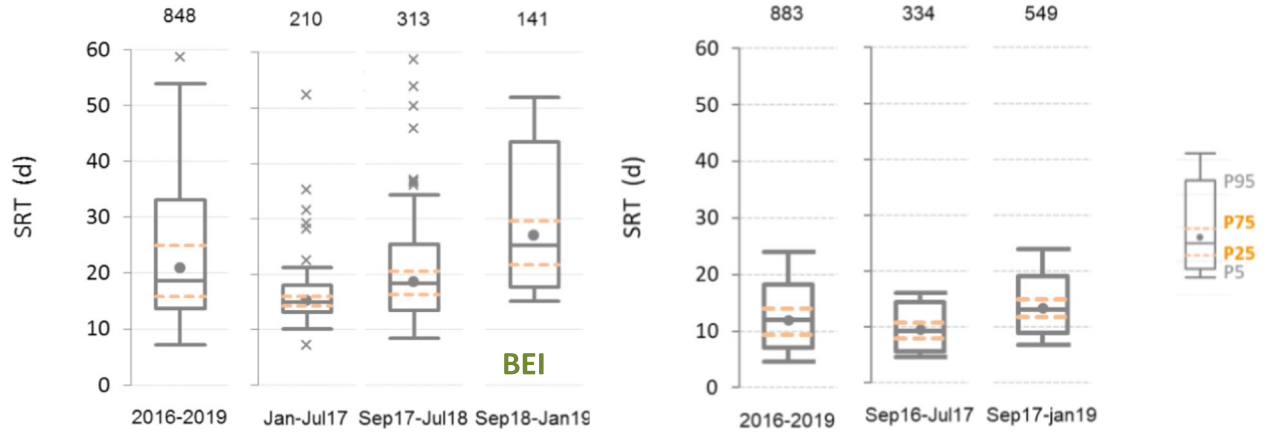

Fig. 10. Solids retention time over the analysed period, and overall box plot and the three/two periods analysed in BEI (left) and FNW (right) WWTPs.

highly removed in BEI and FNW AS-WWTPs, presents, amongst the 24 PhCs analysed, the highest bioaccumulation potential in clams, an important edible resource and widely used as bioindicator species in biomonitoring studies due to their ability to accumulate important amounts of contaminants through the filter feeding strategy of these sedentary organisms [14]. The bulk water quality parameters studied, T254 and TOC, are highly sensitive to the wastewater treatment level. In addition, T254 is commonly used as the key parameter for UV disinfection.

SRT changes were forced in both plants as presented in Fig. 10. The SRT operation ranges were statistically different in the three testing periods in BEI (Anova p-value = 0.026) and in the two periods in FNW (Welch F test of unequal variances; p = 6.3E-80). The ranges considered for SRT in BEI are the three P25-P75 ranges, 14–16 d, 16–21 d, 22–30 d, all in the highest half of the A2O typical range (4–27 d; [31]). In FNW there are two P25-P75 ranges, 8–11 d and 12–15 d, typical of oxidation ditches in the Algarve region (water temperatures from 18 °C in winter to 27 °C in summer).

The other operation variables changed during the studied period due to the abovementioned intentional change of SRT or of the plants regular operation. These variables' effect was statistically investigated using the stepwise approach described in Section 2.4. Based on the bivariate scatter plots of each water quality parameter and operation variable, in addition to SRT, other three variables were selected in BEI and one in FNW to further investigate their effect. The variables were T254, F/M ratio, and MLSS in BEI and alkalinity reduction in FNW. Based on the univariate correlations of variable vs parameter in BEI and FNW (presented as correlation matrices in Fig. S1 and Fig. S2 of supplementary material), for each operation variable, the parameters for the clustering analysis were selected, i.e. those with $r > 0.33$ and p-values <0.05. Then, for each variable, the "turning point" determining two ranges of effluent concentrations was investigated. In BEI, the turning points found were 67 % transmittance and 0.08 d^{-1} F/M (Fig. S3 of supplementary material Fig. S3), and 3500 g/L MLSS. In FNW, the turning point found was 40 % alkalinity reduction (Fig. S4 of supplementary material); no turning points were found for the FNW operating conditions since the ranges tested were narrow (Table 2).

Fig. 11 and Fig. 12 illustrate the overall box plot of the SMX effluent concentration, as well as the box plots per cluster defined by the turning points of the key operation variables found in BEI (T254, F/M, MLSS, and SRT) and the analogous representations for FNW results. Fig. S5 to Fig. S16 (of supplementary material) show this analysis for the remaining 10 PhCs, T254, and TOC, in BEI and in FNW. Fig. 13 shows the SMX and Nt removals vs. the alkalinity reduction in FNW.

The homogeneity of variance of the clusters of each operating condition were assessed for every parameter and the ANOVA (or the Welch F) p-values were computed in BEI (Table S4) and FNW (Table S5) to verify the statistical differences between the clusters identified (those with p-values <0.05). These statistical values were also computed for the non-selected parameters. Table 3 summarises the effects found:

- effluent T254 above 67 % in BEI was associated with lower effluent concentrations of DCF, CBZ, SMX, SPD, SDZ, and MTPL; in FNW, no relation was found with T254, but its range was much narrower with only 3 results above 67 %;

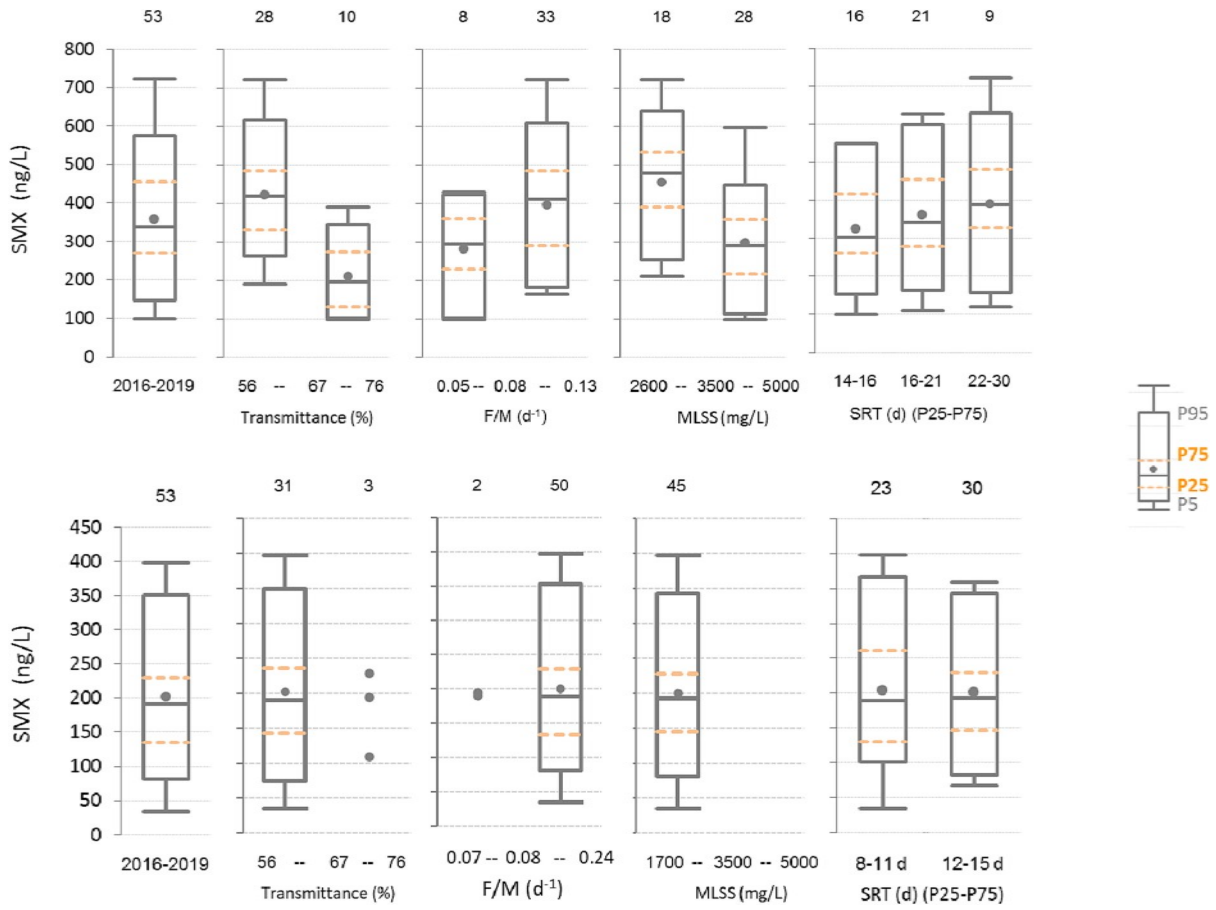

Fig. 11. Box plots of the SMX effluent concentrations for the key variables clusters found in BEI (top) and the representation of FNW results for the same clusters (bottom) (T254 below and above 67 %; F/M below and above 0.08 d^{-1}; MLSS below and above 3500 mg/L; SRT periods).

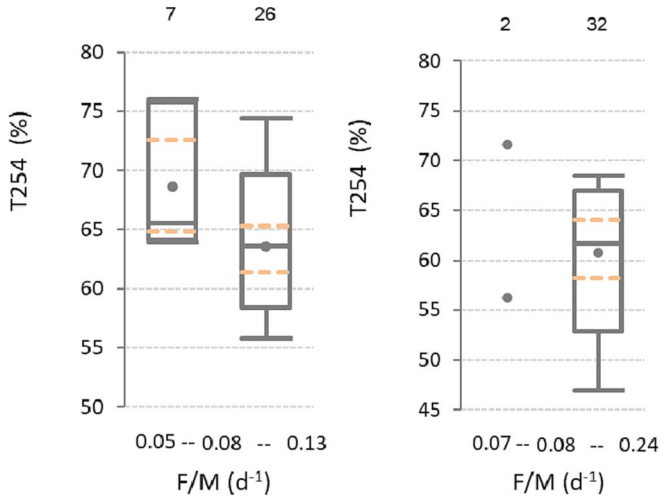

Fig. 12. Box plots of the transmittance for the key two clusters of F/M found in BEI (left) and the representation of FNW results for the same clusters (right).

- a low F/M range (0.05–0.08 $kgBOD_5/(kgMLVSS.d)$) in BEI favoured low effluent concentrations of DCF, CBZ, ERY, SMX, and MTPL and high T254 values; in FNW, for the F/M range tested (0.08–0.24 $kgBOD_5/(kg\ MLVSS.d)$), no effect was observed;
- the MLSS concentration exhibited in BEI the expected opposite effect of F/M though to a lower extent, i.e., values above 3500 mg/L favoured low effluent concentrations of DCF, CBZ, SMX, and SPD; however, the opposite was found on BZF, CAF, and T254, so the effect of MLSS is not as consistent as that of F/M; in FNW, for the MLSS range tested (no PhC results associated with MLSS above 3500 mg/L), no effect was observed;
- in BEI, SRT significantly affected only two PhCs, ATN and BZF – the higher the SRT (> 16 d for ATN and > 22 d for BZF), the lower their effluent concentrations;
- in FNW, the results did not allow concluding about the SRT effect within the ranges tested (P25-P75 not exceeding 15 d); whereas a positive variation was found for ERY, a negative variation (i.e. higher effluent concentrations) was found for ATN, PPNL, BZF, and T254;
- however, in FNW, significantly lower concentrations of ERY, SMX, ATN, and CAF were associated with alkalinity reduction values above 40 %; actually, a linear correlation was found between these PhCs' removals and the alkalinity reduction (Fig. 13 left). Alkalinity consumption occurs with nitrification and values above 40 % were associated with N-total removals above 80 % (Fig. 13 right).

Overall, for BEI A2O process, amongst the three workable conditions, i.e., F/M, MLSS, and SRT, F/M played the most consistent positive role, values below 0.08 kgBOD5/(kg MLVSS.d) favouring lower effluent concentrations of five PhCs and T254 (Table 3). Gani et al. [42] found an analogous F/M effect on diethylhexyl phthalate – the F/M range of 0.04–0.23 d^{-1} provided better removals than the range of 0.34–0.67 d^{-1}. For FNW oxidation ditch, a consistent positive effect was found for alkalinity reductions, values above 40 % being associated with lower effluent concentrations of four PhCs (Table 3).

The SRT significantly affected only two PhCs, but the proposed low-rate operation (SRT > 16 d) is consistent with literature. Based on lab

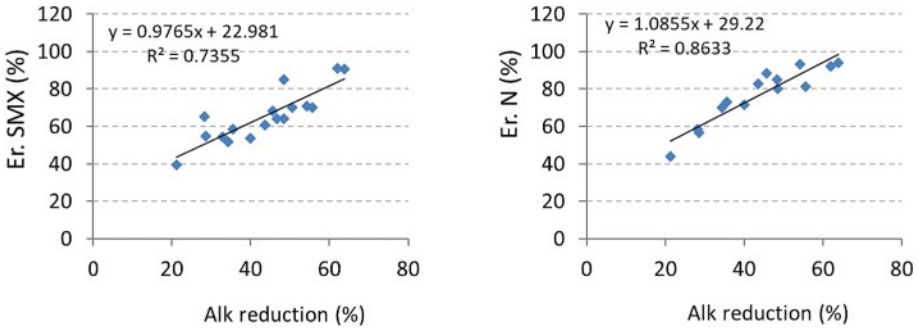

Fig. 13. SMX and Nt removals vs. alkalinity reduction in FNW.

Table 3
Effect of the variables analysed on the effluent quality towards the 11 PhCs for which operational improvement strategies were investigated and for the bulk parameters T254 and TOC.

	BEI				FNW	
	T254%	F/M d^{-1}	MLSS mg/L	SRT d	SRT d	Alkalinity reduction %
Range studied	56–76	0.05–0.13	2450–5550	7–54	5–24	21–64
Turning point	67	0.08	3500	16* or 22**	12	40
DCF	+	-	+			
CBZ	++	-	+			
ERY		-			+	++
SMX	++	-	++			+
SPD	++		+			
SDZ	++					
ATN				+ *	-	+
MTPL	++	-				
PPNL					-	
BZF			-	+ **	-	
CAF			-			+
T254		–	-		-	
TOC						

++ The variable increase strongly favours the effluent quality (i.e., lower effluent concentration).
+ The variable increase favours the effluent quality (i.e., lower effluent concentration).
- The variable increase disfavours the effluent quality (i.e., higher effluent concentration).
– The variable increase strongly disfavours the effluent quality (i.e., higher effluent concentration).
Empty cell means no effect found.

and full-scale (from 5 WWTPs) data, Clara et al. [23] showed AS systems operating SRTs higher than 10 d (refereed to 10 °C) achieved higher PhC and hormones' removals, whereas much lower or no removals were achieved for SRTs ≤2 d. Ternes and Joss [43] reported a significant increase in removal if the sludge age is raised from ≤4 d up to ≥10 d. For some compounds, the removal further increases for higher SRTs, namely from 10 to 20 days (Zabczynski's et al. pilot-scale data in [43]) or significantly above 15 days for nonylphenol, trimethoprim, clarithromycin, and ERY (Wettstein 2004 and Gobel et al. (2006) in [43]).

Although expressed by different parameters (low F/M ratios and high SRT values in BEI and high alkalinity reduction values in FNW), the same mechanism is behind these results – the existence of nitrification conditions, as also found by Di Marcantonio et al. at lab scale [38,44]. Hence, our results corroborate the role of the nitrifying bacteria (and the enzymatic portfolio they made available) in PhC co-metabolism. Favouring nitrification (in terms of SRT and F/M ratio) is therefore an operational strategy to improve PhC control in AS-WWTPs. Alkalinity reduction showed to be an adequate parameter to monitor in FNW, for it is a proxy of PhC removal and it is easy to measure. However, this parameter and particularly its turning point are site-specific for they depend on the ammonia concentration and the alkalinity of the influent water, and the degree of nitrification (decreases alkalinity) and denitrification (increases alkalinity) at the plant. Therefore, the observed site-specific proxy should be always used associated with monitoring parameters of nitrification and Nt removal.

Translating the results obtained into a practical output, the operational strategies identified to enhance PhC removal in AS WWTPs were to operate at low F/M ratios, under nitrifying conditions. Attention must be paid to low F/M in AS-WWTPs so to avoid the development of undesired (viscous or filamentous bulking) phenomena, which hamper the sludge sedimentation and are subsequently responsible for the deterioration of the treated water quality. In practice, a pre-selector (upstream reactor operating at high F/M ratios for preferential growth of non-filamentous microorganisms) is a safe measure to operate at low F/M ratios in the main reactor [31,45], as it is the case in FNW.

Regarding the environmental benefits associated with the proposed strategies, in BEI, the estimates of the reduction of the load released into the environment (values computed with the product of the average treated volume in 2017–2018 (41,388 m^3/d) by the average concentrations computed above and below 0.08 d^{-1} F/M, respectively) are:

- from 34.5 kg/year to 23.8 kg/year (31 % load reduction) of DCF:
- from 10.1 kg/year to 7.4 kg/year (26 % load reduction) of CBZ;
- from 3.5 kg/year to 1.9 kg/year (45 % load reduction) of ERY;
- from 5.8 kg/year to 4.2 kg/year (27 % load reduction) of SMX;
- from 0.6 kg/year to 0.4 kg/year (29 % load reduction) of MTPL.

In FNW, the estimated reductions of the load released into the environment (values computed with the product of the average treated volume in 2017–2018 (4586 m^3/d) by the average concentrations associated with an alkalinity reduction below and above 40 %, respectively) are:

Table 4
Recommendations for AS-WWTP monitoring for enhanced PhC control.

What…		Where…	When…	How… to monitor
PhC	Target PhC classes rather than substance per substance	Raw water, treated water	Different conditions of air/water temperature, covering colder and warmer months, and precipitation conditions	• proper location of the sampling points • set up flow-proportional composite samples (at least 24-h composite, or more depending on hydraulic retention time)
Regular bulk parameters	BOD_5 COD TSS	Influent and effluent of each WWTP barrier Influent and effluent of each WWTP barrier, sludge line and reactor	Regular monitoring (e.g., weekly); a higher frequency may be used for developing parameter behavior patterns and correlations between parameters, which will then allow favouring online monitoring (of e.g., A254) and decrease the lab analyses'	• adapt sampling duration and refer to the hydraulic residence time distribution • use specific materials for sampling (e.g., teflon tubing, glass containers) • adequate cleaning procedures for sampling bottles
	Nt Pt	Raw water, treated water		• thoroughly homogenize the sample while filling the bottles to send to laboratory
Organic matter parameters	TOC DOC	Influent and effluent of each barrier that may affect the parameter		• adequate sampling preservation • adequate and validated methods
Other bulk parameters	Alkalinity Turbidity T254	Raw water, treated water Treated water	Daily Daily	• online meter
Key operating conditions	Daily flows, F/M, SRT, MLSS	Influent to the reactor, return sludge, waste sludge	Daily	• flowmeter for flowrates • computation of the operation variables (F/M, SRT, MLSS)

- from 0.8 kg/year to 0.5 kg/year (23 % reduction) of ERY;
- from 0.5 kg/year to 0.3 kg/year (41 % reduction) of SMX;
- from 0.5 kg/year to 0.2 kg/year (47 % reduction) of ATN;
- from 0.7 kg/year to 0.3 kg/year (61 % reduction) of CAF.

Further reductions of the load released of abundant and recalcitrant PhCs (e.g., DCF and CBZ) are possible with other enhancement treatment strategies, e.g., using adsorption-based solutions [46] as demonstrated in other study in FNW with a low-investment option of powdered activated carbon addition to the activated sludge reactor [34].

The monitoring plan for PhC control must go beyond the PhC analysis and include regular parameters, bulk parameters, and operating conditions determining, affecting or serving as indicators of PhC control in AS systems. BEI and FNW data show effluent T254 is a good indicator of effluent treatment in terms of PhC control, exhibiting reasonable correlation for several PhCs studied. The target value of T254 for improved performance towards PhC removal is 67 % in BEI WWTP. Favouring nitrification was found to be an operational measure to improve PhC control in AS-WWTPs; hence, parameters such as N-total removal (associated with alkalinity reduction in FNW WWTP) is recommended as an easy and good parameter to monitor and control. Table 4 proposes a matrix of what, where, when and how to monitor in an AS-WWTP towards an enhanced PhC control, further explained in supplementary material (S.1).

4. Conclusions

This paper allowed demonstrating the potential for PhC control and identifying the key operating conditions and monitoring parameters in two activated sludge WWTPs (BEI and FNW) with different treatment capacities and processes, both allowing nitrification – BEI with A2O process (14–32 d SRT), FNW with oxidation ditch (8–20 d SRT). The removal efficiencies and effluent concentrations of the 17 PhCs quantified (Sept'16-Jan'19) were generally similar in both WWTPs. The key findings were:

- A 4-class (A, highly removed, to D, no reliable removal) PhC framework (based on k_{bio} and K_d) was proposed for interpreting and predicting PhC control in AS-WWTPs and was validated in these two plants. The framework defines four ranges of k_{bio}, one more than the earlier schemes proposed by other authors, since the PhC removals highly correlated with the k_{bio} in both plants with a turning point at 1 L/(g SS.d), above which the median removals exceeded 86 % in BEI WWTP and 74 % in FNW WWTP. Furthermore, this is a tool of great practical relevance for the water practitioners/policy makers to develop more cost-efficient monitoring plans with target PhCs per class rather than trying to exhaustively analyse as many individual substances as possible;
- Monitoring must go beyond the PhC analysis and include the regular parameters, bulk parameters, and operating conditions determining, affecting, or serving as indicators of PhC control – transmittance (at 254 nm, T254) and Nt removal were both found to be good (cheap and easy to monitor) indicators of effluent treatment in terms of PhCs (the higher, the better).
- Favouring conditions for nitrifiers to grow is an operational strategy to improve PhC control in AS-WWTPs. Amongst the three workable conditions (F/M, MLSS and SRT), F/M showed the most consistent role, with values below 0.08 kgBOD5/(kg MLVSS.d) favouring the PhC removal and the environment protection. BEI operation under F/M $< 0.08\ d^{-1}$ was associated with a further reduction of the PhC load released into the Tagus River estimated in 26–45 % for compounds of classes B, C, and D. In FNW, under the more favourable nitrification conditions, the pharmaceuticals' load released into Ria Formosa was further reduced by 23–61 % for PhCs of classes B and C.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

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