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A step forward on site-specific environmental risk assessment and insight into the main influencing factors of CECs removal from wastewater

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Abstract:	The presence of Contaminants of Emerging Concern (CECs) in water systems has been recognized as a potential source of risk for human health and the ecosystem. The present paper aims at evaluating the effects of different characteristics of full-scale Wastewater Treatment Plants (WWTPs) on the removal of 14 selected CECs belonging to the classes of caffeine, illicit drugs and pharmaceuticals. Particularly, the investigated plants differed because of the treatment lay-out, the type of biological process, the value of the operating parameters, the fate of the treated effluent (i.e. release into surface water or reuse), and the treatment capacity. The activity consisted of measuring concentrations of the selected CECs and also traditional water quality parameters (i.e. COD, phosphorous, nitrogen species and TSS) in the influent and effluent of 8 plants. The study highlights that biodegradable CECs (cocaine, methamphetamine, amphetamine, benzoylecgonine, 11-nor-9carboxy-Δ9-THC, lincomycin, trimethoprim, sulfamethoxazole, sulfadiazine, sulfadimethoxine, carbamazepine, ketoprofen, warfarin and caffeine) were well removed by all the WWTPs, with the best performance achieved by the MBR for antibiotics. Carbamazepine was removed at the lowest extent by all the WWTPs. The environmental risk assessed by using the site-specific value of the dilution factor resulted to be high in 3 out of 8 WWTPs for carbamazepine and less frequently for caffeine. However, the risk was reduced when the dilution factor was assumed equal to the default value of 10 as proposed by EU guidelines. Therefore, a specific determination of this factor is needed taking into account the hydraulic characteristics of the receiving water body.
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	Frederic Béen, Ph.D. Scientific researcher, KWR Water Research Institute frederic.been@kwrwater.nl He is an expert on emerging contaminants monitoring in the water cycle and particularly on wastewater analysis as a tool to monitor human health at the population scale, from the consumption of illicit drugs to the exposure to environmental contaminants

A step forward on site-specific environmental risk assessment and insight into the main influencing factors of CECs removal from wastewater

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To the Editors of Journal of Environmental Management

Rome, 1st August 2022

Dear Editor,

I am pleased to submit the enclosed manuscript titled “Statistical evaluation of the effects of WWTPs characteristics on the removal of Contaminants of Emerging Concern and site-specific Environmental Risk Assessment” by Agostina Chiavola, Valentina Gioia, Simone Leoni, Giancarlo Cecchini, Alessandro Frugis, Claudia Ceci, Massimo Spizzirri, Maria Rosaria Boni and myself to be considered for publication in the Journal of Environmental Management.

The present study aimed at providing a better understanding on the effects of different characteristics (e.g. treatment capacity and layout, type of biological process, sludge retention time) of full-scale wastewater treatment plants (WWTPs) on the removal of contaminants of emerging concern (CECs) belonging to the classes of illicit drugs, pharmaceuticals including antibiotics and caffeine.

To this purpose, the data on the influent and effluent of 8 WWTPs collected for 2 years were statistically analysed and the removal rates were then calculated. The behaviour of the selected CECs in the plants was also correlated to that of traditional water quality, such as COD, nitrogen, suspended solids, by means of the PCA analysis.

The environmental risk assessment (ERA) due to residual concentrations of CECs in the treated effluents was carried out following the procedure outlined by the European Medicines Agency.

The paper presents important elements of novelty with respect to the past literature.

Firstly, in addition to the standard procedure, the ERA was also conducted by applying a site-specific dilution factor calculated based on the flow rate of the receiving water body.

Furthermore, the impact of different characteristics of the plants on CECs removal was deeply analysed. The authors deem the paper able to provide new data for scientist and utility mangers useful to implement technically-costly effective measures for reducing the risk due to CECs for the environment.

We hope that you will share our enthusiasm for these findings and that you will accept this manuscript for publication.

Thanks in advance for your consideration and best regards,

Camilla Di Marcantonio

Reviewer #1: General evaluation:

This paper evaluates the influence of different wastewater treatment plants (WWTPs) configurations and characteristics on the fate and environmental risk of 14 Contaminants of Emerging Concern (CECs). I found the manuscript interesting to read, because it provides a combination of evidences from monitoring campaigns, with advanced statistical analyses and environmental risk assessment, that are all important tools to evaluate the efficacy of current WWTPs in removing CECs. Moreover, I think it further increases our understanding of what are the main drivers for CECs removal in WWTPs and what is important to consider when performing a risk assessment procedure.

The methodology is scientifically-sound, even though some minor methodological inaccuracies should be corrected, and the results are always supported and compared to evidences of previous studies.

However, a few points should be addressed by the authors, expecially related to the correctness of the ERA inputs to ensure that the final outcomes are correct as displayed.

We would really like to thank the reviewer for the careful and constructive revision. The manuscript highly benefited in terms of clarity and strengthening of the achieved conclusions. All the comments were addressed.

Specific comments:

1) Keywords: I would suggest adding a keyword related to the statistical analyses. Can be "Principal Component Analysis" or "Advanced statistical analyses".

R: We modified the keywords according to the reviewer suggestion:

Keywords: Advanced statistical analyses, Caffeine, Dilution factor, Illicit drugs, Pharmaceuticals, Principal component analysis

2) Lines 82-85: Authors state that previous studies showed that MBBR and MBR configurations achieved better removals compared to conventional activated sludge process followed by secondary sedimentation. In the following rows removal efficiencies are reported only for MBBR and MBR, without data about the conventional activated sludge process. Please, report at least a range of efficiencies achieved by activated sludge for the same CECs, to help the reader understanding the order of magnitude of such difference in removals.

R: More data and references were added according to the comment:

Line 87: The removals of particularly recalcitrant compounds, such as carbamazepine and sulfamethoxazole, in the conventional activated sludge process are usually lower than MBR and MBBR, e.g. they range from -110% - 3% for carbamazepine and (Krzeminski et al., 2019) from 32% - 98% for sulfamethoxazole (Couto et al., 2019; Verlicchi, 2012).

3) Line 123 and Line 182: "Di Marcantonio et al., 2020" is cited but in the reference list there are two "Di Marcantonio et al., 2020". Please explicitly report which of these two papers is the correct one.

R: We corrected the citation thanks to the comment: in both cases it was Di Marcantonio et al. 2020b.

4) Lines 122-123: Authors state that the eight WWTPs analysed in this study were selected among a wider list of plants considered in a previous study. How did you select those eight WWTPs? Does this selection alter the results of the statistical analysis or having chosen other plants the conclusions would

have been the same? Authors should justify why among these eight WWTPs there is only one WWTPs having MBBR and another one having MBR technologies. In fact, I think that having at least two WWTPs where these two technologies are present would have improved the robustness of the reported statistical results.

R: The plants were selected being representative of the different types of plant present in the study area (i.e. Central Italy), in terms of applied technologies. Indeed, we included in the study several plants using the conventional activated sludge which represents the most diffused technology in the area; however, these plants differed for the treatment capacity, the disinfection process, the final receiving water body, in order to investigate how these characteristics can affect the removal efficiency of the activated sludge process. In the same area, the MBR and MBBR are used only in the WWTPs that were monitored in the present study. To have more data about these technologies, we referred to other studies available in the scientific literature.

5) Table 1: This Table is clear and helpful for understanding the following results. My only question is related to the co-presence in WWTP 8 of the secondary sedimentation and the MBR. Please, check whether this is correct. Moreover, please report in the caption that the flowrates values are the average values.

R: We wish to thank the reviewer for the careful revision. We modified the table to correct the typo and address also comment n. 11. We improved the caption accordingly:

Table 1 Main characteristics of the monitored WWTPs and number of sampling days (Samples). Abbreviations: SRT= Sludge Retention Time, QWWTP= average flow rate of the WWTP, Qrec= average flow rate of the receiving water body, Ca= sewage catchment area, PEau= Authorized treatment capacity, BS=Bar Screening, DD=Degreasing-Degritting, PS=Primary Sedimentation, O=Aerobic activated sludge process (oxidation), DN=Anoxic activated sludge process (denitrification), SS=Secondary Sedimentation, MBR=Membrane Biological Reactor (ultrafiltration), MBBR=Moving Bed Biofilm Reactor, III=Sand filtration followed by UV disinfection, DC=Hypochlorite disinfection, DP=Peracetic acid disinfection.

WWTPs	**SRT [d]**	**Q_{WWTP} [mc/s]**	**Q_{rec} [mc/s]**	**Ca [sqkm]**	**PE_{au} [n.]**	**Samples [n.]**	**BS**	**DD**	**PS**	**DN**	**O**	**SS**	**MBBR**	**MBR**	**III**	**DC**	**DP**
1	9	0.22	0	22	90 000	31	●	●	●	●	●	●			●	●	
2	14	2.82	165	81	300 000	23	●	●	●		●	●				●	
3	10	1.22	7.5	44	600 000	11	●	●	●	●	●	●				●	
4	13	1.79	7.5	65	350 000	17	●	●	●	●	●	●				●	
5	10	9.2	177	195	780 000	24	●	●	●		●	●					●
6	-	0.16	0	14	1 090 000	18	●	●					●				●
7	13	0.93	188	53	90 000	20	●	●	●	●	●	●				●	
8	27	0.05	0	2	18 000	17	●	●		●	●	●		●			

6) Line 151: the paragraphs numberings from this paragraph on are wrong. Please, correct them.

R: The paragraphs numberings were corrected.

7) Lines 212-214: Authors state that the median CECs concentration was used for the "average scenario" and the 95th percentile was used for the "worst case scenario". How the concentration values

below the MRL were considered in calculating the median/95th percentile concentration, the median removal efficiency, and the risk? Were they eliminated or substituted with a specific value (maybe half of the MRL value)? Please, esplicitly state this in the Materials and Methods section.

R: Thanks to the reviewer we added this sentence in the manuscript:

Line 201: When the concentration resulted to be below the MRL, the value was set equal to half of the MRL in the calculation of statistical descriptors and removal efficiency and application of ERA (European Commission, 2009).

8) Lines 218-221: Authors used the average flowrates for both the WWTP effluent and the receiving water body for the calculation of the dilution factor. However, expecially for the receiving water body flowrate, an asymmetric probability density curve (usually log-normal or Weibull) is expected. Therefore, as the authors correctly did for the MEC, also for the flowrates authors should test the normality of the statistical distribution and, in case this is not verified, the median (instead of the average) of such flowrates should be used for calculations.

R: We totally agree with the reviewer; however, the data about the flowrates of the river were provided by the competent local authority only as average yearly value. In the next studies, we will perform a specific investigation in order to collect more data about the river.

9) Lines 224-226: The dilution factors reported in this sentence do not match the dilution factors that can be calculated from Table 1. It seems the dilution factors do not correspond to the corresponding WWTPs. Please, not only correct this order in the sentence, but check whether such wrong combination was used in the ERA calculations.

R: Thank you for the very careful revision. We corrected the order into the text and checked the calculations and found out that the correct value for each WWTP was used.

10) Lines 239-255: it is hard to follow this paragraph. Maybe a graph could be added in the SI correlating compounds concentrations (also only the three reported in the text: CAF, BEG, KTP) with the WWTPs catchment area to visually evaluate whether the assumption proposed by the authors is correct and only WWTP8 is an exception to this assumption. In general, it is hard to understand how concentration peaks and time variations due to the sewer HRT or catchment area could be detected by 24-hours mixed samples.

R: Thanks to the reviewer suggestion, we determined the correlation between the influent concentrations of the CECs detected at the highest extent (i.e. CAF, BEG and KTP) and the catchment area served by the WWTPs. The entire paragraph was modified accordingly:

Line 262: The differences in the influent concentrations of the same pollutant measured in the WWTPs might be related to the characteristics and extension of the catchment area served by the plants. The assumption is that the larger the served area, the higher is the equalization effect on the concentration due to the longer retention in the sewage network; this longer retention time reduces the peak values and attenuate the time variations of the influent concentrations. Indeed, the highest concentration of CAF, BEG and KTP were found in WWTP6 and WWTP1 which serve sewage basins of 15 km2 and 22 km2, respectively, corresponding to average influent volumetric flowrates of 0.16 m3/s and 0.22 m3/s, respectively (treatment capacity of 90’000 PE) (see Figure S.M. 1). In agreement with the assumption reported above, the lowest concentrations were measured in the influent of WWTP5 which serves a much larger area (about 195 km2, corresponding to an average influent volumetric flowrate of 9.2 m3/s, for a treatment capacity of 1’090’000). To confirm these observations, the Spearmen correlation coefficient was calculated between influent concentrations and catchment area for the three CECs measured at the highest extent (i.e. CAF, BEG and KTP). The value of the correlation coefficient resulted to be always significant (i.e. p-value < 0.05): -0.37 for BEG, -0.45 for KTP and -0.27 for CAF. It is therefore confirmed the assumption that the higher the catchment area, the lower the influent concentration. Similarly, McCall et al. (2017) depicted an influence of the catchment scale on illicit drugs biomarkers. The only exception was represented by WWTP8, which serves the smallest catchment area and receives influent concentrations being not so high as expected. However, it might be argued that in this case the treatment capacity is so low (i.e. 18’000 PE) to highlight concentration peaks. Further studies must be carried out to confirm the assumption and to better elucidate the causes of the influent concentration time patterns, considering all the possible influencing factors (e.g. the ratio between catchment area and overall length of sewage pipes, the retention time and transformation and degradation processes of pollutants within the sewage network).

11) Figure 1: I do not think it is necessary to have this figure in the Manuscript for readers to understand the paper. Data related to the catchment area and treatment capacity can be added to Table 1 and this Figure can be moved in the SI.

R: The figure was moved to supplementary materials and the catchment area was added into Table 1 (as reported in the reply to comment n.5.

12) Table 2: This table is useful for the reader as an overview of the fate of different CECs in different WWTPs. However, it is not clear to me how a median removal efficiency was calculated for CECs/WWTPs having both influent and effluent median concentration below the MRL. An example is for THC-COOH that has median influent concentration below the MRL for all the WWTP but for some of them a removal efficiency is calculated. I think this is due to how authors considered values below the MRL and how they calculated the "median removal efficiency". Please, report at least in the SI the procedure you followed to calculate this median removal efficiency.

R: According to the reviewer comment, we added the following explanation in the Calculation method section:

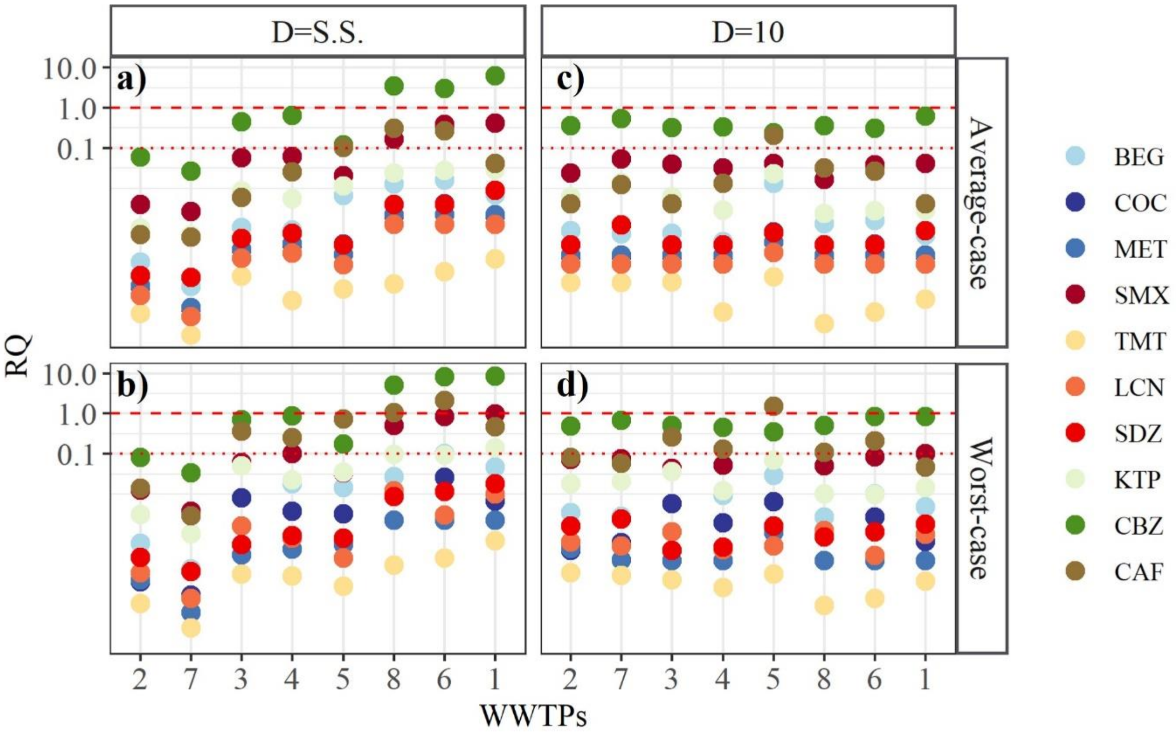
Line 203: Additionally, removal was not calculated if the influent and effluent concentration were both equal to MRL. Indeed, the daily median removal could be calculated when the concentration was above MRL at least in the influent samples.

13) Lines 500-502: this sentence is already present in the caption of Figure 6. So it can be eliminated.

R: The sentence was delated according to the comment.

14) Figure 6: This figure is hardly visible. I would suggest to use a logarithmic scale for the y-axis. In this way, it will be easier for the reader to evaluate the graph and distinguish situations of low risk (0.01<RQ<0.1), medium risk (0.1<RQ<1) and high risk (RQ>1).

R: According to the reviewer suggestion, the figure (now Figure 5) was modified as shown below:



15) Section 2.5: Authors decided not to calculate the environmental risk for those CECs having frequencies of detection below 10% (i.e. THC-COOH, APT, WRF, SDM). I agree that estimating the median/95th percentile of effluent concentrations for these compounds could be difficult and lead to under/over-estimations of the risk. However, I think it is important to notice that for THC-COOH the MRL of the used analytical method (0.1 µg/L) is much higher than its PNEC reported in Table S.M. 3 (0.005 µg/L). Therefore, I think authors should explicitly state in this paragraph that the higher MRL compared to the PNEC does not allow to evaluate whether a high risk can be posed by TCH-COOH and, thus, further evaluations should be performed on this compound.

R: Thanks to the reviewer comment, we added the following consideration:

Line 548: As mentioned above, ERA was not performed for the CECs with FD below 10% (i.e. THC-COOH, APT, WRF, SDM). However, it is important to notice that for THC-COOH, the MRL of the analytical method (0.1 µg/L) was much higher than its PNEC as reported in Table S.M. 3 (0.005 µg/L). Therefore, the higher MRL compared to the PNEC did not allow to evaluate whether a high risk can be posed by THC-COOH. Thus, further evaluations should be performed on this compound.

16) Line 555: Authors state that the PNEC used for carbamazepine in this study is 0.005 µg/L. However, in Table S.M. 3, carbamazepine's PNEC was reported as 0.05 µg/L (that is the correct value that can be found in NORMAN database for freshwater). Please, not only correct the sentence, but also check whether the wrong PNEC was used in the ERA calculations since the resulting risk will decrease 10 times and will become lower than 1 for all the WWTPs.

R: Thank you for the correction. It was a text typo, but the calculations were correctly performed.

Line 619: They obtained quite different results from the present site-specific ERA: no risk for CBZ, likely due to the high value of PNEC used (i.e. 2.5 µg/L vs 0.05 µg/L), …

Reviewer #2: The present work entitled "Statistical evaluation of the effects of WWTPs characteristics on the removal of Contaminants of Emerging Concern and site-specific Environmental Risk Assessment" is of potential interest to deepen the knowledge on CEC occurrence and removal at WWTPs. The manuscript is well structured, and the analytical methods are properly reported.

Based on the specific comments reported below, the manuscript requires some improvements to make it suitable for publication in "Journal of Environmental Management".

We would like to thank the reviewer for the useful suggestions.

- Please check the section numeration throughout the entire manuscript.

R: The paragraph numberings were corrected.

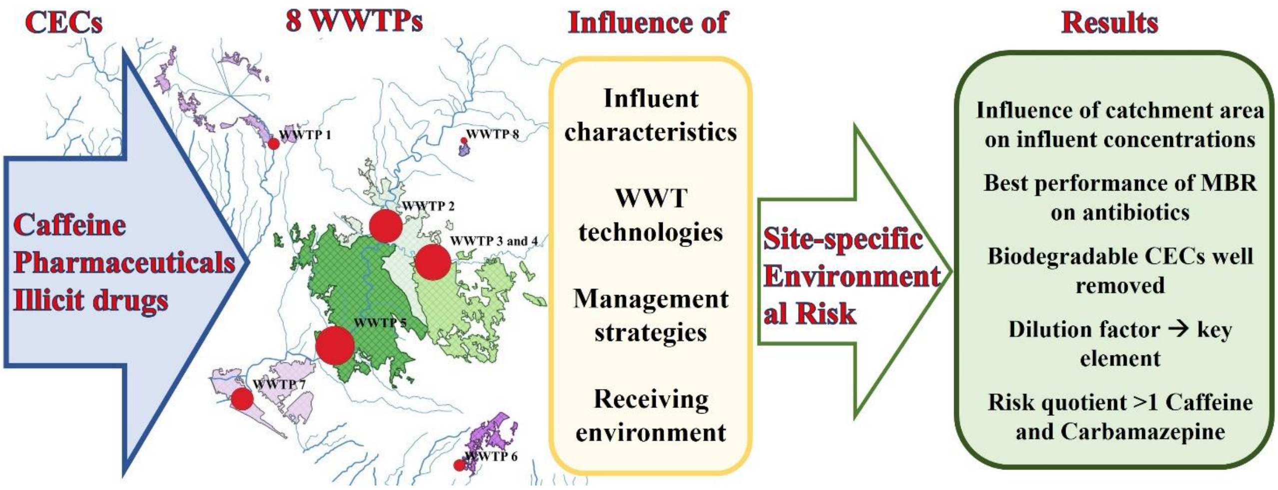
- The title should be more meaningful and impressive.

R: The title was modified as follows:

A step forward on site-specific environmental risk assessment and insight into the main influencing factors of CECs removal from wastewater

- Please improve the graphical abstract. It is poor in terms of image quality, and it lacks the most relevant research findings of the present work.

R: The graphical abstract was modified as follows:



- The following statement "the data were collected for a long time-frame of observation (i.e. 2 years)" should be revised. Indeed, the sampling campaigns in some WWTPs investigated are limited, with less than 1 measurement per month (e.g., WWTP 3 only 11 sampling days).

R: According to the reviewer comment we modified the sentence:

Line 123: Finally, the data were collected for a time-frame of observation of 2 years, thus allowing to catch different weather and influent conditions.

- Critical discussion should be strengthened by comparing the obtained results with other findings eventually reported in the literature.

R: We improved the discussion adding additional comparisons with the scientific literature:

Line 277: Similarly, McCall et al. (2017) depicted an influence of the catchment scale on illicit drugs biomarkers.

Line 402: Luongo et al. (2020) compared peracetic acid performances on different CECs removal with other disinfectants, including sodium hypochlorite, and observed a lower removal but also a lower number of degradation by-products. Nonetheless, additional studies are required to elucidate the best conditions for this treatment.

Line 462: As known, the MBR exploits the high retention capacity of the membrane to produce a treated effluent of very high quality (Krzeminski et al., 2019). Furthermore, the longer sludge retention time favours the degradation of more complex molecules, such as those of CECs.

- Lines 258-260: citing another study in the Figure 1 caption it seems that the figure is derived from another study. Please clarify it.

The caption was modified, and the figure moved to Supplementary materials according a comment of the other reviewer.

- Line 327: revise the section title, it is unclear.

R: The title was modified as follows:

Statistical insight into the removal of CECs belonging to the intermediate removal category

- Please try to shorten figure captions such as Figure 6.

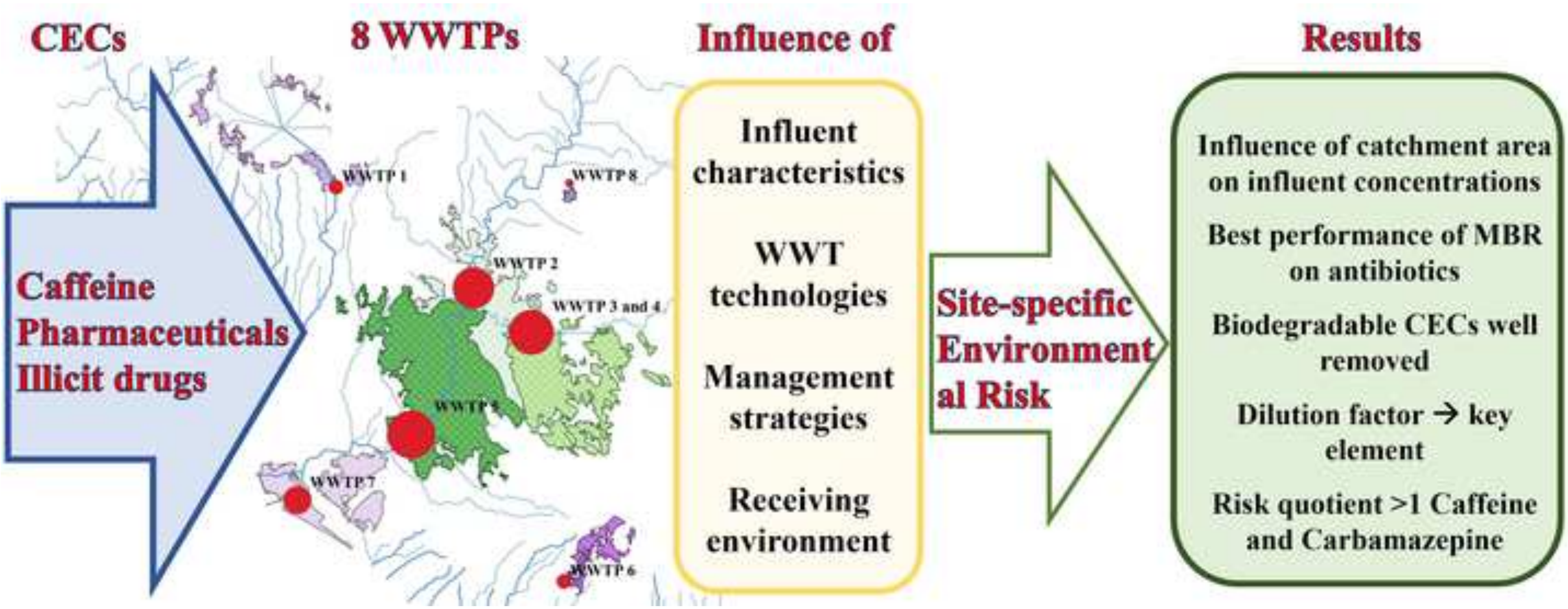
R: The caption was shortened according to the comment and some information was moved above, as follows:

Line 561: The RQ was considered acceptable if below 1. The classes of Risk are defined as: high risk for RQs > 1, medium risk for $0.1 \leq$ RQs ≤ 1, and low risk for RQ ≤ 0.1.

Figure 5 Risk quotient resulted from the ERA assuming different values of MEC in the effluent and D: a) D=S.S., MEC=median value; b) D=S.S., MEC=95th percentile value; c) D=10, MEC=median value; d) D=10, MEC=95th percentile value.

- A revision of the English language is strongly recommended.

R: The entire manuscript was carefully revised.



CECs

Caffeine
Pharmaceuticals
Illicit drugs

8 WWTPs

Influence of

Influent characteristics

WWT technologies

Management strategies

Receiving environment

Site-specific Environmental Risk

Results

Influence of catchment area on influent concentrations

Best performance of MBR on antibiotics

Biodegradable CECs well removed

Dilution factor → key element

Risk quotient >1 Caffeine and Carbamazepine

Highlights

- 14 CECs were monitored in 8 different full-scale WWTPs for 2-years
- The CECs removal was mainly dependent on biological process
- The Membrane Biological Reactor achieved the best performance
- A high environmental risk was observed for carbamazepine and caffeine
- The risk changed depending on the dilution factor of effluent into the rivers

A step forward on site-specific environmental risk assessment and insight into the main influencing factors of CECs removal from wastewater

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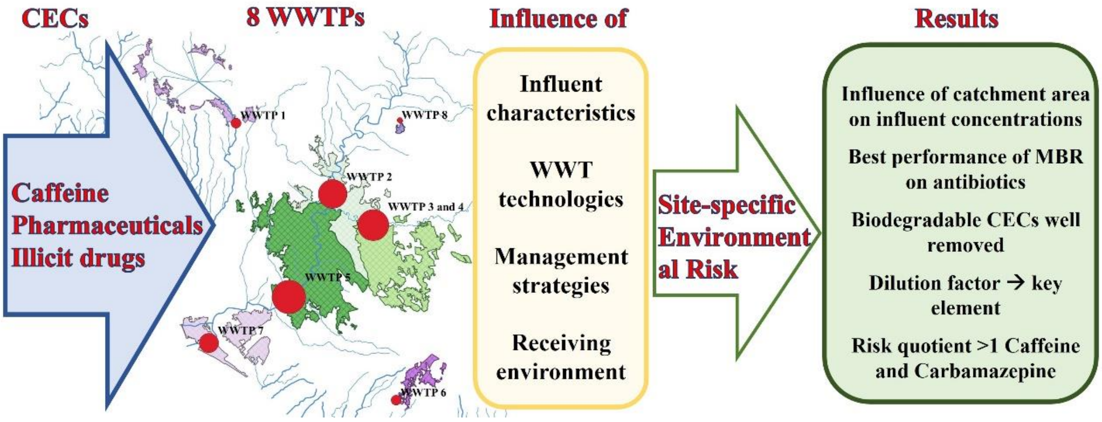
Abstract

The presence of Contaminants of Emerging Concern (CECs) in water systems has been recognized as a potential source of risk for human health and the ecosystem. The present paper aims at evaluating the effects of different characteristics of full-scale Wastewater Treatment Plants (WWTPs) on the removal of 14 selected CECs belonging to the classes of caffeine, illicit drugs and pharmaceuticals. Particularly, the investigated plants differed because of the treatment lay-out, the type of biological process, the value of the operating parameters, the fate of the treated effluent (i.e. release into surface water or reuse), and the treatment capacity. The activity consisted of measuring concentrations of the selected CECs and also traditional water quality parameters (i.e. COD, phosphorous, nitrogen species and TSS) in the influent and effluent of 8 plants. The study highlights that biodegradable CECs (cocaine, methamphetamine, amphetamine, benzoylecgonine, 11-nor-9carboxy-Δ9-THC, lincomycin, trimethoprim, sulfamethoxazole, sulfadiazine, sulfadimethoxine, carbamazepine, ketoprofen, warfarin and caffeine) were well removed by all the WWTPs, with the best performance achieved by the MBR for antibiotics. Carbamazepine was removed at the lowest extent by all the WWTPs. The environmental risk assessed by using the site-specific value of the dilution factor resulted to be high in 3 out of 8 WWTPs for carbamazepine and less frequently for caffeine. However, the risk was reduced when the dilution factor was assumed equal to the default value of 10 as proposed by EU guidelines. Therefore, a specific determination of this factor is needed taking into account the hydraulic characteristics of the receiving water body.

Graphical Abstract



Keywords Advanced statistical analyses, Caffeine, Dilution factor, Illicit drugs, Pharmaceuticals, Principal component analysis

1. Introduction

Wastewaters contain a huge variety of micropollutants, many of which have been classified as Contaminants of Emerging Concern (CECs) or Organic Micropollutants. Disinfection by-products, pharmaceuticals, personal care products, steroids, licit and illicit drugs are among the more widely diffused contaminants classified as CECs (Aemig et al., 2021). The studies conducted on these pollutants have demonstrated that they are widely present in water bodies (Archer et al., 2017; Barchiesi et al., 2021; OECD, 2019). Indeed, they enter the sewage collection systems as a consequence of many sources, such as the release from the domestic use of household chemicals (detergents, cleaning products, textile fibres and personal care products) and human consumption, improper disposal, as well as through urban runoff (Parida et al., 2021). Through the sewage network, the CECs reach the Urban Wastewater Treatment Plants (UWWTPs) where they undergo the same processes as the other pollutants. However, since UWWTPs are not specifically designed to accomplish the CECs removal, many of them remain in the treated effluent and then are transferred to the water bodies. The communication of the Commission of 2019, “European Union Strategic Approach to Pharmaceuticals in the Environment” (adopted by the European Parliament in 2020) stresses that pharmaceuticals reach the environment through excreted and unused products entering sewage collection systems and WWTPs (European Commission, 2019a; European Parliament, 2020). The same concern issue was also highlighted in the conclusions of the document “Evaluation of the Urban Wastewater Treatment Directive (UWWTD)” which reports that contaminants of emerging concern, which are not included in the scope of the actual UWWTD, are receiving more attention since the treatment required under the directive reduces such pollutants of wastewater to some extent but does not target them directly neither remove satisfactorily (European Commission, 2019b). The Environmental Quality Standards (EQSs) on surface water already consider some of the CECs (The European Parliament and the Council, 2013).

The definition of the EQS by the EU legislation was supported and guided by the Environmental Risk Assessment (ERA), based on the data available on the occurrence of selected CECs and their ecotoxicological effects in the receiving environment (EU, 2003). The application of the ERA approach is now recognized as the most suitable tool to establish the maximum allowable concentrations and consequently to identify and design the reduction measures to implement for contrasting harmful substances. However, firstly a comprehensive knowledge of the efficiency achieved by the different treatment units of the WWTPs in the CECs removal is needed, to provide data about the type of contaminants which are still found in the effluent and their concentration (Kumar et al., 2022). Afterwards, it can be evaluated by the ERA if the residual effluent concentrations represent a real risk for the environment and human health. Finally, the reduction measures can be identified if the ERA shows the presence of an unacceptable risk (Bailey et al., 2018).

Previous studies showed that the CECs removal by the existing WWTPs is dependent on several factors, such as physicochemical properties of the pollutants, type of treatment process, operating parameters (hydraulic retention time (HRT), sludge retention time (SRT), pH, temperature, etc.), reactor configuration, microorganism type (Parida et al., 2021). For instance, the removal of highly polar substances, such as most pharmaceuticals, is mainly achieved by the biological oxidation carried out by microorganisms. Recent studies have shown that the Moving Bed Biofilm Reactor (MBBR) and Membrane Biological Reactor (MBR) are more efficient than the conventional activated sludge process followed by secondary sedimentation. The removals of particularly recalcitrant compounds, such as carbamazepine and sulfamethoxazole, in the conventional activated sludge process are usually lower than MBR and MBBR, e.g. they range from -110% - 3% for carbamazepine and (Krzeminski et al., 2019) from 32% - 98% for sulfamethoxazole (Couto et al., 2019; Verlicchi, 2012). However, most of the studies on MBBR were carried out at lab-scale (Krzeminski et al., 2019): e.g. Zhang et al. (2020) observed removal of sulfadiazine and carbamazepine in a laboratory MBBR equal to 61% and 28%, respectively. The MBRs, which are characterized by higher values of SRT than conventional activated sludge, showed varying performance in the CECs removal: for instance, removal of sulfamethoxazole, carbamazepine and caffeine fell in the range of 75%–95%, whereas that of trimethoprim and some pesticides was below 40% (Ahmed et al., 2017). According to the Swiss VSA Platform "Process Engineering Micropollutants", the best available technologies for WWTPs upgrading to enhance CECs removal are activated carbon adsorption and ozonation ("VSA Micropoll," 2018). However, the tertiary treatments commonly applied, such as sand filtration and UV or peracetic acid or hypochlorite disinfection, can provide a certain abatement of CECs concentration (Rizzo et al., 2020). Cai et al. (2017) achieved removal of seven pharmaceuticals below 11% using 1 mg/L of peracetic acid under laboratory conditions; additionally, a significant increase was observed after the activation of the oxidant by UV. Similar findings were obtained by Wang et al. (2016) using UV combined with chlorine as disinfectant.

This investigation belongs to a wide research activity carried out since 2017 having the aim to assess the occurrence and removal of CECs in full-scale Wastewater Treatment Plants for domestic sewage (Di Marcantonio et al., 2020b). The present study aims to provide better knowledge of the effects of different treatment layouts and other characteristics of full-scale wastewater treatment plants on the removal of CECs: particularly, 8 WWTPs were selected for the study based on different characteristics of the water treatment processes, the extension of the area served by the sewage network feeding the plant and the type of final disposal of the treated water. The CECs selected for the study belong to the classes of illicit drugs and pharmaceuticals (including antibiotics and caffeine). The traditional water quality parameters were also monitored, and their removal correlated with that of CECs. The environmental risk assessment (ERA) was carried out following the procedure outlined by the European Medicines Agency (2018) and considering the residual concentrations measured in the treated effluents. In addition to the standard procedure, the dilution effects of the effluent in the receiving water bodies were also taken into account in the analysis. Therefore, the results of the ERA were more site-specific, which represents an innovative element of the present study compared the past. Additionally, the ERA was performed considering two contamination scenarios: i.e. the average-case and the worst-case. The former (average) can be representative of chronic exposure whereas the latter (worst) of the acute exposure. Therefore, these data can be useful as a reference for future ecotoxicological studies.

The other novelty is represented by the comparison of full-scale WWTPs using different biological processes, such as activated sludge, MBR and MBBR, and also different tertiary treatments. Finally, the data were collected for a time-frame of observation of 2 years, thus allowing to catch different weather and influent conditions.

2. Materials and methods

2.1. WWTPs

The WWTPs of the present investigation were selected among the wide list of 76 plants considered in the study by Di Marcantonio et al. (2020b). They are representative of different water treatment processes, type of final disposal of the treated water and characteristics and extension of the area served by the sewage network feeding the plants. The main characteristics of these plants are reported in Table 1, including the treatment capacity (as average influent flow rate, Q_{WWTP}, and authorized treatment capacity, PE_{au}), the average sludge retention time (SRT), the average flow rate of the receiving water body at the point of the treated effluent release (Q_{rec}) and water treatment line layout. Some of the WWTPs (i.e. WWTP 1, WWTP 6, WWTP 8) release the treated effluent into a stream which is characterized by a wide flow rate variation from dry to wet season. Precautionary, in these cases, Italian environmental legislation assumes that the main flow rate of the stream is associated with the effluent flow rate from the plant. As a consequence, the acceptable maximum concentrations as established by the regulation are lower as compared to the release into rivers. Therefore, the flow rate of the receiving stream, Q_{rec}, was assumed to be 0 in the Environmental Risk Assessment performed on these WWTPs. The characterization of the influent on the investigated WWTPs (as concentration of total suspended solids, chemical oxygen demand, ammonium nitrogen and total phosphorus) is reported Table S.M. *1*.

Table 1 Main characteristics of the monitored WWTPs and number of sampling days (Samples). Abbreviations: SRT= Sludge Retention Time, QWWTP= average flow rate of the WWTP, Qrec= average flow rate of the receiving water body, Ca= sewage catchment area, PE_{au}*= Authorized treatment capacity, BS=Bar Screening, DD=Degreasing-Degritting, PS=Primary Sedimentation, O=Aerobic activated sludge process (oxidation), DN=Anoxic activated sludge process (denitrification), SS=Secondary Sedimentation, MBR=Membrane Biological Reactor (ultrafiltration), MBBR=Moving Bed Biofilm Reactor, III=Sand filtration followed by UV disinfection, DC=Hypochlorite disinfection, DP=Peracetic acid disinfection.*

WWTPs	**SRT [d]**	**Q_{WWTP} [mc/s]**	**Q_{rec} [mc/s]**	**Ca [sqkm]**	**PE_{au} [n.]**	**Samples [n.]**	**BS**	**DD**	**PS**	**DN**	**O**	**SS**	**MBBR**	**MBR**	**III**	**DC**	**DP**
1	9	0.22	0	22	90 000	31	●	●	●	●	●	●			●	●	
2	14	2.82	165	81	300 000	23	●	●	●		●	●				●	
3	10	1.22	7.5	44	600 000	11	●	●	●	●	●	●				●	
4	13	1.79	7.5	65	350 000	17	●	●	●	●	●	●				●	
5	10	9.2	177	195	780 000	24	●	●	●		●	●					●
6	-	0.16	0	14	1 090 000	18	●	●					●				●
7	13	0.93	188	53	90 000	20	●	●	●	●	●	●				●	
8	27	0.05	0	2	18 000	17	●	●		●	●	●		●			

Regarding WWTP 6, the biological compartment consists of an MBBR equipped with the AnoxKaldnes technology; it is composed of three parallel lines, each one made up of two anoxic tanks followed by three aerobic reactors. Following, the Actiflo Turbo® (i.e. coagulation-flocculation and dephosphation) is present with the addition of ferric chloride, polyelectrolyte and micro-sand.

2.2. Sampling campaign

The monitoring campaign was conducted from January 2020 to December 2021 and consisted of 161 sampling days for an overall number of collected samples equal to 322. Autosamplers were used for the collection of 24-hourly mixed samples from the influent and effluent almost every month in each plant. The total number of sampling days for each WWTP is reported in Table 1. A 1 L Nalgene bottle was used to collect the sample, which was then transferred to the laboratory for pre-treatment and finally stored at T = 4 °C until analysis.

The following 14 CECs, belonging to the classes of pharmaceuticals and illicit drugs, were measured in each sample: cocaine (COC), methamphetamine (MET), amphetamine (APT), benzoylecgonine (BEG), 11-nor-9carboxy- Δ9-THC (THC-COOH), lincomycin (LCN), trimethoprim (TMT)), sulfamethoxazole (SMX), sulfadiazine (SDZ), sulfadimethoxine (SDM), carbamazepine (CBZ), ketoprofen (KTP), warfarin (WFR) and caffeine (CAF). In Table S.M. *2* were reported the main physico-chemical properties of the target CECs. In addition, the following traditional water quality parameters were determined on each sample: total suspended solids (TSS), chemical oxygen demand (COD), ammonium nitrogen, nitrite and nitrate nitrogen (NH_4^+-N, NO_2^--N and NO_3^--N, respectively) and total phosphorus (Ptot).

2.3. Analytical methods

The water quality parameters were measured by following the standard methods: TSS through APAT CNR IRSA 2090 B Man 29/2003, COD through APAT CNR IRSA 5135 Man 29/2003, P_{tot} through M.U. 2252:08/1, NH_4^+−N, NO_2^-−N, and NO_3^-−N through Standard Methods 4500 2, 4500H and 4500 1, respectively (APAT IRSA-CNR, 2003; APHA, 2017).

The CECs were quantified using ultrahigh performance liquid chromatography coupled with tandem mass spectrometry. The analytical method was specifically developed by the same research group and validated for most analytes by ACCREDIA. All details are reported in a previous paper (Di Marcantonio et al., 2021). CEC standard solutions (COC, BE, THC-COOH, APT, MET, CBZ, KTP, SMX, TMT, LCN, SDM, SDZ, WFR, CAF) and internal standards Cocaine-d3 and carbamazepine-d10 were purchased from Sigma-Aldrich Company (Gillingham, UK) at a concentration of 100 µg/ml in agent methanol. The Minimum Reporting Levels (MRL) were posed equal to the following values: 0.05 µg/L for KTP, 0.1 µg/L for THC-COOH, APT, CAF and 0.01 µg/L for the other contaminants.

2.4. Calculation methods

Frequency of detection (Fd) and removal efficiencies (R) were calculated according to Di Marcantonio et al. (2020). When the concentration resulted to be below the MRL, the value was set equal to half of the MRL in the calculation of statistical descriptors and removal efficiency and application of ERA (European Commission, 2009). Additionally, removal was not calculated if the influent and effluent concentrations were both equal to MRL. Indeed, the daily median removal could be calculated when the concentration was above MRL at least in the influent samples. The significance of the differences between the removal efficiency achieved by each WWTP, for the different target compounds, was statistically assessed. The normality of the series of data was, firstly, checked through the Shapiro-Wilk normality test and it was never satisfied. As consequence, the non-parametric Kruskal-Wallis Test was applied followed by the pairwise Wilcox post-hoc test. The evaluation was carried out through the R package “stats” (R Core Team, 2021). The results of the post-hoc test (i.e. p-value adjusted according to the Benjamini and Hochberg method) were reported in the corresponding plot labelling the boxes not significantly different by the same letter (Benjamini and Hochberg, 1995).

The whole data set was processed through the Principal Component Analysis (PCA), to reduce their dimensionality and to extract further insight into the effects of the different treatment stages. The PCA was performed using the R package “Fac- toMineR” (Lê et al., 2008). Specifically, the PCA was applied to the removal efficiency data, to find out possible clusters and evidence about the biological technology and other characteristics of the WWTPs. Additionally, the correlation between the concentrations of water quality parameters and CECs was also assessed by PCA and reported as a correlation circle. The analysis was performed excluding the analytes detected in less than 10% of the samples for statistical reasons (i.e. THC-COOH, APT, WRF, SDM, NO_2^--N). More details about PCA interpretation are reported in Di Marcantonio et al. (2021).

2.5. Environmental Risk Assessment

The ERA was performed for each WWTP considering the residual concentrations of the CECs in the effluent and the hydraulic characteristics of the receiving water bodies. The assessment procedure proposed by the Environmental Medicine Agency was applied with some more implementations (European Medicines Agency, 2018).

The risk quotient (RQ) was calculated for each contaminant using the following equation:

$$RQ\ [/] = \frac{MEC/D}{PNEC} \qquad (1)$$

where MEC is the measured environmental concentration, D is the dilution factor and PNEC is the predicted no-effect concentration. If the RQ is < 1, the contaminant is unlikely to represent a risk to surface water. The values of PNEC, as reported in Table S.M. *3*, were mainly collected from the open-access NORMAN Database System and derived using ecotoxicity data for freshwater species (Norman

Network, 2022). The ERA was carried out for two different contamination scenarios (i.e., average and worst case) depending on the effluent concentrations assumed as MECs: specifically, the median value for the average scenario and the 95th percentile for the worst scenario. MEC values were divided by the dilution factor to take into account the effect on the CECs concentrations of the effluent released into the receiving waters, which represents the actual exposure to the ecosystem. The suggested value of D is equal to 10, referred to as default D (European Medicines Agency, 2018); however, a site-specific estimation of D (D=S.S) allows a more accurate assessment of the environmental risk. Hence, D was defined, as in the equation reported below, considering the average water body flow rate (Q_{rec}) and the average WWTP effluent flow rate (Q_{WWTP}), which was assumed equal to the average influent flow rate (European Commission, 2003):

$$D\ [/] = \frac{Q_{WWTP} + Q_{rec}}{Q_{WWTP}} \qquad (2)$$

For WWTP1, WWTP6 and WWTP8, as mentioned before, Q_{rec} was assumed to be equal to 0; as a consequence, D was settled equal to 1.

Based on these assumptions and the values of Q_{rec} and Q_{WWTP} reported in Table 1, the dilution factors for each WWTP were found to be as follows: 1, 60, 7, 5, 20, 1, 203, 1 for WWTP1, WWTP2, WWTP3, WWTP4, WWTP5, WWTP6, WWTP7 and WWTP8, respectively.

The ERA was performed only for those CECs detected in more than 10% of the samples, to have statistical reliability of the results.

3. Results

3.1. Measured concentrations

The results of the sampling campaign on the influent and effluent of the eight WWTPs were summarized as minimum, median ad maximum values and frequency of detection (F_D), as reported in Table S.M. 4. CAF was the pollutant found at the highest concentration in the influent of all the WWTPs, followed by BEG and KTP (i.e. median values equal to 24.10 µg/L, 1.73 µg/L and 1.62 µg/L, respectively). However, CAF values were more than 10 times higher than BEG and KTP. Regarding the frequency of detection, CAF, BEG, KTP, TMT, SMX and CBZ were all detected in most of the influent samples (i.e. $F_D > 90\%$). By contrast, THC-COOH, WRF, APT and SDM were found in less than 10% of the collected samples.

The differences in the influent concentrations of the same pollutant measured in the WWTPs might be related to the characteristics and extension of the catchment area served by the plants. The assumption is that the larger the served area, the higher the equalization effect on the concentration due to the longer retention in the sewage network; this longer retention time reduces the peak values and attenuates the time variations of the influent concentrations. Indeed, the highest concentration of CAF, BEG and KTP were found in WWTP6 and WWTP1 which serve sewage basins of 15 km^2 and 22 km^2, respectively, corresponding to average influent volumetric flowrates of 0.16 m^3/s and 0.22 m^3/s (treatment capacity of both plants equal to 90’000 PE) (see Figure S.M. 1). In agreement with the assumption reported above, the lowest concentrations were measured in the influent of WWTP5 which serves a much larger area (about 195 km^2, corresponding to an average influent volumetric flowrate of 9.2 m^3/s, for a treatment capacity of 1’090’000 PE). To confirm these observations, the Spearmen correlation coefficient was calculated between influent concentrations and catchment area for the three CECs measured at the highest extent (i.e. CAF, BEG and KTP). The value of the correlation coefficient resulted to be always significant (i.e. $p\text{-value} < 0.05$): -0.37 for BEG, -0.45 for KTP and -0.27 for CAF. It is therefore confirmed the assumption that the higher the catchment area, the lower the influent concentration. Similarly, McCall et al. (2017) depicted the influence of the catchment scale on illicit drug biomarkers. The only exception was represented by WWTP8, which serves the smallest catchment area and receives influent concentrations being not as high as expected. However, it might be argued that in this case, the treatment capacity is so low (i.e. 18’000 PE) to highlight concentration peaks. Further studies must be carried out to confirm the assumption and to better elucidate the causes of the influent concentration time patterns, considering all the possible influencing factors (e.g. the ratio between catchment area and overall length of sewage pipes, the retention time and transformation and degradation processes of pollutants within the sewage network).

Regarding the effluent concentrations from all the WWTPs (data reported in Table S.M. 4), the highest medians were measured for SMX and CBZ (i.e. 0.23 µg/L and 0.18 µg/L, respectively) which also showed an $F_D = 99\%$. By contrast, the median concentrations of COC, MET, LCN, SDZ, SDM, WRF, THC-COOH and APT were below the MRL with $F_D < 35\%$. These results can be explained based on the removal capability of the different WWTPs, as it will be afforded in detail in the discussion below.

3.2. Removal efficiencies

The median removal efficiencies are reported in Table 2. They were classified into three categories according to the Swiss experience: high, intermediate and low, corresponding to R ≥80%, 20%< R<80%, and R ≤20%, respectively (Rizzo et al., 2019; The Swiss Federal Council, 2021).

Table 2 Median removal efficiencies for each CEC and WWTP: in italic the low removal (R ≤20%), in bold the high removal (R ≥80%) and underlined the intermediate removal (20%< R<80%).

WWTP	**BEG**	**COC**	**THC-COOH**	**MET**	**APT**	**SMX**	**TMT**	**LCN**	**SDZ**	**SDM**	**KTP**	**CBZ**	**WRF**	**CAF**
1	**98**	**97**	/	64	/	*9*	72	*-3*	50	/	**96**	*-12*	/	**100**
2	**98**	**97**	63	**83**	/	42	38	66	75	/	**88**	*-4*	78	**99**
3	**99**	**97**	/	79	/	*17*	43	50	71	/	**90**	*18*	/	**99**
4	**98**	**98**	50	54	/	40	**88**	50	75	/	**97**	*-13*	/	**99**
5	35	58	/	50	/	*-8*	*9*	*0*	36	/	38	*0*	/	33
6	**98**	**98**	64	50	/	23	**90**	50	63	/	**97**	32	69	**98**
7	**98**	**98**	58	75	/	*19*	45	50	32	/	**89**	*-15*	/	**98**
8	**98**	**98**	52	71	/	64	**94**	71	75	/	**98**	*18*	55	**97**

APT and SDM were not detected in any sample and as consequence, the removal was not calculated. BEG, COC, CAF and KTP were classified as belonging to the high removal category since the median values of the removal efficiency were above 80% for all the WWTPs with the only exception of WWTP5. These results are well in agreement with previous studies. For instance, a wide investigation, concerning 76 WWTPs carried out by the same research group, found comparable removal values (Di Marcantonio et al., 2020b). Similar results were measured for KTP (i.e. R from 78% to 93%) also by Palli et al. (2019) investigating an Italian WWTP; R > 80% for BEG were determined by Yadav et al. (2019) in Australia and by Styszko et al. (2021) in Poland. Khasawneh and Palaniandy (2021) reviewed 73 studies and highlighted removal above 90% for CAF. These high removal rates are mainly ascribed to the effect of the secondary compartment of the WWTPs, specifically due to biodegradation and photodegradation, since these compounds are highly hydrophilic (log Kow < 3) and soluble (Chiavola et al., 2019; Couto et al., 2019). It is important to notice that the same pollutants, i.e. BEG, COC, CAF and KTP, were also present at the highest concentration in the influent of all the WWTPs. This might boost the removal by biodegradation for the biodegradable CECs which can be used as a primary or secondary source of carbon and energy. For instance, Quintana et al. (2005) studied the microbial degradation of five acidic pharmaceuticals using activated sludge as inoculum under aerobic conditions and found that ketoprofen demonstrated a metabolic biodegradation capability.

These results also highlight that the monitored WWTPs can comply with the removal target recommended by the Swiss legislation (i.e. R≥80%), which represents at the moment the reference for Europe on CECs management in the water sector

CBZ was the only CEC whose removal was in most cases less than 20% (therefore it was classified within the low removal category), or even negative. There was only one exception, represented by WWTP 6, which showed a median removal equal to 32%. These low removals were also observed by other studies; as an example, Kumar et al. (2022) reported R=-92%- 18%. The high persistence of CBZ in water is due to its chemical-physical properties. The value of k_{biol} is very low (i.e. 0.005–0.389 L/gMLSS d), and this determines a high resistance to biodegradation; additionally, the value of K_{ow} (equal to 2.1) indicates that the molecule is highly hydrophilic and therefore it preferably remains dissolved in solution instead of being adsorbed onto primary or secondary sludge (Kumar et al., 2022). This behaviour is also confirmed by the values of the solid/liquid partition coefficient (K_d) reported being K_d 8–314 L/kg MLSS, which suggests negligible sorption onto sludge (Rout et al., 2021). The higher removal observed in the WWTP6 compared to the other WWTPs might be due to the different layout of treatment. Firstly, the biological compartment consists of a Moving Bed Biological Reactor (MBBR), which is reported to be able of a higher biodegradation rate because of the increased biomass density and longer retention time (Sonwani et al., 2022). Furthermore, there is a coagulation-flocculation unit following the MBBR, where a further improvement of the removal capability is expected to occur. However, the contribution of the latter compartment should be low since Matamoros and Salvadó (2013) demonstrate that for hydrophilic compounds, and particularly CBZ, this process provide a positive removal but at low values (i.e. <5 %). The negative removal values of CBZ observed in many of the investigated plants and also referred by other authors (Di Marcantonio et al., 2021, 2020a; Moslah et al., 2018; Nas et al., 2021; Tran and Gin, 2017) might be explained through a combination of more effects: the desorption from faecal particles due to the hydrophilic characteristic of the molecule and the hydrolysis of its human metabolites with reconversion into the original compound (Kumar et al., 2022). Based on these results, it can be deemed that the removal of CBZ needs treatment processes other than those implemented in the existing WWTPs designed to remove traditional compounds. This goal was implemented already in Switzerland where CBZ was included among the proxy CECs to be monitored and removed (Eggen et al., 2014).

Regarding the CECs belonging to the intermediate removal category (i.e. THC-COOH, MET, SMX, TMT, LCN, SDZ and WRF), the median values showed a wide variability which was speculated to be ascribed to the effects of the plant layout. To better understand this dependence, the removal data of this category were further statistically analysed in the section below.

3.3. Statistical insight into the removal of CECs belonging to the intermediate removal category

The removal efficiency data of the intermediate removal category were plotted in a boxplot (Figure 1), and then analysed through Principal Component Analysis (Figure 2 and Figure 3). The graph in Figure 1 shows their statistical variation around the median value. The statistical tests (Kruskal and Wilcoxon) provided the letters reported above the boxplot: the same letter indicates that the removal of a specific CEC achieved by a plant does not differ statistically from that observed in a different plant for the same compound.

THC-COOH and WRF were excluded from this analysis since they were both detected in less than 10% of the collected samples (i.e. influent: F_D = 7% and F_D = 4%, respectively; effluent: F_D = 0% and F_D = 0%, respectively).

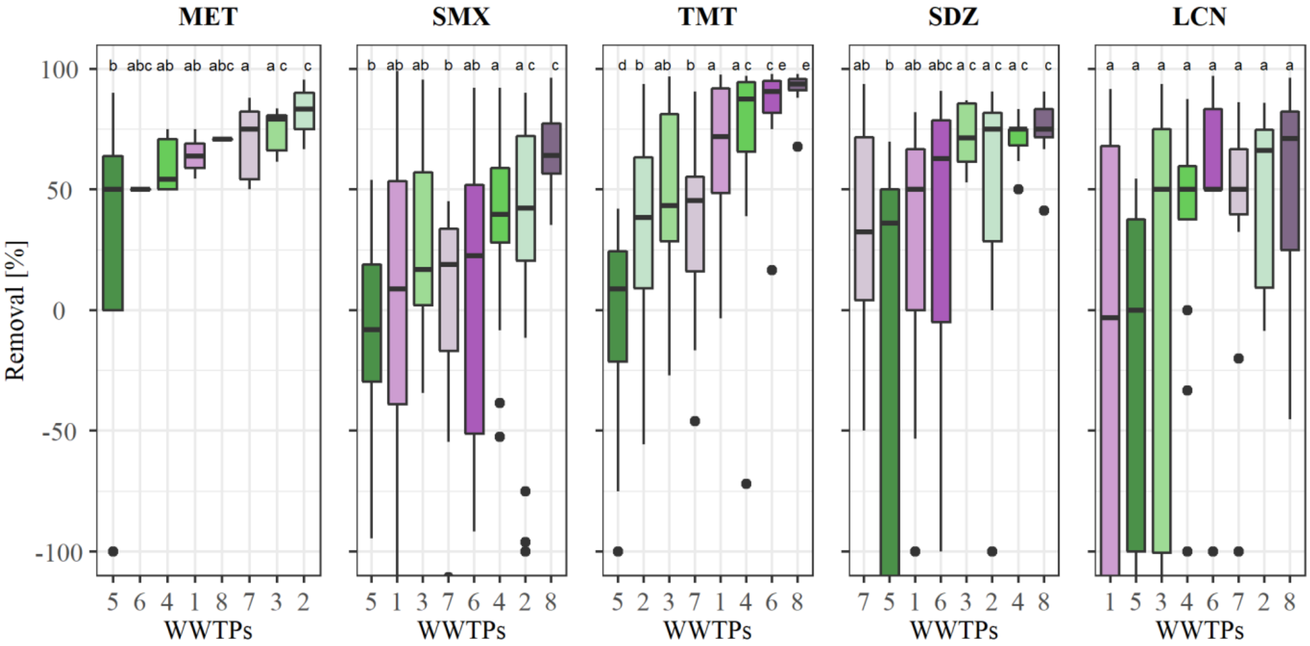


Figure 1 Removal efficiency considering the CECs belonging to the intermediate removal category. The letters on the top of the plot indicate significant statistical differences between data sets via Kruskal ($p \leq 0.05$) and post hoc pairwise Wilcoxon tests; boxes labelled with the same letter are not significantly different.

Median removal of MET ranged between 50% in WWTP5 and WWTP6 and around 80% in WWTP2 and WWTP3. The highest median removal was achieved by WWTP2 and WWTP3 which are not statistically different since both were labelled with the letter c. They are characterized by a biological process consisting of the aerobic stage and anoxic-aerobic stages, respectively. This suggests that aerobic biodegradation provides a significant contribution to the removal. MBR and MBBR technologies do not provide a relevant improvement on MET removal. Concerning the possible effects of the tertiary compartment and disinfection, based on the median removal it was possible to observe that the lowest removal efficiency was achieved in the two plants where the disinfection is provided by peracetic acid. By contrast in the other WWTPs where the MET removal was higher (except WWTP 8 where the disinfection is achieved by ultrafiltration), the disinfection is performed by sodium hypochlorite. Luongo et al. (2020) compared peracetic acid performances on different CECs removal with other disinfectants, including sodium hypochlorite, and observed a lower removal but also a lower number of degradation by-products. Nonetheless, additional studies are required to elucidate the best conditions for this treatment. MET is a soluble and hydrophilic compound with a negligible tendency to be adsorbed on the activated sludge, as reported by several experimental studies (Boni et al., 2018; Yadav et al., 2019). Di Marcantonio et al. (2021) investigated the main treatment stages of a full-scale WWTP and found that no appreciable removal was achieved by pre-treatment and primary treatments whereas the main reduction (up to 60 %) was carried out by the secondary compartment.

For the antibiotics (i.e. LCN, SDZ, SMX and TMT), the highest median removal efficiency was always achieved by WWTP8, which is equipped with the MBR technology. The better removal of this system for complex contaminants as CECs is reported to be related to the sorption on the membrane as well as the biotransformation due to the development of slower-growing microbial species (Alvarino et al., 2018).

Among antibiotics, the removal did not change statistically between the plants only for LCN (i.e. p-value of the Kruskal test > 0.05). This can be due to the very low concentration measured in the influent and also the effluent (close to the MRL of 0.01 µg/L) of all plants. None of the investigated WWTPs was able to provide an appreciable improvement of the removal. Nonetheless, there is a relevant abundance of negative removal values, particularly in WWTP5, WWTP1 and WWTP3. Indeed, LCN is considered recalcitrant to biodegradation, and it is not expected to be adsorbed onto sludge; instead, it can more easily dissociate in the aqueous phase (LogKow < 3 and pKa = 7.6) (Tran et al., 2018).

In the case of SDZ, WWTP2, WWTP3, WWTP4 and WWTP8 showed a median removal in the range 71%-75%. WWTP7, WWTP6, WWTP5, and WWTP1 (labelled by letter B) featured a median removal in the range 32%-63%. Furthermore, the latter group of plants showed a higher variability of the removal values, ranging from negative up to 94%. Regarding the performances of the MBBR processes (WWTP6), Sonwani et al. (2022) reported removal of SDZ in a lab-scale MBBR of 61.1 ± 8.8%, which is comparable with the median value observed in the present study (i.e. 63%).

SMX and TMT are usually assumed by patients in combination. Indeed, the frequency of detection in the influent was similar in all the plants, (i.e. around 100%). However, the behaviour was different. Particularly, TMT was removed at a higher and similar extent by WWTP8, WWTP6 and WWTP4 (i.e. median removal equal to 94%, 90% and 88%, respectively). Consistently, Gurung et al. (2019) achieved a median TMT removal of 86% in a pilot-scale MBR and Wolff et al. (2021) observed improved biotransformation of TMT by attached biomass compared to suspended biomass. In the other WWTPs, the median removal was widely variable.

The median removal of SMX was below 25% in WWTP1, WWTP3, WWTP5, WWTP7 and WWTP6 and roughly 40% in WWTP4 and WWTP2. A relevant increase in abatement was observed only in the plant where the biological compartment is made by an MBR (i.e. WWTP8, with a median removal equal to 64%). A slight improvement of slowly degradable substances including SMX was observed by Abegglen et al. (2009) in the MBR systems (Wolff et al., 2021). Regardless of the removal efficiency, no relevant decrease of the F_D in the effluents was observed for all the WWTPs (i.e. F_D ranged from 91%-100%). This is of particular concern because SMX is hydrophilic (i.e. $LogK_{ow}$ equal to 0.89), mobile in the aquatic environment (Dong et al., 2016; Grenni et al., 2019) and considered persistent in conventional WWTP by several authors (Di Marcantonio et al., 2020b; Estrada-Arriaga et al., 2016).

The PCA was applied to the removal values of the CECs belonging to the intermediate removal category for a better understanding of the driving factors. This analysis allowed the evaluation of the relative role of the biological compartment, the treatment capacity and the average SRT. The results of the PCA were reported as individual plots: in Figure 2 the individuals were coloured based on the main characteristics of the WWTPs layout according to Table 1, whereas in Figure 3 the same individuals were coloured based on the average SRT and grouped considering the type of biological process.

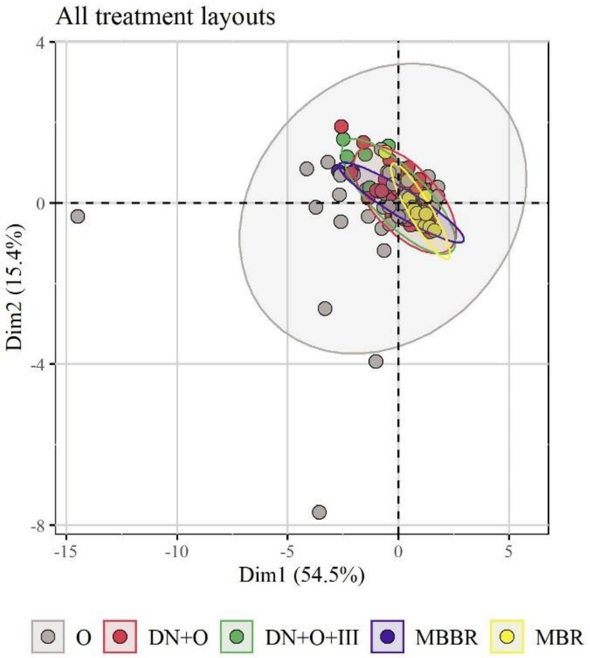


Figure 2 Individual plot obtained through PCA of the removal efficiency of intermediate category. The individuals are coloured based on the type of treatment layout.

The two main dimensions describe most of the variance of the data (i.e. 69.9%), which makes the following considerations sufficiently reliable. The individual plot highlighted that even if the data are mainly positioned in the same area, there are evident differences in the clusters formed depending on the type of biological process. Specifically, the most stable performances were achieved by the MBR followed by the MBBR as highlighted by the smallest ellipses, which correspond to 95% of the variance of each group of data. As known, the MBR exploits the high retention capacity of the membrane to produce a treated effluent of very high quality. As known, the MBR exploits the high retention capacity of the membrane to produce a treated effluent of very high quality (Krzeminski et al., 2019). Furthermore, the longer sludge retention time favours the degradation of more complex molecules, such as those of CECs. The replacement of the secondary settlement by the membrane separation makes the system to be more resilient versus the variations of the influent characteristics and operating parameters. MBBR technology exploits the natural ability of microorganisms (e.g. bacteria, fungi, and algae) to adhere to the surfaces of carriers (or support media) and grow as biofilms, either as pure or mixed cultures. The wastewater flows in direct contact with the developed biofilm and allows to exchange of substrate, nutrients, and products between the biofilm and bulk liquid (Sonwani et al., 2022). Both MBR and MBBR, for the intrinsic features, provide a more stable operation as confirmed by the results of the PCA analysis.

The two groups named DN+O (i.e. anoxic-aerobic activated sludge) and DN+O+III (i.e. anoxic-aerobic activated sludge+sand filtration+UV) showed quite overlapped ellipses: therefore, the presence of the tertiary treatment (III) cannot be considered statistically relevant.

The highest dispersion of data within the plot was observed for the plants where the biological process was made by the aerobic activated sludge only (i.e. WWTP2 and WWTP5, named O in Figure 2) and which have the largest treatment capacity (i.e. 9.2 mc/s and 2.3 mc/s for WWTP5 and WWTP2 respectively). This indicates instability and high variability of the removal values. However, WWTP2 always provided higher values of the median removal efficiencies than WWTP5 (Table 2): therefore, for these WWTPs the treatment capacity and biological reactor type are not the discerning factors. Figure 3a shows the data of WWTP5 and WWTP2, with the individuals coloured based on the SRT: it can be noted an indisputable difference between the plants. The difference might be due to the slightly higher SRT of WWTP2 (14 d vs 10 d for WWTP2 and WWTP5, respectively) which is known to enhance efficiency (Douziech et al., 2018). However, other site-specific conditions and characteristics of the plants might be responsible for the difference observed: e.g. in WWTP5 the biological process is of Carrousel-type, which is considered not to be highly efficient, additionally the low influent organic load (Table S.M. *1*).

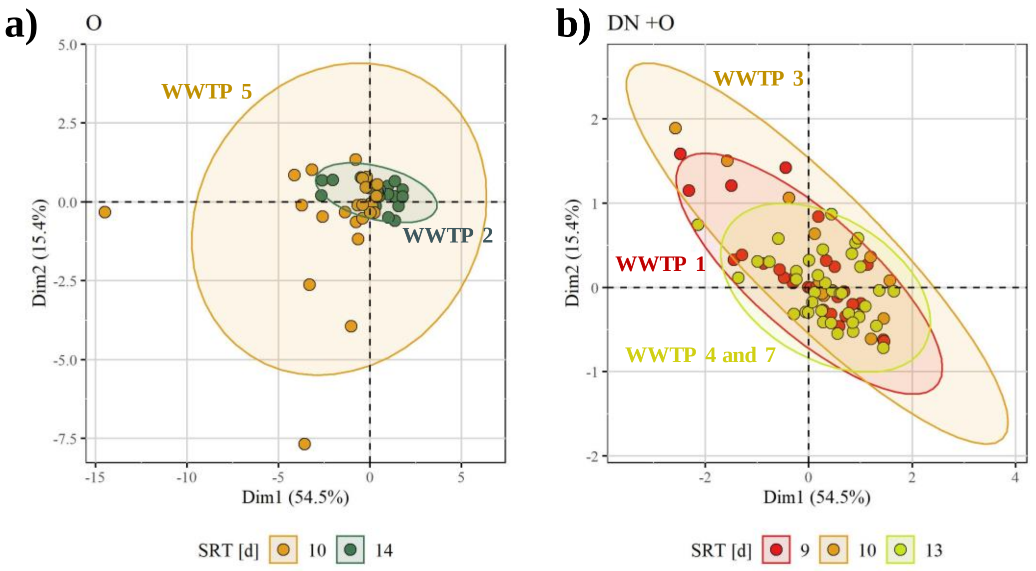


Figure 3 Individual plot considering separately: a) WWTPs equipped only with aerobic activated sludge treatment, b) WWTPs equipped with anoxic followed by aerobic activated sludge treatment. The individuals are coloured based on SRT.

Among the plants where the biological compartment was composed of DN+O (see Figure 3b), the most stable performances were observed in WWTP4 and WWTP7 which were operated at the highest SRT (i.e. 13 d). The most dispersed values were found for WWTP3 whose SRT was about 10 d. WWTP6 showed an intermediate dispersion of the data: although the lowest SRT (i.e. 9 d), the presence of the tertiary treatment (which is absent in the above-mentioned WWTPs) might have contributed to equalization.

3.4. Correlation of CECs with traditional water quality parameters

The PCA was also applied to assess any correlation of CECs with the water quality parameters traditionally measured on a routine-basis in the wastewater treatment plants. The results are reported as correlation circles in Figure 4. This evaluation can be useful to understand if specific management strategies, implemented in the water treatment line of existing WWTPs, might also contribute to improving the CECs removal.

In Figure 4a, related to the CECs belonging to the high removal category, 74% of the data variance is explained by the two main dimensions and all the variables are well represented by the PCA, since the cos2 is above 0.55, with the only exception of NO_3^--N and P_{tot}.

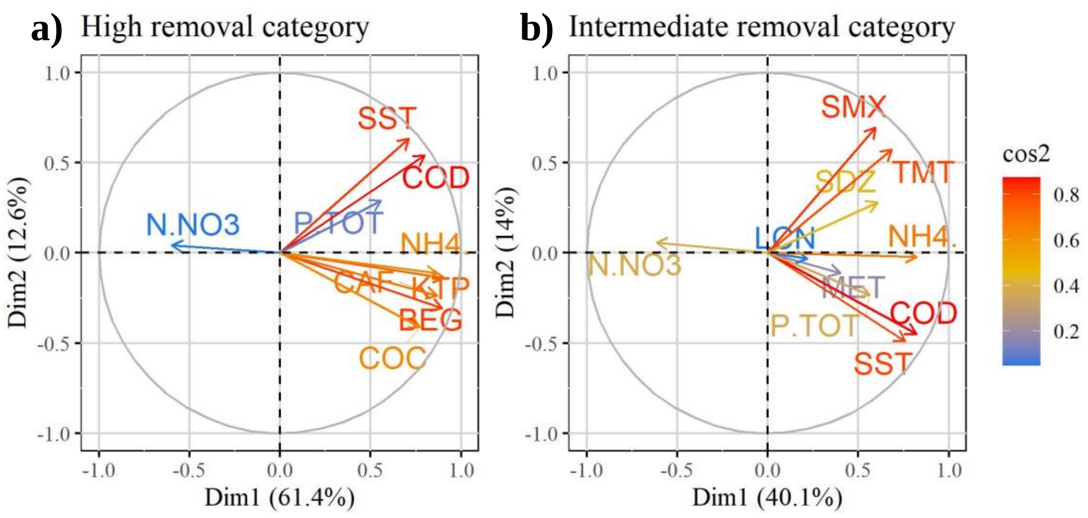


Figure 4 Correlation circle obtained through PCA on the measured concentrations of: a) CECs of the high removal category and water quality parameters and b) CECs of the intermediate removal category and water quality parameters.

The plot of Figure 4a shows a significant positive correlation of the concentrations of CAF, KTP, BEG and COC with NH_4^+-N, considering both influent and effluent. This evidence can be explained by taking into account that CAF, KTP, BEG and COC are mainly removed in the biological compartment as well as ammonia nitrogen (Di Marcantonio et al., 2021; Metcalf & Eddy, 2015; Rigueto et al., 2020). The positive correlation with ammonia suggests that CECs degradation is accomplished along with nitrification. Indeed, several studies proved that the removal of KTP and BEG is enhanced by ammonia-oxidizing bacteria, suggesting the importance of nitrification in the degradation of these compounds (Chiavola et al., 2019; Maeng et al., 2013; Tran et al., 2009). Additionally, the main pathway for most CECs elimination was found to be via cometabolism with ammonia being utilized as the main substrate/energy source (Nsenga Kumwimba and Meng, 2019). Some other studies proved that biodegradable contaminants, such as CAF and KTP, are degraded in either presence or absence of nitrification inhibitor (i.e. N-Allylthiourea), suggesting that the removal can be carried out by means of the microbial activity regardless of the presence of ammonia-oxidizing bacteria (Falås et al., 2016; Park et al., 2017).

Figure 4b shows the results of the PCA applied to the concentrations of CECs falling in the intermediate removal category (i.e. MET, LCN, SMX, TMT, SDZ) and the water quality parameters. The two main dimensions explain most of the variance of the data (i.e. 54.1%), even if the robustness of the statistical analysis is lower than in the above evaluation (Figure 4a). For SMX, TMT and SDZ, no correlation with COD, SST and P_{tot}, and a partial direct correlation with ammonia was found. These results agree with the moderate biodegradability of these CECs, which are only slightly removed by the conventional activated sludge process. A removal percentage achieved by this compartment equal to 47%, 59% and 50% for SMX, TMT and SDZ, respectively, was referred by Di Marcantonio et al. (2021). SMX and TMT were also defined as moderately biodegradable in the activated sludge processes by Tran et al. (2018) based on the biodegradation rate constant (k_{biol}): 0.1-5 L/gMLSS d and 0.05 – 5.04 L/gMLSS d for SMX and TMT, respectively. The LCN and MET behaviour was positively correlated with SST, P_{tot} and particularly with COD: however, they are characterized by a low value of the cos2, which indicates that the significance of these correlations is not particularly reliable. However, a previous study on MET also observed a correlation with the COD removal pathway in an aerobic activated sludge process, suggesting a co-metabolism operated mainly by heterotroph bacteria (Boni et al., 2018).

3.5. Environmental risk assessment (ERA)

The ERA was carried out to evaluate whether the residual concentration of CECs in the final effluent of the WWTPs can pose a risk to the receiving ecosystems. As mentioned above, ERA was not performed for the CECs with F_D below 10% (i.e. THC-COOH, APT, WRF, SDM). However, it is important to notice that for THC-COOH, the MRL of the analytical method (0.1 μg/L) was much higher than its PNEC as reported in Table S.M. *3* (0.005 μg/L). Therefore, the higher MRL compared to the PNEC did not allow for the evaluation of the risk eventually posed by THC-COOH. Thus, further evaluations should be performed on this compound. The four plots reported in Figure 5 differed for the values of the CECs used as MEC (i.e. measured environmental concentration) and for the value used as D. Specifically, the median effluent value and the 95th percentile were applied to evaluate the average and worst-case, respectively. Regarding D, the assessment was carried out with a value (S.S.) determined as site-specific for each WWTP considering the flow rate of both the treated effluent and the receiving water body, and also the default value equal to 10 as proposed by the EU guidelines. The RQ was considered acceptable if below 1 and it is defined as: high risk for RQs > 1, medium risk for 0.1 ≤ RQs ≤ 1, and low risk for RQ ≤ 0.1.

The results in terms of RQ corresponding to each case are reported in Table S.M. 6.

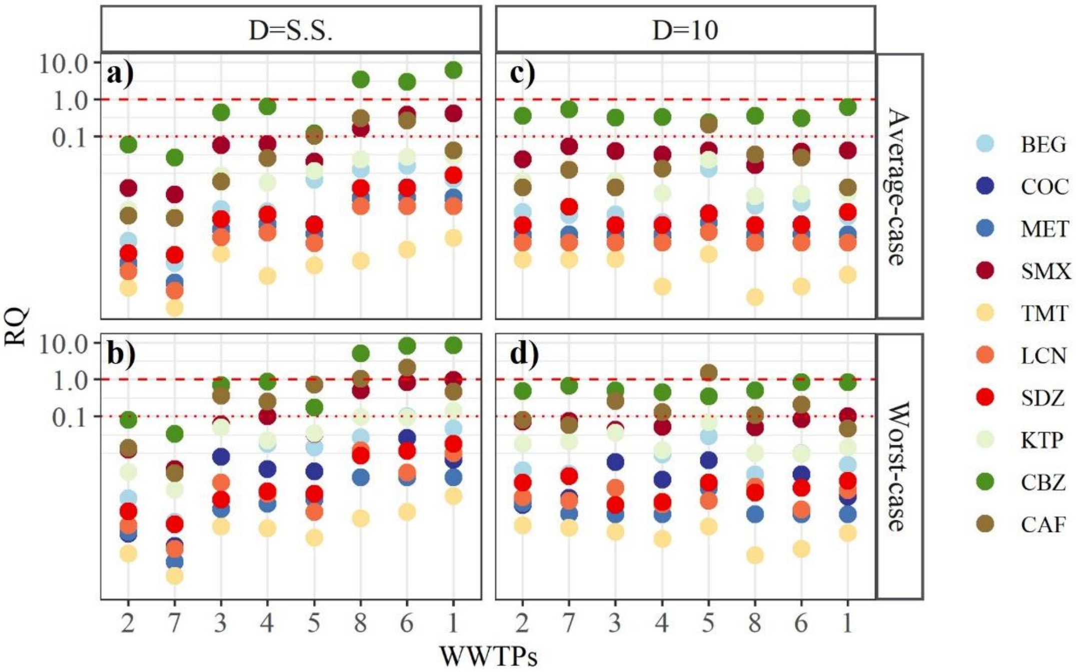


Figure 5 Risk quotient resulted from the ERA assuming different values of MEC in the effluent and D: a) D=S.S., MEC=median value; b) D=S.S., MEC=95th percentile value; c) D=10, MEC=median value; d) D=10, MEC=95th percentile value.

The results obtained by the site-specific ERA (Figure 5a,b) highlight that CBZ was the contaminant posing the higher and more frequent risk in the investigated plants. For instance, RQ values for CBZ resulted to be in the range indicating a high risk for the environment (according to the European Medicines Agency, 2018) in WWTP1, WWTP6 and WWTP8. A medium acceptable risk (i.e. 0.1<RQ<1) was found in WWTP3, WWTP4 and WWTP5.

Among the other contaminants, CAF represented a source of risk only in the worst scenario: the risk was considered high in the effluent of WWTP6 and WWTP8, and medium acceptable in the effluent of WWTP1, WWTP3, WWTP4 and WWTP5. For the other CECs, the risk was always acceptable.

CBZ and CAF were the contaminants found at the highest concentration in the effluent among the CECs investigated. CAF was very abundant in the influent and therefore, although high removal efficiency was achieved by all plants, a high concentration was still found in the effluent. CBZ was the contaminant removed to the least extent, in accordance with the scientific literature which widely reports its refractory nature. These can be the reasons for the high risk measured in the effluent of some plants.

The results obtained by application of ERA using the default value D=10 (Figure 5c,d) show a significant reduction of the RQ values, for all the contaminants, compared to the site-specific assessment above described. Only CAF in WWTP5 and for the worst scenario poses a high risk (RQ>1). Indeed, the application of a common dilution factor may contribute to misestimating the risk quotient (Aemig et al., 2021).

The major finding obtained by this comparison is that the environmental risk is strictly related to the value assumed for the dilution factor (D). Indeed, the highest values of RQ were observed for those plants where D was posed equal to 1 since the flow rate of the receiving river essentially consisted of the effluent (i.e. WWTP1, WWTP6 and WWTP8). This is very clear by comparing WWTP8 and WWTP5 in the site-specific ERA. The former showed the best removal of the monitored CECs, although the environmental risk was high for CBZ and CAF (only in the worst-case) and medium for CAF and SMX: these patterns can be ascribed to the low dilution factor, i.e. D=1. By contrast, the WWTP5 showed the lowest removal efficiency for most of the CECs, while the environmental risk always resulted to be acceptable (even if classified as a medium for CBZ and CAF): the high value of S.S. D (equal to 20) may be responsible for this result.

The importance of the best choice of the dilution factor was also proved by Abily et al. (2021). Indeed, they highlighted the relevance of this parameter for its significant and positive correlation with the ecological status of European rivers. Besides, Link et al. (2017) demonstrated that the assumption of the dilution factor equal to 10 mainly provides an underestimation of the environmental concentration and thus of the environmental risk. Nonetheless, many studies that applied the same ERA procedure never reported the site-specific value of the dilution factor (Patrolecco et al., 2015; Rivera-Jaimes et al., 2018). In the present study, the site-specific D was determined considering the average annual flow rate of the receiving water body; it would be important also to verify the impact on the final risk due to the seasonal variation of the river flow rate.

Finally, it is worth noting that the results of ERA are also strictly dependent on the selection of the PNEC values. The present study used the lowest PNEC for surface water as proposed by the NORMAN Network. Rivera-Jaimes et al. (2018) performed the ERA for several pharmaceuticals in plants located in Mexico and calculated the PNEC as the ratio between the lowest acute toxicity value found for three selected trophic levels and a pertinent assessment factor posed equal to 1000. They obtained quite different results from the present site-specific ERA: no risk for CBZ, likely due to the high value of PNEC used (i.e. 2.5 μg/L vs 0.05 μg/L), and a relevant risk for KTP and TMT whose PNECs were lower (i.e. 0.03 μg/L and 0.16 μg/L, respectively) than the values applied in the present study (i.e. 2.1 μg/L and 120 μg/L, respectively).

4. Conclusions

The study provides a comparative evaluation of the performances of 8 WWTPs, representative of different layouts, treatment capacity, biological process and operating parameters, concerning the removal of 14 CECs. The results were then used for the ERA implementation.

The main conclusions of the study can be summarized as follows:

- the wider the sewage catchment area the higher the equalization effect on all the influent characteristics including also CECs concentrations;
- a high removal (a median value above 80%) was always observed for CAF, BEG, KTP and COC, regardless of the differences among the WWTPs;
- an intermediate removal (20%<R<80%) was found for all the antibiotics and MET, with the highest reduction achieved by the MBR;
- CBZ was removed at the lowest extent by all the WWTPs, with no relevant difference among them;
- the behaviour of CECs, particularly of CAF, BEG, KTP and COC, was positively correlated with that of ammonia, thus suggesting that improving the nitrification process might also enhance CECs removal;
- the type of biological process was depicted as the main impacting factor on CECs removal, although a slight influence of the SRT was also observed;
- results of ERA highlighted a high risk for the plants characterized by no dilution of the final effluent, for the worst-case CAF and always for CBZ;
- for the other CECs, the risk was found to be always acceptable.

Overall, the investigation showed the need to implement specific measures (additional treatment stages) to reduce the risk when high concentrations of CECs are still present in the effluent (such as for refractory compounds like CBZ and pollutants entering the plants at very high concentrations like CAF). However, the risk must be assessed considering the site-specific value of the dilution factor, which in turn requires to carry hydraulic studies on the receiving water bodies. Additionally, the identification of univocal PNEC values is needed to make the assessments comparable.

These findings highlight that when implementing the ERA for CECs, it is of paramount importance to properly select the values of PNEC and D, to obtain reliable and site-specific outcomes. Only by proper care of these parameters, technically-costly effective measures can be implemented case-by-case to reduce the risk to the environment.

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Tables

Table 1 Main characteristics of the monitored WWTPs and number of sampling days (Samples). Abbreviations: SRT= Sludge Retention Time, QWWTP= average flow rate of the WWTP, Qrec= average flow rate of the receiving water body, Ca= sewage catchment area, PEau= Authorized treatment capacity, BS=Bar Screening, DD=Degreasing-Degritting, PS=Primary Sedimentation, O=Aerobic activated sludge process (oxidation), DN=Anoxic activated sludge process (denitrification), SS=Secondary Sedimentation, MBR=Membrane Biological Reactor (ultrafiltration), MBBR=Moving Bed Biofilm Reactor, III=Sand filtration followed by UV disinfection, DC=Hypochlorite disinfection, DP=Peracetic acid disinfection.

Table 2 Median removal efficiencies for each CEC and WWTP: in italic the low removal (R ≤20%), in bold the high removal (R ≥80%) and underlined the intermediate removal (20%< R<80%).

Figures

Figure 1 Removal efficiency considering the CECs belonging to the intermediate removal category. The letters on the top of the plot indicate significant statistical differences between data sets via Kruskal ($p \leq 0.05$) and post hoc pairwise Wilcoxon tests; boxes labelled with the same letter are not significantly different.

Figure 2 Individual plot obtained through PCA of the removal efficiency of intermediate category. The individuals are coloured based on the type of treatment layout

Figure 3 Individual plot considering separately: a) WWTPs equipped only with aerobic activated sludge treatment, b) WWTPs equipped with anoxic followed by aerobic activated sludge treatment. The individuals are coloured based on SRT.

Figure 4 Correlation circle obtained through PCA on the measured concentrations of: a) CECs of the high removal category and water quality parameters and b) CECs of the intermediate removal category and water quality parameters.

Figure 5 Risk quotient resulted from the ERA assuming different values of MEC in the effluent and D: a) D=S.S., MEC=median value; b) D=S.S., MEC=95th percentile value; c) D=10, MEC=median value; d) D=10, MEC=95th percentile value.

Supplementary materials

Figure S.M. 1 Map of the WWTPs concerning the correspondent sewage catchment areas and the main hydrographic network according to bottom-up hierarchy of stream (i.e. orders 1 and 2 of the Hack stream order).

Table S.M. 1 Characterization of the influent to the WWTPs: Minimum, median and maximum concentration (mg/L) of COD, SST, Ptot, NH4+-N.

Table S.M. 2 Main chemical-physical characteristics of the target CECs: CAS n.=CAS number; Formula=Chemical formula; MW=Molecular Weight; pK_a=-log of acid dissociation constant; Log K_{ow}=log of octanol-water partition coefficient; K_H=Henry's law constant; Log K_{oc}=log of organic carbon-water partition coefficient; S=water solubility; p_v= vapour pressure (“NORMAN Database System,” 2020; Williams et al., 2017).

Table S.M. 3 PNEC values used for the Environmental Risk Assessment.

Table S.M. 4 Minimum, median and maximum CECs concentration (µg/L) measured in the influent and effluents to the WWTPs and the correspondent frequency of detection (reported between brackets).

Table S.M. 5 Median removal efficiencies of the water quality parameters.

Table S.M. 6 Values of the RQ obtained through the ERA, for the average-case and worst-case and considering both the site-specific dilution factor (D=S.S.) and the default value (D=10). The environmental risk was classified as follows: high risk (red), medium risk (yellow), low or negligible risk (green).

A step forward on site-specific environmental risk assessment and insight into the main influencing factors of CECs removal from wastewater ~~Statistical evaluation of the effects of WWTPs characteristics on the removal of Contaminants of Emerging Concern and site-specific Environmental Risk Assessment~~

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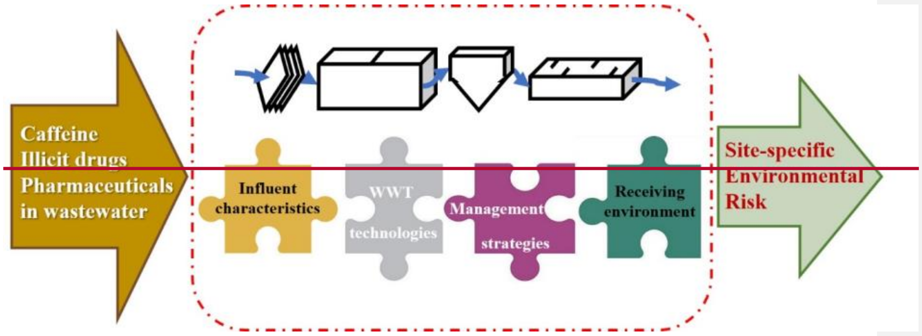
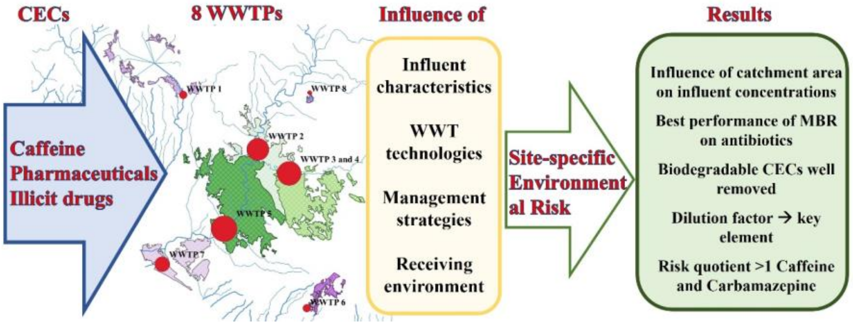
Abstract

The presence of Contaminants of Emerging Concern (CECs) in water systems has been recognized as a potential source of risk for human health and the ecosystem. The present paper aims at evaluating the effects of different characteristics of full-scale Wastewater Treatment Plants (WWTPs) on the removal of 14 selected CECs belonging to the classes of caffeine, illicit drugs and pharmaceuticals. Particularly, the investigated plants differed because of the treatment lay-out, the type of biological process, the value of the operating parameters, the fate of the treated effluent (i.e. release into ~~a~~ surface water or reuse), and the treatment capacity. The activity consisted of measuring concentrations of the selected CECs and also traditional water quality parameters (i.e. COD, phosphorous, nitrogen species and TSS) in the influent and effluent of 8 plants. The study highlights that biodegradable CECs (cocaine, methamphetamine, amphetamine, benzoylecgonine, 11-nor-9carboxy-Δ9-THC, lincomycin, trimethoprim, sulfamethoxazole, sulfadiazine, sulfadimethoxine, carbamazepine, ketoprofen, warfarin and caffeine) were well removed by all the WWTPs, with the best performance achieved by the MBR for antibiotics. Carbamazepine was removed at the lowest extent by all the WWTPs. The environmental risk assessed by using the site-specific value of the dilution factor resulted to be high in 3 out of 8 WWTPs for carbamazepine and less frequently for caffeine. However, the risk was reduced when the dilution factor was assumed equal to the default value of 10 as proposed by EU guidelines. Therefore, a specific determination of this factor is needed taking into account the hydraulic characteristics of the receiving water body.

Graphical Abstract





Keywords Advanced statistical analyses, Caffeine, Dilution factor, Illicit drugs, Pharmaceuticals, Principal component analysis ~~Biological process, Caffeine, Dilution factor, Emerging contaminants, Illicit drugs, Pharmaceuticals~~

1. Introduction

Wastewaters contain a huge variety of micropollutants, many of which have been classified as Contaminants of Emerging Concern (CECs) or Organic Micropollutants. Disinfection by-products, pharmaceuticals, personal care products, steroids, licit and illicit drugs are among the more widely diffused contaminants classified as CECs (Aemig et al., 2021). The studies conducted on these pollutants have demonstrated that they are widely present in ~~the~~ water bodies (Archer et al., 2017; Barchiesi et al., 2021; OECD, 2019). Indeed, they enter the sewage collection systems as a consequence of many sources, such as the release from the domestic use of household chemicals (detergents, cleaning products, textile fibres and personal care products) and human consumption, improper disposal, as well as through urban runoff (Parida et al., 2021). Through the sewage network, the CECs reach the Urban Wastewater Treatment Plants (UWWTPs) where they undergo the same processes as the other pollutants. However, since UWWTPs are not specifically designed to accomplish the CECs removal, many of them remain in the treated effluent and then are transferred to the water bodies. The communication of the Commission of 2019, “European Union Strategic Approach to Pharmaceuticals in the Environment” (adopted by the European Parliament in 2020) stresses that pharmaceuticals reach the environment through excreted and unused products entering sewage collection systems and WWTPs (European Commission, 2019a; European Parliament, 2020). The same concern issue was also highlighted in the conclusions of the document “Evaluation of the Urban Wastewater Treatment Directive (UWWTD)” which reports that contaminants of emerging concern, which are not included in the scope of the actual UWWTD, are receiving more attention since the treatment required under the directive reduces such pollutants of wastewater to some extent but does not target them directly neither remove satisfactorily (European Commission, 2019b). The Environmental Quality Standards (EQSs) on surface water already consider some of the CECs (The European Parliament and the Council, 2013).

The definition of the EQS by the EU legislation was supported and guided by the Environmental Risk Assessment (ERA), based on the data available on the occurrence of selected CECs and their ecotoxicological effects in the receiving environment (EU, 2003). The application of the ERA approach is now recognized as the most suitable tool to establish the maximum allowable concentrations and consequently to identify and design the reduction measures to implement for contrasting harmful substances. However, firstly a comprehensive knowledge of the efficiency achieved by the different treatment units of the WWTPs in the CECs removal is needed, to provide ~~the~~ data about the type of contaminants which are still found in the effluent and their concentration (Kumar et al., 2022). Afterwards, it can be evaluated by the ERA if the residual effluent concentrations represent a real risk for the environment and human health. Finally, the reduction measures can be identified if the ERA shows the presence of an unacceptable risk (Bailey et al., 2018).

Previous studies showed that the CECs removal by the existing WWTPs ~~are~~ is dependent on several factors, such as physicochemical properties of the pollutants, type of treatment process, operating parameters (hydraulic retention time (HRT), sludge retention time (SRT), pH, temperature, etc.), reactor configuration, microorganism type (Parida et al., 2021). For instance, the removal of highly polar substances, such as most pharmaceuticals, is mainly achieved by the biological oxidation carried out by microorganisms. Recent studies have shown that the Moving Bed Biofilm Reactor (MBBR) and Membrane Biological Reactor (MBR) are more efficient than the conventional activated sludge process followed by secondary sedimentation. The removals of particularly recalcitrant compounds, such as carbamazepine and sulfamethoxazole, in the conventional activated sludge process are usually lower than MBR and MBBR, e.g. they range from -110% - 3% for carbamazepine and (Krzeminski et al., 2019) from 32% - 98% for sulfamethoxazole (Couto et al., 2019; Verlicchi, 2012). However, most of the studies on MBBR ~~was~~ were carried out at lab-scale (Krzeminski et al., 2019): e.g. Zhang et al. (2020) observed removal of sulfadiazine and carbamazepine in a laboratory MBBR equal to 61% and 28%, respectively. The MBRs, which are characterized by higher values of SRT than conventional activated sludge, showed

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varying performance in the CECs removal: for instance, removal of sulfamethoxazole, carbamazepine and caffeine fell in the range of 75%–95%, whereas that of trimethoprim and some pesticides was below 40% (Ahmed et al., 2017). According to the Swiss VSA Platform "Process Engineering Micropollutants", the best available technologies for WWTPs upgrading to enhance CECs removal are ~~the~~ activated carbon adsorption and ozonation ("VSA Micropoll," 2018). However, the tertiary treatments commonly applied, such as sand filtration and UV or peracetic acid or hypochlorite disinfection, can provide a certain abatement of CECs concentration (Rizzo et al., 2020). Cai et al. (2017) achieved ~~a~~ removal of seven pharmaceuticals below 11% using 1 mg/L of peracetic acid under laboratory conditions; additionally, a significant increase was observed after the activation of the oxidant by UV. Similar findings were obtained by Wang et al. (2016) using UV combined with chlorine as disinfectant. This investigation belongs to a wide research activity carried out since 2017 having the aim to assess the occurrence and removal of CECs in full-scale Wastewater Treatment Plants for domestic sewage ~~(Di Marcantonio et al., 2020b)~~ (Di Marcantonio et al., 2020b). The present study aims to provide ~~a~~ better knowledge on the effects of different treatment layouts and other characteristics of full-scale wastewater treatment plants on the removal of CECs: particularly, 8 WWTPs were selected for the study based on different characteristics of the water treatment processes, extension of the area served by the sewage network feeding the plant and type of final disposal of the treated water. The CECs selected for the study belong to the classes of illicit drugs and of pharmaceuticals (including antibiotics and caffeine). The traditional water quality parameters were also monitored, and their removal correlated with that of CECs. The environmental risk assessment (ERA) was carried out following the procedure outlined by the European Medicines Agency (2018) and considering the residual concentrations measured in the treated effluents. In addition to the standard procedure, the dilution effects of the effluent in the receiving water bodies were also taken into account in the analysis. Therefore, the results of the ERA were more site-specific, which represents an innovative element of the present study with respect to the past. Additionally, the ERA were performed considering two contamination scenarios: i.e. the average-case and the worst-case. The former (average) can be representative of chronic exposure whereas the latter (worst) of the acute exposure. Therefore, these data can be useful as a reference for future ecotoxicological studies.

The other novelty is represented by the comparison of full-scale WWTPs using different biological processes, such as activated sludge, MBR and MBBR, and also different tertiary treatments. Finally, the

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data were collected for a time-frame of observation of 2 years, thus allowing to catch different weather and influent conditions~~Finally, the data were collected for a long time-frame of observation (i.e. 2 years) thus making the results more statistically relevant since considered different weather and influent conditions~~.

2. Materials and methods

2.1. *WWTPs*

The WWTPs of the present investigation were selected among the wide list of 76 plants considered in the study by Di Marcantonio et al. (2020b). They are representative of different water treatment processes, type of final disposal of the treated water and characteristics and extension of the area served by the sewage network feeding the plants. The main characteristics of these plants are reported in Table 1, including~~:~~ the treatment capacity (as average influent flow rate, Q_{WWTP}, and authorized treatment capacity, PE_{au}), the average sludge retention time (SRT), the average flow rate of the receiving water body at the point of the treated effluent release (Q_{rec}) and water treatment line lay-out. Some of the WWTPs (i.e. WWTP 1, WWTP 6, WWTP 8) release the treated effluent into a stream which is characterized by a wide flow rate variation from dry to wet season. Precautionary, in these cases, ~~the~~ Italian environmental legislation assumes that the main flow rate of the stream is associated ~~to~~ with the effluent flow rate from the plant. As a consequence, the acceptable maximum concentrations as established by the regulation are lower as compared to the release into rivers. Therefore, the flow rate of the receiving stream, Q_{rec}, was assumed to be 0 in the Environmental Risk Assessment performed on these WWTPs. The characterization of the influent ~~to~~ on the investigated WWTPs (as concentration of total suspended solids, chemical oxygen demand, ammonium nitrogen and total phosphorus) is reported Table S.M. *1*.

Table 1 Main characteristics of the monitored WWTPs and number of sampling days (Samples). Abbreviations: SRT= Sludge Retention Time, QWWTP= average flow rate of the WWTP, Qrec= average flow rate of the receiving water body, Ca= sewage catchment area, PE$_{au}$= Authorized treatment capacity, BS=Bar Screening, DD=Degreasing-Degritting, PS=Primary Sedimentation, O=Aerobic activated sludge process (oxidation), DN=Anoxic activated sludge process (denitrification), *SS=Secondary Sedimentation, MBR=Membrane Biological Reactor (ultrafiltration), MBBR=Moving Bed Biofilm Reactor, III=Sand filtration followed by UV disinfection, DC=Hypochlorite disinfection, DP=Peracetic acid disinfection~~Main characteristics of the monitored WWTPs and number of sampling days (Samples). Abbreviations: BS=Bar Screening, DD=Degreasing-Degritting, PS=Primary Sedimentation, O=Aerobic activated sludge process (oxidation), DN=Anoxic activated sludge process (denitrification), SS=Secondary Sedimentation, MBR=Membrane Biological Reactor (ultrafiltration), MBBR=Moving Bed Biofilm Reactor, III=Sand filtration followed by UV disinfection, DC=Hypochlorite disinfection, DP=Peracetic acid disinfection~~.*

WWTPs	**SRT [d]**	**Q_{WWTP} [mc/s]**	**Q_{rec} [mc/s]**	**Ca [sqkm]**	**PE_{au} [n.]**	**Samples [n.]**	**BS**	**DD**	**PS**	**DN**	**O**	**SS**	**MBBR**	**MBR**	**III**	**DC**	**DP**
1	9	0.22	0	22	90 000	31	●	●	●	●	●	●			●	●	
2	14	2.82	165	81	300 000	23	●	●	●		●	●				●	
3	10	1.22	7.5	44	600 000	11	●	●	●	●	●	●				●	
4	13	1.79	7.5	65	350 000	17	●	●	●	●	●	●				●	
5	10	9.2	177	195	780 000	24	●	●	●		●	●					●
6	-	0.16	0	14	1 090 000	18	●	●					●				●
7	13	0.93	188	53	90 000	20	●	●	●	●	●	●				●	
8	27	0.05	0	2	18 000	17	●	●		●	●	●		●			

~~**WWTPs**~~	~~**SRT [d]**~~	~~**Q_{WWTP} [mc/s]**~~	~~**Q_{rec} [mc/s]**~~	~~**Samples [n.]**~~	~~**BS**~~	~~**DD**~~	~~**PS**~~	~~**DN**~~	~~**O+SS**~~	~~**MBBR**~~	~~**MBR**~~	~~**III**~~	~~**DC**~~	~~**DP**~~
~~**1**~~	~~9~~	~~0.22~~	~~0~~	~~31~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~			~~●~~	~~●~~	
~~**2**~~	~~14~~	~~2.82~~	~~165~~	~~23~~	~~●~~	~~●~~	~~●~~		~~●~~				~~●~~	
~~**3**~~	~~10~~	~~1.22~~	~~7.5~~	~~11~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~				~~●~~	
~~**4**~~	~~13~~	~~1.79~~	~~7.5~~	~~17~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~				~~●~~	
~~**5**~~	~~10~~	~~9.2~~	~~177~~	~~24~~	~~●~~	~~●~~	~~●~~		~~●~~					~~●~~
~~**6**~~	-	~~0.16~~	~~0~~	~~18~~	~~●~~	~~●~~				~~●~~				~~●~~
~~**7**~~	~~13~~	~~0.93~~	~~188~~	~~20~~	~~●~~	~~●~~	~~●~~	~~●~~	~~●~~				~~●~~	
~~**8**~~	~~27~~	~~0.05~~	~~0~~	~~17~~	~~●~~	~~●~~		~~●~~	~~●~~		~~●~~			

~~With regard~~ Concerning ~~the~~ WWTP 6, the biological compartment consists of an MBBR equipped with the AnoxKaldnes technology; it is composed ~~by~~ of three ~~in~~ parallel lines, each one made up of two anoxic tanks followed by three aerobic reactors. Following, the Actiflo Turbo$^{®}$ (i.e. coagulation-flocculation and dephosphation) is present with the addition of ferric chloride, polyelectrolyte and micro-sand.

~~1.1.~~2.2. *Sampling campaign*

The monitoring campaign was conducted from January 2020 to December 2021 and consisted of 161 sampling days for an overall number of collected samples equal to 322. Autosamplers were used for the collection of 24-hourly mixed samples from the influent and effluent almost every month in each plant. The total number of sampling days for each WWTP is reported in Table 1. A 1 L Nalgene bottle was used to collect the sample, which was then transferred to the laboratory for pre-treatment and finally stored at T = 4 °C until analysis.

The following 14 CECs, belonging to the classes of pharmaceuticals and illicit drugs, were measured in each sample: cocaine (COC), methamphetamine (MET), amphetamine (APT), benzoylecgonine (BEG), 11-nor-9carboxy- Δ9-THC (THC-COOH), lincomycin (LCN), trimethoprim (TMT)), sulfamethoxazole (SMX), sulfadiazine (SDZ), sulfadimethoxine (SDM), carbamazepine (CBZ), ketoprofen (KTP), warfarin (WFR) and caffeine (CAF). In Table S.M. *2* were reported the main physico-chemical properties of the target CECs. In addition, the following traditional water quality parameters were determined on each sample: total suspended solids (TSS), chemical oxygen demand (COD), ammonium nitrogen, nitrite and nitrate nitrogen (NH_4^+-N, NO_2^--N and NO_3^--N, respectively) and total phosphorus (Ptot).

~~1.2.~~2.3. *Analytical methods*

The water quality parameters were measured by following the standard methods: TSS through APAT CNR IRSA 2090 B Man 29/2003, COD through APAT CNR IRSA 5135 Man 29/2003, P_{tot} through M.U. 2252:08/1, NH_4^+−N, NO_2^-−N, and NO_3^-−N through Standard Methods 4500 2, 4500H and 4500 1, respectively (APAT IRSA-CNR, 2003; APHA, 2017).

The CECs were quantified using ultrahigh performance liquid chromatography coupled with tandem mass spectrometry. The analytical method was specifically developed by the same research group and validated for most analytes by ACCREDIA. All details are reported in a previous paper (Di Marcantonio et al., 2021). CEC standard solutions (COC, BE, THC-COOH, APT, MET, CBZ, KTP, SMX, TMT, LCN, SDM, SDZ, WFR, CAF) and internal standards Cocaine-d3 and carbamazepine-d10 were purchased from Sigma-Aldrich Company (Gillingham, UK) at a concentration of 100 µg/ml in agent methanol. The Minimum Reporting Levels (MRL) were posed equal to the following values: 0.05 µg/L for KTP, 0.1 µg/L for THC-COOH, APT, CAF and 0.01 µg/L for the other contaminants.

~~1.3.~~2.4. *Calculation methods*

Frequency of detection (Fd) and removal efficiencies (R) were calculated according to Di Marcantonio et al. (2020). When the concentration resulted to be below the MRL, the value was set equal to half of the MRL in the calculation of statistical descriptors and removal efficiency and application of ERA (European Commission, 2009). Additionally, removal was not calculated if the influent and effluent concentrations were both equal to MRL. Indeed, the daily median removal could be calculated when the concentration was above MRL at least in the influent samples.

The significance of the differences between the removal efficiency achieved by each WWTP, ~~with respect to~~for the different target compounds, was statistically assessed. The normality of the series of data ~~were~~was, firstly, checked through the Shapiro-Wilk normality test and it was never satisfied. As consequence, the non-parametric Kruskal-Wallis Test was applied followed by the pairwise Wilcox post-hoc test. The evaluation was carried out through the R package "stats" (R Core Team, 2021). The results of the post-hoc test (i.e. p-value adjusted according to the Benjamini and Hochberg method) were reported in the corresponding plot labelling the boxes not significantly different by the same letter (Benjamini and Hochberg, 1995).

The whole data set was processed through the Principal Component Analysis (PCA), ~~in order~~ to reduce their dimensionality and to extract ~~a~~ further insight into the effects of the different treatment stages. The PCA was performed ~~by means of~~using the R package "Fac- toMineR" (Lê et al., 2008). Specifically, the PCA was applied to the removal efficiency data, to find out possible clusters and evidence about the biological technology and other characteristics of the WWTPs. Additionally, the correlation ~~among~~ between the concentrations of water quality parameters and CECs was also assessed by PCA and reported as a correlation circle. The analysis was performed excluding the analytes detected in less than 10% of the samples for statistical reasons (i.e. THC-COOH, APT, WRF, SDM, NO_2^--N). More details about PCA interpretation are reported in Di Marcantonio et al. (2021).

~~1.4.~~2.5. *Environmental Risk Assessment*

The ERA was performed for each WWTP considering the residual concentrations of the CECs in the effluent and the hydraulic characteristics of the receiving water bodies. The assessment procedure proposed by the Environmental Medicine Agency was applied with some more implementations (European Medicines Agency, 2018).

The risk quotient (RQ) was calculated for each contaminant using the following equation:

$$RQ\ [/] = \frac{MEC/D}{PNEC} \quad (1)$$

where MEC is the measured environmental concentration, D is the dilution factor and PNEC is the predicted ~~no~~ no-effect concentration. If the RQ is < 1, the contaminant is unlikely to represent a risk to surface water. The values of PNEC, as reported in Table S.M. *3*, were mainly collected from the open-access NORMAN Database System and derived using ecotoxicity data for freshwater species (Norman Network, 2022). The ERA was carried out for two different contamination scenarios (i.e., average and worst case) depending on the effluent concentrations assumed as MECs: specifically, the median value for the average scenario and the 95th percentile for the worst scenario. MEC values were divided by the dilution factor ~~in order~~ to take into account the effect on the CECs concentrations of the effluent release into the receiving waters, which represents the actual exposure to the ecosystem. The suggested value of D is equal to 10, referred to as default D (European Medicines Agency, 2018); however, a site-specific estimation of D (D=S.S) allows a more accurate assessment of the environmental risk. Hence, D was defined, as in the equation reported below, considering the average water body flow rate (Q_{rec}) and the average WWTP effluent flow rate (Q_{WWTP}), which was assumed equal to the average influent flow rate (European Commission, 2003):

$$D\ [/] = \frac{Q_{WWTP} + Q_{rec}}{Q_{WWTP}} \quad (2)$$

For WWTP1, WWTP6 and WWTP8, as mentioned before, Q_{rec} was assumed to be equal to 0; as a consequence, D was settled equal to 1.

Based on these assumptions and the values of Q_{rec} and Q_{WWTP} reported in Table 1, the dilution factors for each WWTP were found to be as follows: 1, 60, 7, 5, 20, 1, 203, 1 ~~1, 7, 5, 203, 60, 20, 1, 1~~ for WWTP1, WWTP2, WWTP3, WWTP4, WWTP5, WWTP6, WWTP7 and WWTP8, respectively.

The ERA was performed only for those CECs detected in more than 10% of the samples, ~~in order~~ to have ~~a~~ statistical reliability of the results.

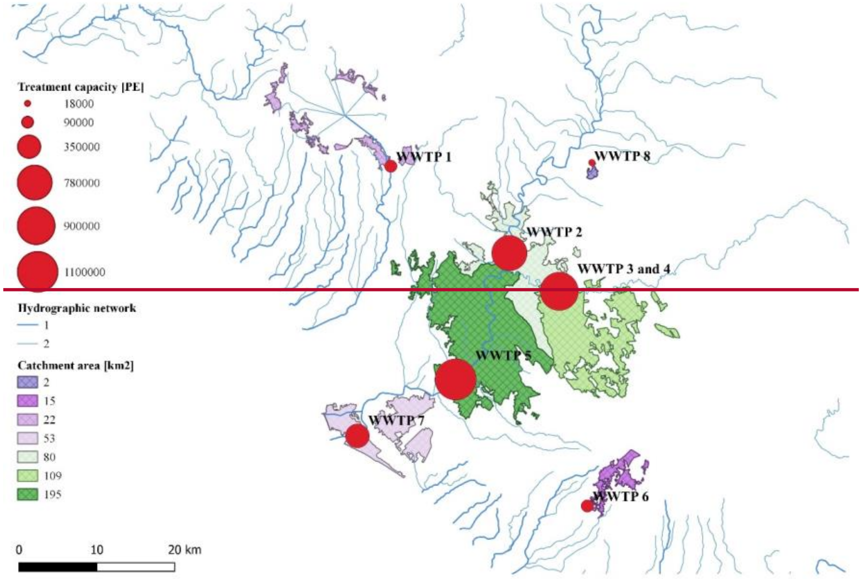
~~2.~~3. Results

~~2.1.~~3.1. Measured concentrations

The results of the sampling campaign on the influent and effluent of the eight WWTPs were summarized as minimum, median ad maximum values and frequency of detection (F_D), as reported in Table S.M. 4. CAF was the pollutant found at the highest concentration in the influent of all the WWTPs, followed by BEG and KTP (i.e. median values equal to 24.10 µg/L, 1.73 µg/L and 1.62 µg/L, respectively). However, CAF values were more than 10 times higher than BEG and KTP. ~~About~~ Regarding the frequency of detection, CAF, BEG, KTP, TMT, SMX and CBZ were all detected in most of the influent samples (i.e. $F_D > 90\%$). By contrast, THC-COOH, WRF, APT and SDM were found in less than 10% of the collected samples.

The differences in the influent concentrations of the same pollutant measured in the WWTPs might be related to the characteristics and extension of the catchment area served by the plants. The assumption is that the larger the served area, the higher ~~is~~ the equalization effect on the concentration due to the longer retention in the sewage network; this longer retention time reduces the peak values and attenuates the time variations of the influent concentrations. Indeed, the highest concentration of CAF, BEG and KTP were found in WWTP6 and WWTP1 which serve sewage basins of 15 km^2 and 22 km^2, respectively, corresponding to average influent volumetric flowrates of 0.16 m^3/s and 0.22 m^3/s, respectively (treatment capacity of 90’000 PE) (see Figure S.M. 1). In agreement with the assumption reported above, the lowest concentrations were measured in the influent of WWTP5 which serves a much larger area (about 195 km^2, corresponding to an average influent volumetric flowrate of 9.2 m^3/s, for a treatment capacity of 1’090’000). To confirm these observations, the Spearmen correlation coefficient was calculated between influent concentrations and catchment area for the three CECs measured at the highest extent (i.e. CAF, BEG and KTP). The value of the correlation coefficient resulted to be always significant (i.e. p-value < 0.05): -0.37 for BEG, -0.45 for KTP and -0.27 for CAF. It is therefore confirmed the assumption that the higher the catchment area, the lower the influent concentration. Similarly, McCall et al. (2017) depicted ~~an~~the influence of the catchment scale on illicit drug~~s~~ biomarkers. The only exception was represented by WWTP8, which serves the smallest catchment area and receives influent concentrations being not ~~so~~as high as expected. However, it might be argued that in this case, the treatment capacity is so low (i.e. 18’000 PE) to highlight concentration peaks. Further studies must be carried out to confirm the assumption and to better elucidate the causes of the influent concentration time patterns, considering all the possible influencing factors (e.g. the ratio between catchment area and overall length of sewage pipes, the retention time and transformation and degradation processes of pollutants within the sewage network).

~~The differences in the influent concentrations of the same pollutant measured in the WTTPs might be related to the characteristics and extension of the catchment area served by the plant. The assumption is that the larger the served area, the higher is the equalization effect on the concentration due to the long retention in the sewage until the inlet of the WWTP, which reduces peaks and time variations. Indeed, the highest concentration of CAF, BEG and KTP were found in WWTP6 and WWTP1 which serve sewage basins of 15 km^2 and 22 km^2, respectively, corresponding to average influent volumetric flowrates of 0.16 m^3/s and 0.22 m^3/s, respectively (treatment capacity of 90’000 PE) (see Figure 1). By contrast, the lowest concentrations were measured in the influent of WWTP5 which serves a much larger area (about 195 km^2, corresponding to an average influent volumetric flowrate of 9.2 m^3/s, for a treatment capacity of 1’090’000). The foregoing assumption seems not to be complied with by the case of WWTP8, which serves the smallest catchment area but receives influent concentrations being not so high as expected. However, it might be argued that in this case the treatment capacity is so low (i.e. 18’000 PE) to be unable to determine the occurrence of concentration peaks. Further studies must be carried out to confirm the assumption and better elucidate the causes of the influent concentration time patterns, considering all the possible influencing factors (e.g. the ratio between catchment area and overall length of sewage pipes, the retention time and transformation and degradation of pollutants in the sewage network).~~



~~*Figure 1 Map of the WWTPs with respect to the correspondent sewage catchment areas and the main hydrographic network according to bottom up hierarchy of stream (i.e. order 1 and 2 of the Hack stream order)* (Hack, 1957).~~

Regarding the effluent concentrations ~~effluent~~ from all the WWTPs (data reported in Table S.M. 4), the highest medians were measured for SMX and CBZ (i.e. 0.23 µg/L and 0.18 µg/L, respectively) which also showed an $F_D = 99\%$. By contrast, the median concentrations of COC, MET, LCN, SDZ, SDM, WRF, THC-COOH and APT were below the MRL with $F_D < 35\%$. These results can be explained based on the removal capability of the different WWTPs, as it will be afforded in detail in the discussion below.

~~2.2.~~3.2. *Removal efficiencies*

The median removal efficiencies are reported in Table 2. They were classified into three categories according to the Swiss experience: high, intermediate and low, corresponding to $R \geq 80\%$, $20\% < R < 80\%$, and $R \leq 20\%$, respectively (Rizzo et al., 2019; The Swiss Federal Council, 2021).

Table 2 Median removal efficiencies for each CEC and WWTP: in italic the low removal (R ≤20%), in bold the high removal (R ≥80%) and underlined the intermediate removal (20%< R<80%).

WWTP	BEG	COC	THC-COOH	MET	APT	SMX	TMT	LCN	SDZ	SDM	KTP	CBZ	WRF	CAF
1	**98**	**97**	/	64	/	*9*	72	*-3*	50	/	**96**	*-12*	/	**100**
2	**98**	**97**	63	**83**	/	42	38	66	75	/	**88**	*-4*	78	**99**
3	**99**	**97**	/	79	/	*17*	43	50	71	/	**90**	*18*	/	**99**
4	**98**	**98**	50	54	/	40	**88**	50	75	/	**97**	*-13*	/	**99**
5	35	58	/	50	/	*-8*	*9*	*0*	36	/	38	*0*	/	33
6	**98**	**98**	64	50	/	23	**90**	50	63	/	**97**	32	69	**98**
7	**98**	**98**	58	75	/	*19*	45	50	32	/	**89**	*-15*	/	**98**
8	**98**	**98**	52	71	/	64	**94**	71	75	/	**98**	*18*	55	**97**

APT and SDM were not detected in any sample and as consequence, the removal was not calculated.

BEG, COC, CAF and KTP were classified as belonging to the high removal category since the median values of the removal efficiency were above 80% for all the WWTPs with the only exception of WWTP5. These results are well in agreement with previous studies. For instance, a wide investigation, concerning 76 WWTPs carried out by the same research group, found ~~out~~ comparable removal values (Di Marcantonio et al., 2020b). Similar results were measured for KTP (i.e. R from 78% to 93%) also by Palli et al. (2019) investigating an Italian WWTP; R > 80% for BEG were determined by Yadav et al. (2019) in Australia and by Styszko et al. (2021) in Poland. Khasawneh and Palaniandy (2021) reviewed 73 studies and highlighted removal above 90% for CAF. These high removal rates are mainly ascribed to the effect of the secondary compartment of the WWTPs, specifically due to ~~and to~~ biodegradation and photodegradation, ~~being~~ since these compounds are highly hydrophilic (log Kow < 3) and soluble (Chiavola et al., 2019; Couto et al., 2019). It is important to notice that the same pollutants, i.e. BEG, COC, CAF and KTP, were also present at the highest concentration in the influent of all the WWTPs. This might boost the removal by biodegradation for the biodegradable CECs which can be used as a primary or secondary source of carbon and energy. For instance, Quintana et al. (2005) studied the microbial degradation of five acidic pharmaceuticals using activated sludge as inoculum under aerobic conditions and found that ketoprofen demonstrated a metabolic biodegradation capability.

These results also highlight that the monitored WWTPs ~~are able to~~can comply with the removal target recommended by the Swiss legislation (i.e. R≥80%), which represents at the moment the reference for Europe on CECs management in the water sector

CBZ was the only CEC whose removal was in most cases less than 20% (therefore it was classified within the low removal category), or even negative. There was only ~~an~~ one exception, represented by

WWTP 6, ~~whose~~ which showed a median removal equal to 32%. These low removals were also observed by other studies; as an example, Kumar et al. (2022) reported R=-92%- 18%. The high persistence of CBZ in water is due to its chemical-physical properties. The value of k_{biol} is very low (i.e. 0.005–0.389 L/gMLSS d), and this determines a high resistance to biodegradation; additionally, the value of K_{ow} (equal to 2.1) indicates that the molecule is highly hydrophilic and therefore it preferably remains dissolved in solution instead of being adsorbed onto primary or secondary sludge (Kumar et al., 2022). This behaviour is also confirmed by the values of the solid/liquid partition coefficient (K_d) reported ~~to be~~being K_d 8–314 L/kg MLSS, which suggests ~~a~~ negligible sorption onto ~~the~~ sludge (Rout et al., 2021). The higher removal observed in the WWTP6 ~~with respect~~compared to the other WWTPs might be due to the different layout of treatment. Firstly, the biological compartment consists of a Moving Bed Biological Reactor (MBBR), which is reported to be able of a higher biodegradation rate because of the increased biomass density and longer retention time (Sonwani et al., 2022). Furthermore, there is a coagulation-flocculation unit following the MBBR, where a further improvement of the removal capability is expected to occur. However, the contribution of the latter compartment should be low since Matamoros and Salvadó (2013) demonstrate that for hydrophilic compounds, and particularly CBZ, this process provide a positive removal but at low values ~~at very low extend~~ (i.e. <5 %). The negative removal values of CBZ observed in many of the investigated plants and also referred by other authors (Di Marcantonio et al., 2021, 2020a; Moslah et al., 2018; Nas et al., 2021; Tran and Gin, 2017) might be explained through a combination of more effects: the desorption from faecal particles due to the hydrophilic characteristic of the molecule and the hydrolysis of its human metabolites with reconversion into the original compound (Kumar et al., 2022). Based on these results, it can be deemed that the removal of CBZ needs treatment processes other than those implemented in the existing WWTPs designed to remove traditional compounds. This goal was implemented already in Switzerland where CBZ was included among the proxy CECs to be monitored and removed (Eggen et al., 2014).

Regarding the CECs belonging to the intermediate removal category (i.e. THC-COOH, MET, SMX, TMT, LCN, SDZ and WRF), the median values showed a wide variability which was speculated to be ascribed to the effects of the plant layout. To better understand this dependence, the removal data of this category were further statistically analysed in the section below.

~~2.3.~~3.3. Statistical insight into the removal of CECs belonging to the intermediate removal category~~Statistical analysis of the intermediate removal category removal efficiencies~~

The removal efficiency data of the intermediate removal category were plotted in a boxplot (Figure 1), and then analysed through Principal Component Analysis (Figure 2 and Figure 3). The graph in Figure 1 ~~is able to~~ shows their statistical variation around the median value. The statistical tests (Kruskal and Wilcoxon) provided the letters reported above the boxplot: the same letter indicates that the removal of a specific CEC achieved by a plant does not differ statistically from that observed in a different plant for the same compound.

THC-COOH and WRF were excluded from this analysis since they were both detected in less than 10% of the collected samples (i.e. influent: F_D = 7% and F_D = 4%, respectively; effluent: F_D = 0% and F_D = 0%, respectively).

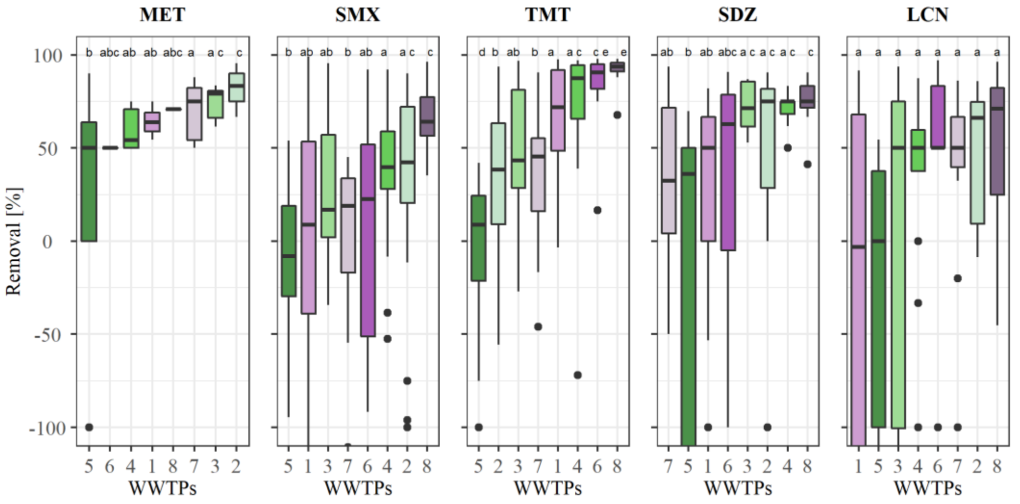


Figure 1 Removal efficiency considering the CECs belonging to the intermediate removal category. The letters on the top of the plot indicate significant statistical differences between data sets via Kruskal ($p \leq 0.05$) and post hoc pairwise Wilcoxon tests; boxes labelled with the same letter are not significantly different.

Median removal of MET ranged between 50% in WWTP5 and WWTP6 and around 80% in WWTP2 and WWTP3. The highest median removal was achieved by WWTP2 and WWTP3 which are not statistically different since both were labelled with letter c. They are characterized by a biological process consisting of the aerobic stage and anoxic-aerobic stages, respectively. This suggests that aerobic biodegradation provides a significant contribution to the removal. MBR and MBBR technologies do~~es~~ not provide a relevant improvement on MET removal. Concerning the possible effects of the tertiary compartment and disinfection, based on the median removal it was possible to observe that the lowest removal efficiency was achieved in the two plants where the disinfection is provided by peracetic acid. By contrast in the other WWTPs where the MET removal was higher (except WWTP 8 where the disinfection is achieved by ~~the~~ ultrafiltration), the disinfection is performed by sodium hypochlorite. Luongo et al. (2020) compared peracetic acid performances on different CECs removal with other disinfectants, including sodium hypochlorite, and observed a lower removal but also a lower number of degradation by-products. Nonetheless, additional studies are required to elucidate the best conditions for this treatment. MET is a soluble and hydrophilic compound with a negligible tendency to be adsorbed on the activated sludge, as reported by several experimental studies (Boni et al., 2018; Yadav et al., 2019). Di Marcantonio et al. (2021) investigated the main treatment stages of a full-scale WWTP and found ~~out~~ that no appreciable removal was achieved by pre-treatment and primary treatments whereas the main reduction (up to 60 %) was carried out by the secondary compartment.

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For the antibiotics (i.e. LCN, SDZ, SMX and TMT), the highest median removal efficiency was always achieved by WWTP8, which is equipped with the MBR technology. The better removal of this system for complex contaminants as CECs is reported to be related to the sorption on the membrane as well as the biotransformation due to the development of ~~slower~~ slower-growing microbial species (Alvarino et al., 2018).

Among antibiotics, the removal did not change statistically between the plants only for LCN (i.e. p-value of the Kruskal test > 0.05). This can be due to the very low concentration measured in the influent and also the effluent (close to the MRL of 0.01 µg/L) of all plants. None of the investigated WWTPs was able to provide an appreciable improvement of the removal. Nonetheless, there is a relevant abundance of negative removal values, particularly in WWTP5, WWTP1 and WWTP3. Indeed, LCN is considered recalcitrant to biodegradation, and it is not expected to be adsorbed onto sludge; instead, it can more easily dissociate in the aqueous phase (LogKow < 3 and pKa = 7.6) (Tran et al., 2018).

In the case of SDZ, WWTP2, WWTP3, WWTP4 and WWTP8 showed a median removal in the range 71%-75%. WWTP7, WWTP6, WWTP5, WWTP1 (labelled by letter B) featured a median removal in the range 32%-63%. Furthermore, the latter group of plants showed a higher variability of the removal values, ranging from negative up to 94%. ~~About~~ Regarding the performances of the MBBR processes (WWTP6), Sonwani et al. (2022) reported ~~a~~ removal of SDZ in a lab-scale MBBR of 61.1 ± 8.8%, which is comparable with the median value observed in the present study (i.e. 63%).

SMX and TMT are usually assumed by patients in combination. Indeed, the frequency of detection in the influent was similar in all the plants, (i.e. around 100%). However, the behaviour was different. Particularly, TMT was removed at a higher and similar extent by WWTP8, WWTP6 and WWTP4 (i.e. median removal equal to 94%, 90% and 88%, respectively). Consistently, Gurung et al. (2019) achieved a median TMT removal of 86% in a pilot-scale MBR and Wolff et al. (2021) observed ~~an~~ improved biotransformation of TMT by attached biomass compared to suspended biomass. In the other WWTPs the median removal was widely variable.

The median removal of SMX was below 25% in WWTP1, WWTP3, WWTP5, WWTP7 and WWTP6 and roughly 40% in WWTP4 and WWTP2. A relevant increase ~~of~~ in ~~the~~ abatement was observed only in the plant where the biological compartment is made by an MBR (i.e. WWTP8, with a median removal equal to 64%). A slight improvement of slowly degradable substances including SMX was observed by Abegglen et al. (2009) in the MBR systems (Wolff et al., 2021). Regardless of the removal efficiency, no relevant decrease of the F_D in the effluents was observed for all the WWTPs (i.e. F_D ranged from 91%-100%). This is of particular concern because SMX is hydrophilic (i.e. $LogK_{ow}$ equal to 0.89), mobile in the aquatic environment (Dong et al., 2016; Grenni et al., 2019) and considered persistent in conventional WWTP by several authors (Di Marcantonio et al., 2020b; Estrada-Arriaga et al., 2016).

The PCA was applied to the removal values of the CECs belonging to the intermediate removal category for a better understanding of the driving factors. This analysis allowed the evaluation of the relative role of the biological compartment, the treatment capacity and the average SRT. The results of the PCA were reported as individual plots: in Figure 2 the individuals were coloured based on the main characteristics of the WWTPs layout according to Table 1, whereas in Figure 3 the same individuals were coloured based on the average SRT and grouped considering the type of biological process.

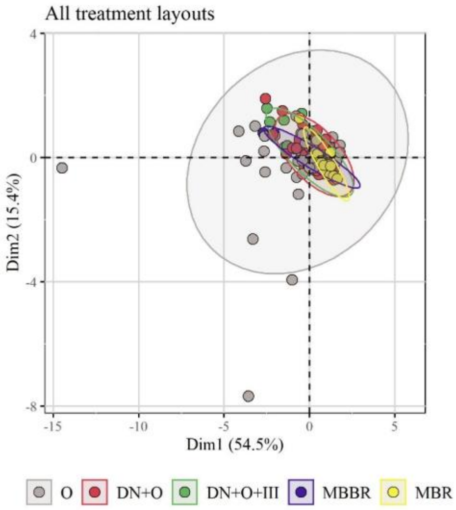


Figure 2 Individual plot obtained through PCA of the removal efficiency of intermediate category. The individuals are coloured based on the type of treatment layout.

The two main dimensions describe most of the variance of the data (i.e. 69.9%), which makes the following considerations sufficiently reliable. The individual plot highlighted that even if the data are mainly positioned in the same area, there are evident differences in the clusters formed depending on the type of biological process. Specifically, the most stable performances were achieved by the MBR followed by the MBBR as highlighted by the smallest ellipses, which correspond to 95% of the variance of each group of data. As known, the MBR exploits the high retention capacity of the membrane to produce a treated effluent of ~~a~~ very high quality. As known, the MBR exploits the high retention capacity of the membrane to produce a treated effluent of very high quality (Krzeminski et al., 2019). Furthermore, the longer sludge retention time favours the degradation of more complex molecules, such as those of CECs. The replacement of the secondary settlement by the membrane separation makes the system to be more resilient versus the variations of the influent characteristics and operating parameters. MBBR technology exploits the natural ability of microorganisms (e.g. bacteria, fungi, and algae) to adhere to the surfaces of carriers (or support media) and grow as biofilms, either as pure or mixed cultures. The wastewater flows in direct contact with the developed biofilm and allows to exchange of substrate, nutrients, and products between the biofilm and bulk liquid (Sonwani et al., 2022). Both MBR and MBBR, for the intrinsic features, provide a more stable operation as confirmed by the results of the PCA analysis.

The two groups named DN+O (i.e. anoxic-aerobic activated sludge) and DN+O+III (i.e. anoxic-aerobic activated sludge+sand filtration+UV) showed quite overlapped ellipses: therefore, the presence of the tertiary treatment (III) cannot be considered statistically relevant.

The highest dispersion of data within the plot was observed for the plants where the biological process was made by the aerobic activated sludge only (i.e. WWTP2 and WWTP5, named O in Figure 2) and which have the largest treatment capacity (i.e. 9.2 mc/s and 2.3 mc/s for WWTP5 and WWTP2 respectively). This indicates instability and high variability of the removal values. However, WWTP2 always provided higher values of the median removal efficiencies than WWTP5 (Table 2): therefore, for these WWTPs the treatment capacity and biological reactor type are not the discerning factors. Figure 3a shows the data of WWTP5 and WWTP2, with the individuals coloured based on the SRT: it can be noted an indisputable difference between the plants. The difference might be due to the slightly higher SRT of WWTP2 (14 d vs 10 d for WWTP2 and WWTP5, respectively) which is known to enhance the efficiency (Douziech et al., 2018). However, other site-specific conditions and characteristics of the plants might be responsible ~~of~~ for the difference observed: e.g. in WWTP5 the biological process is of Carrousel-type, which is considered not to be highly efficient, additionally the low influent organic load (Table S.M. *1*).

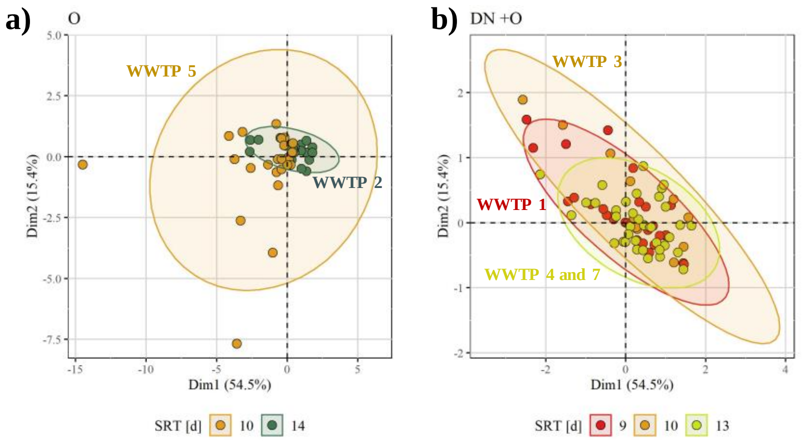


Figure 3 Individual plot considering separately: a) WWTPs equipped only with aerobic activated sludge treatment, b) WWTPs equipped with anoxic followed by aerobic activated sludge treatment. The individuals are coloured based on SRT.

Among the plants where the biological compartment was composed ~~by~~ of DN+O (see Figure 3b), the most stable performances were observed in WWTP4 and WWTP7 which were operated at the highest SRT (i.e. 13 d). The most dispersed values were found for WWTP3 whose SRT was about 10 d. WWTP6 showed an intermediate dispersion of the data: although the lowest SRT (i.e. 9 d), the presence of the tertiary treatment (which ~~are~~ is absent in the ~~above~~ above-mentioned WWTPs) might have ~~provided a contribution of~~contributed to equalization.

~~2.4.~~3.4. Correlation of CECs with traditional water quality parameters

The PCA was also applied to assess any correlation of CECs with the water quality parameters traditionally measured on a routine-basis in the wastewater treatment plants. The results are reported as correlation circles in Figure 4. This evaluation can be useful to understand if specific management strategies, implemented in the water treatment line of existing WWTPs, might also contribute to ~~improve~~ improving the CECs removal.

In Figure 4a, related to the CECs belonging to the high removal category, 74% of the data variance is explained by the two main dimensions and all the variables are well represented by the PCA, since the cos2 is above 0.55, with the only exception of NO_3^--N and P_{tot}.

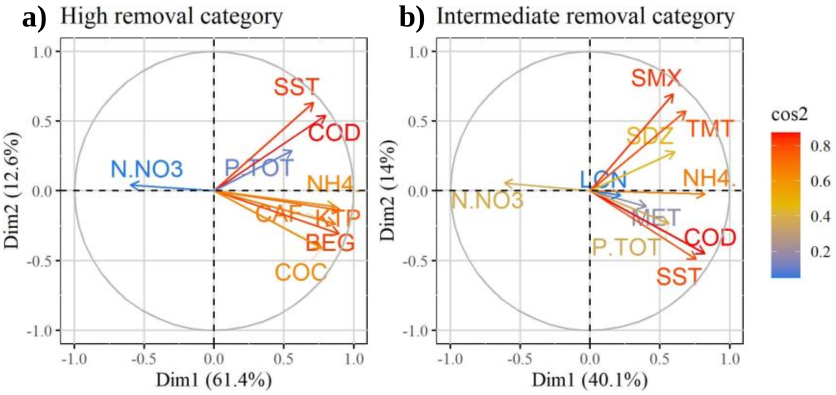


Figure 4 Correlation circle obtained through PCA on the measured concentrations of: a) CECs of the high removal category and water quality parameters and b) CECs of the intermediate removal category and water quality parameters.

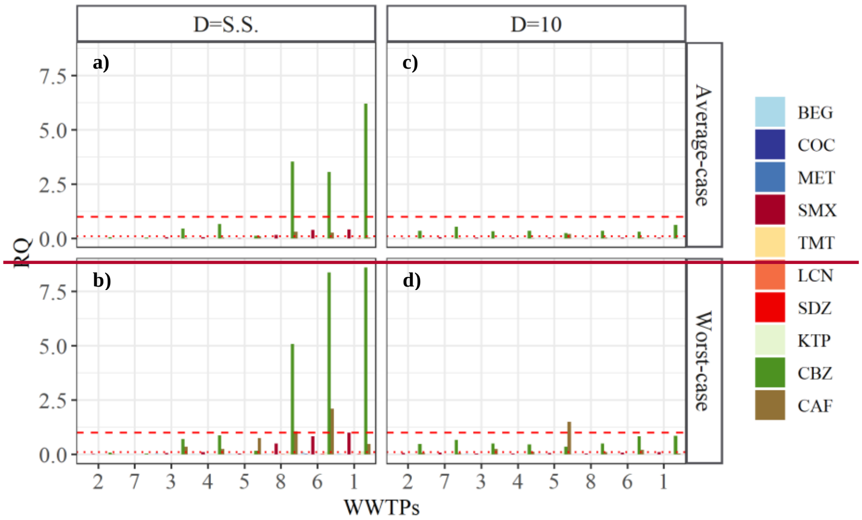
The plot of Figure 4a shows a significant positive correlation of the concentrations of CAF, KTP, BEG and COC with NH_4^+-N, considering both influent and effluent. This evidence can be explained by taking into account that CAF, KTP, BEG and COC are mainly removed in the biological compartment as well as ammonia nitrogen (Di Marcantonio et al., 2021; Metcalf & Eddy, 2015; Rigueto et al., 2020). The positive correlation with ammonia suggests that CECs degradation is accomplished along with nitrification. Indeed, several studies proved that the removal of KTP and BEG is enhanced by ~~ammonia~~ ammonia-oxidizing bacteria, suggesting the importance of nitrification in the degradation of these compounds (Chiavola et al., 2019; Maeng et al., 2013; Tran et al., 2009). Additionally, the main pathway for most CECs elimination was found to be via cometabolism with ammonia being utilized as the main substrate/energy source (Nsenga Kumwimba and Meng, 2019). Some other studies proved that biodegradable contaminants, such as CAF and KTP, are degraded in either presence or absence of nitrification inhibitor (i.e. N-Allylthiourea), suggesting that the removal can be carried out by means of the microbial activity regardless of the presence of ~~ammonia~~ ammonia-oxidizing bacteria (Falås et al., 2016; Park et al., 2017).

Figure 4b shows the results of the PCA applied to the concentrations of CECs falling the intermediate removal category (i.e. MET, LCN, SMX, TMT, SDZ) and the water quality parameters. The two main dimensions explain most of the variance of the data (i.e. 54.1%), even if the robustness of the statistical analysis is lower than in the above evaluation (Figure 4a). For SMX, TMT and SDZ, no correlation with COD, SST and P_{tot}, and a partial direct correlation with ammonia was found. These results agree with the moderate biodegradability of these CECs, which are only slightly removed by the conventional activated sludge process. Di Marcantonio et al. (2021) referred ~~of~~ a removal percentage achieved by this compartment equal to 47%, 59% and 50% for SMX, TMT and SDZ, respectively. SMX and TMT were also defined as moderately biodegradable in the activated sludge processes by Tran et al. (2018) based on the biodegradation rate constant (k_{biol}): 0.1-5 L/gMLSS d and 0.05 – 5.04 L/gMLSS d for SMX and TMT, respectively. The LCN and MET behaviour was positively correlated with SST, P_{tot} and particularly with COD: however, they are characterized by a low value of the cos2, which indicates that the significance of these correlations is not particularly reliable. However, a previous study on MET also observed a correlation with the COD removal pathway in an aerobic activated sludge process, suggesting a co-metabolism operated mainly by heterotroph bacteria (Boni et al., 2018).

~~2.5.~~3.5. *Environmental risk assessment (ERA)*

The ERA was carried out ~~in order~~ to evaluate whether the residual concentration of CECs in the final effluent of the WWTPs can pose a risk for the receiving ecosystems. As mentioned above, ERA was not performed for the CECs with F_D below 10% (i.e. THC-COOH, APT, WRF, SDM). However, it is important to notice that for THC-COOH, the MRL of the analytical method (0.1 µg/L) was much higher than its PNEC as reported in Table S.M. *3* (0.005 µg/L). Therefore, the higher MRL compared to the PNEC did not allow ~~to~~for the evauation of the ~~evaluate whether a high~~ risk eventually ~~can be~~ posed by THC-COOH. Thus, further evaluations should be performed on this compound. The four plots reported in Figure 5 differed for the values of the CECs used as MEC (i.e. measured environmental concentration) and for the value used as D. Specifically, the median effluent value and the 95th percentile were applied to evaluate the average and worst~~-~~case, respectively. Regarding D, the assessment was carried out with a value (S.S.) determined as site-specific for each WWTP considering the flow rate of both the treated effluent and the receiving water body, and also the default value equal to 10 as proposed by the EU guidelines. ~~Consequently, the four plots of Figure 6 represent: a) D=S.S., MEC=median effluent concentration; b) D=S.S., MEC=95th percentile effluent concentration; c) D=10, MEC=median effluent concentration; d) D=10, MEC=95th percentile effluent concentration.~~The RQ was considered acceptable if below 1 and it is defined as: high risk for RQs > 1, medium risk for 0.1 ≤ RQs ≤ 1, and low risk for RQ ≤ 0.1.

The results in terms of RQ corresponding to each case are reported in Table S.M. 6.



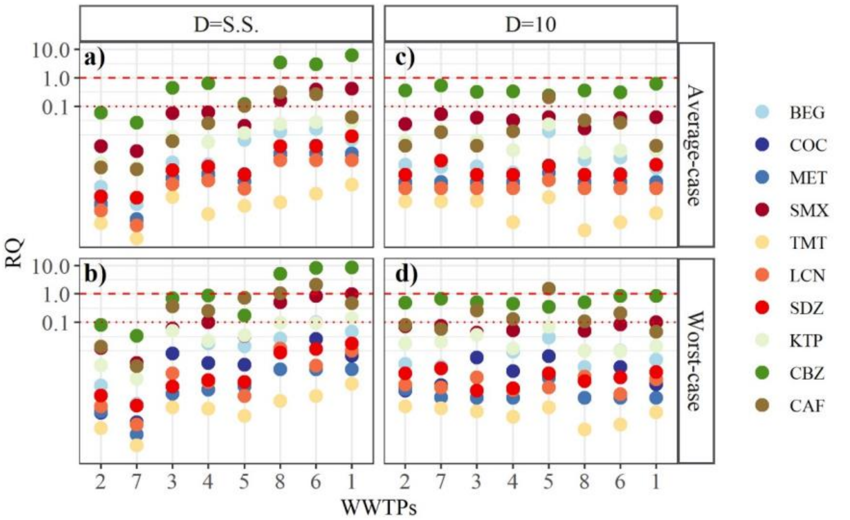


Figure 5 Risk quotient resulted from the ERA assuming different values of MEC in the effluent and D: a) D=S.S., MEC=median value; b) D=S.S., MEC=95th percentile value; c) D=10, MEC=median value; d) D=10, MEC=95th percentile value~~*Risk quotient resulted from the environmental risk assessment assuming different values of MEC and D: a) D=S.S., MEC=median effluent concentration; b) D=S.S., MEC=95th percentile effluent concentration; c) D=10, MEC=median effluent concentration; d) D=10, MEC=95th percentile effluent concentration. The RQ is considered acceptable if below 1 and it is defined as: high risk (RQs values higher than 1 represented by the red dashed line), medium risk (RQs values between 1 and 0.1 represented by the red dotted line), and low risk (RQ between 0.1 and 0.01)*~~.

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The results obtained by the site-specific ERA (Figure 5a,b) highlight that CBZ was the contaminant posing the higher and more frequent risk in the investigated plants. For instance, RQ values for CBZ resulted to be in the range indicating a high risk for the environment (according to the European Medicines Agency, 2018) in WWTP1, WWTP6 and WWTP8. A medium acceptable risk (i.e. $0.1<RQ<1$) was found in WWTP3, WWTP4 and WWTP5.

Among the other contaminants, CAF represented a source of risk only in the worst scenario: the risk was considered high in the effluent of WWTP6 and WWTP8, and medium acceptable in the effluent of WWTP1, WWTP3, WWTP4 and WWTP5. For the other CECs, the risk was always acceptable.

CBZ and CAF were the contaminants found at the highest concentration in the effluent among the CECs investigated. CAF was very abundant in the influent and therefore, although the high removal efficiency achieved by all plants, a high concentration was still found in the effluent. CBZ was the contaminant removed to the least extent, in accordance with the scientific literature which widely reports its refractory nature. These can be the reasons for the high risk measured in the effluent of some plants.

The results obtained by application of ERA using the default value D=10 (Figure 5c,d) show a significant reduction of the RQ values, for all the contaminants, compared to the site-specific assessment above described. Only CAF in WWTP5 and for the worst scenario poses a high risk (RQ>1). Indeed, the application of a common dilution factor may contribute to misestimating the risk quotient (Aemig et al., 2021).

The major finding obtained by this comparison is that the environmental risk is strictly related to the value assumed for the dilution factor (D). Indeed, the highest values of RQ were observed for those plants where D was posed equal to 1 since the flow rate of the receiving river essentially consisted of the effluent (i.e. WWTP1, WWTP6 and WWTP8). This is very clear by comparing WWTP8 and WWTP5 in the site-specific ERA. The former showed the best removal of the monitored CECs, although the environmental risk was high for CBZ and CAF (only in the worst-case) and medium for CAF and SMX: these patterns can be ascribed to the low dilution factor, i.e. D=1. By contrast, the WWTP5 showed the lowest removal efficiency for most of the CECs, while the environmental risk always resulted to be acceptable (even if classified as a medium for CBZ and CAF): the high value of S.S. D (equal to 20) may be responsible for this result.

The importance of the best choice of the dilution factor was also proved by Abily et al. (2021). Indeed, they highlighted the relevance of this parameter for its significant and positive correlation with the ecological status of European rivers. Besides, Link et al. (2017) demonstrated that the assumption of the dilution factor equal to 10 mainly provides an underestimation of the environmental concentration and thus of the environmental risk. Nonetheless, many studies that applied the same ERA procedure never reported the site-specific value of the dilution factor (Patrolecco et al., 2015; Rivera-Jaimes et al., 2018). In the present study, the site-specific D was determined considering the average annual flow rate of the receiving water body; it would be important also to verify the impact on the final risk due to the seasonal variation of the river flow rate.

Finally, it is worth noting that the results of ERA are also strictly dependent on the selection of the PNEC values. The present study used the lowest PNEC for surface water as proposed by the NORMAN Network. Rivera-Jaimes et al. (2018) performed the ERA for several pharmaceuticals in plants located in Mexico and calculated the PNEC as the ratio between the lowest acute toxicity value found for three selected trophic levels and a pertinent assessment factor posed equal to 1000. They obtained quite different results from the present site-specific ERA: no risk for CBZ, likely due to the high value of PNEC used (i.e. 2.5 μg/L vs 0.0~~0~~5 μg/L), and a relevant risk for KTP and TMT whose PNECs were lower (i.e. 0.03 μg/L and 0.16 μg/L, respectively) than the values applied in the present study (i.e. 2.1 μg/L and 120 μg/L, respectively).

~~3.~~4. Conclusions

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The study provides a comparative evaluation of the performances of 8 WWTPs, representative of different layouts, treatment capacity, biological process and operating parameters, concerning the removal of 14 CECs. The results were then used for the ERA implementation.

The main conclusions of the study can be summarized as follows:

- the wider the sewage catchment area the higher the equalization effect on all the influent characteristics including also CECs concentrations;
- a high removal (a median value above 80%) was always observed for CAF, BEG, KTP and COC, regardless of the differences among the WWTPs;
- an intermediate removal (20%<R<80%) was found for all the antibiotics and MET, with the highest reduction achieved by the MBR;
- CBZ was removed at the lowest extent by all the WWTPs, with no relevant difference among them;
- the behaviour of CECs, particularly of CAF, BEG, KTP and COC, was positively correlated with that of ammonia, thus suggesting that improving the nitrification process might also enhance CECs removal;
- the type of biological process was depicted as the main impacting factor on CECs removal, although a slight influence of the SRT was also observed;
- results of ERA highlighted a high risk for the plants characterized by no dilution of the final effluent, for the worst-case CAF and always for CBZ;
- for the other CECs, the risk was found to be always acceptable.

Overall, the investigation showed the need to implement specific measures (additional treatment stages) to reduce the risk when high concentrations of CECs are still present in the effluent (such as for refractory compounds like CBZ and pollutants entering the plants at very high concentrations like CAF). However, the risk must be assessed considering the site-specific value of the dilution factor, which in turn requires to carry hydraulic studies on the receiving water bodies. Additionally, the identification of univocal PNEC values is needed to make the assessments comparable.

These findings highlight that when implementing the ERA for CECs, it is of paramount importance to properly select the values of PNEC and D, to obtain reliable and site-specific outcomes. Only by proper care of these parameters, technically-costly effective measures can be implemented case-by-case to reduce the risk to the environment.

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Tables

Table 1 Main characteristics of the monitored WWTPs and number of sampling days (Samples). Abbreviations: SRT= Sludge Retention Time, QWWTP= average flow rate of the WWTP, Qrec= average flow rate of the receiving water body, Ca= sewage catchment area, PEau= Authorized treatment capacity, BS=Bar Screening, DD=Degreasing-Degritting, PS=Primary Sedimentation, O=Aerobic activated sludge process (oxidation), DN=Anoxic activated sludge process (denitrification), SS=Secondary Sedimentation, MBR=Membrane Biological Reactor (ultrafiltration), MBBR=Moving Bed Biofilm Reactor, III=Sand filtration followed by UV disinfection, DC=Hypochlorite disinfection, DP=Peracetic acid disinfection.

Table 2 Median removal efficiencies for each CEC and WWTP: in italic the low removal (R ≤20%), in bold the high removal (R ≥80%) and underlined the intermediate removal (20%< R<80%).

Figures

Figure 1 Removal efficiency considering the CECs belonging to the intermediate removal category. The letters on the top of the plot indicate significant statistical differences between data sets via Kruskal ($p \leq 0.05$) and post hoc pairwise Wilcoxon tests; boxes labelled with the same letter are not significantly different.

Figure 2 Individual plot obtained through PCA of the removal efficiency of intermediate category. The individuals are coloured based on the type of treatment layout

Figure 3 Individual plot considering separately: a) WWTPs equipped only with aerobic activated sludge treatment, b) WWTPs equipped with anoxic followed by aerobic activated sludge treatment. The individuals are coloured based on SRT.

Figure 4 Correlation circle obtained through PCA on the measured concentrations of: a) CECs of the high removal category and water quality parameters and b) CECs of the intermediate removal category and water quality parameters.

Figure 5 Risk quotient resulted from the ERA assuming different values of MEC in the effluent and D: a) D=S.S., MEC=median value; b) D=S.S., MEC=95th percentile value; c) D=10, MEC=median value; d) D=10, MEC=95th percentile value.

Supplementary materials

Figure S.M. 1 Map of the WWTPs concerning the correspondent sewage catchment areas and the main hydrographic network according to bottom-up hierarchy of stream (i.e. orders 1 and 2 of the Hack stream order).

Table S.M. 1 Characterization of the influent to the WWTPs: Minimum, median and maximum concentration (mg/L) of COD, SST, Ptot, NH4+-N.

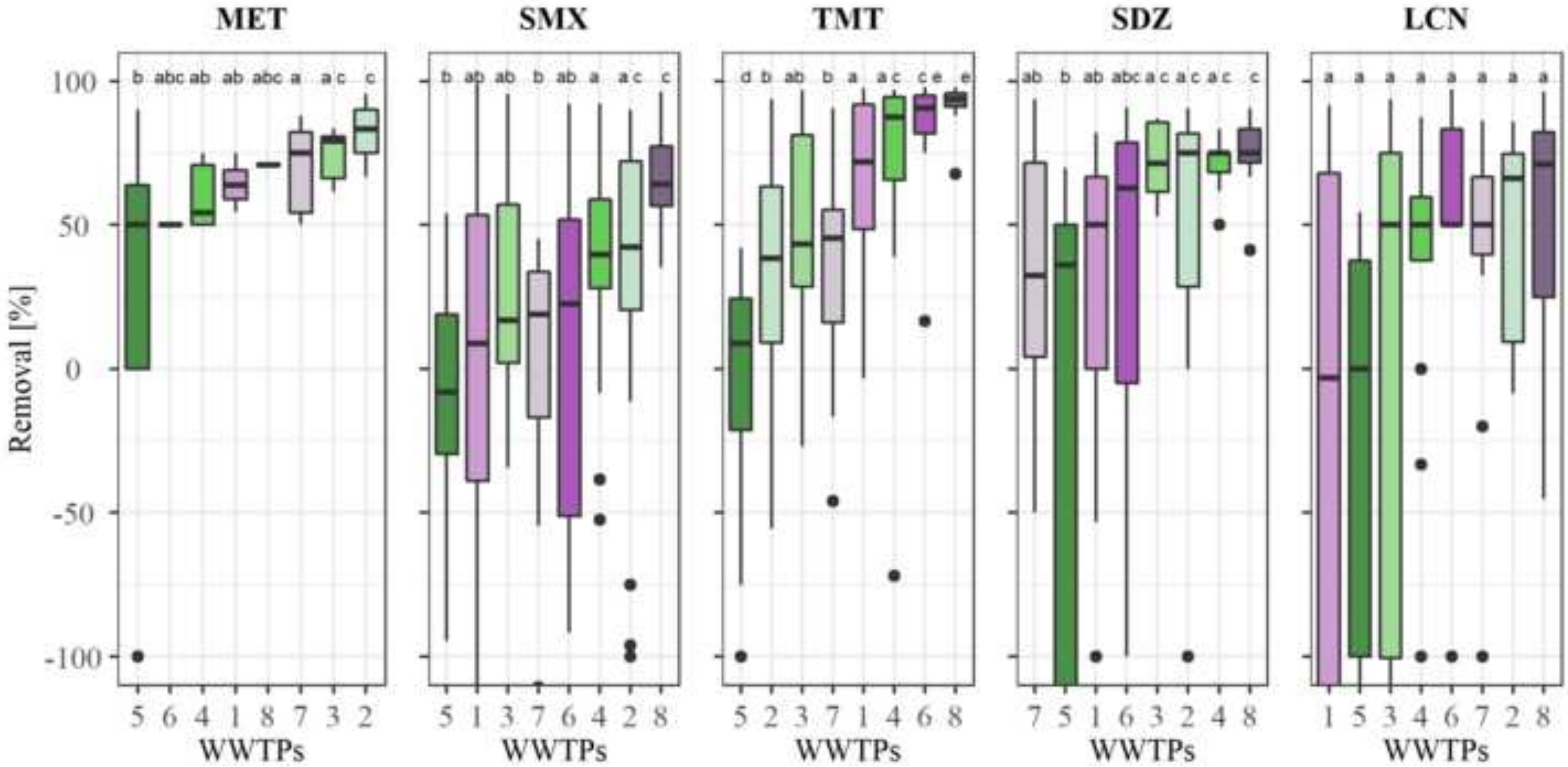
Table S.M. 2 Main chemical-physical characteristics of the target CECs: CAS n.=CAS number; Formula=Chemical formula; MW=Molecular Weight; pK_a=-log of acid dissociation constant; Log K_{ow}=log of octanol-water partition coefficient; K_H=Henry's law constant; Log K_{oc}=log of organic carbon-water partition coefficient; S=water solubility; p_v= vapour pressure (“NORMAN Database System,” 2020; Williams et al., 2017).

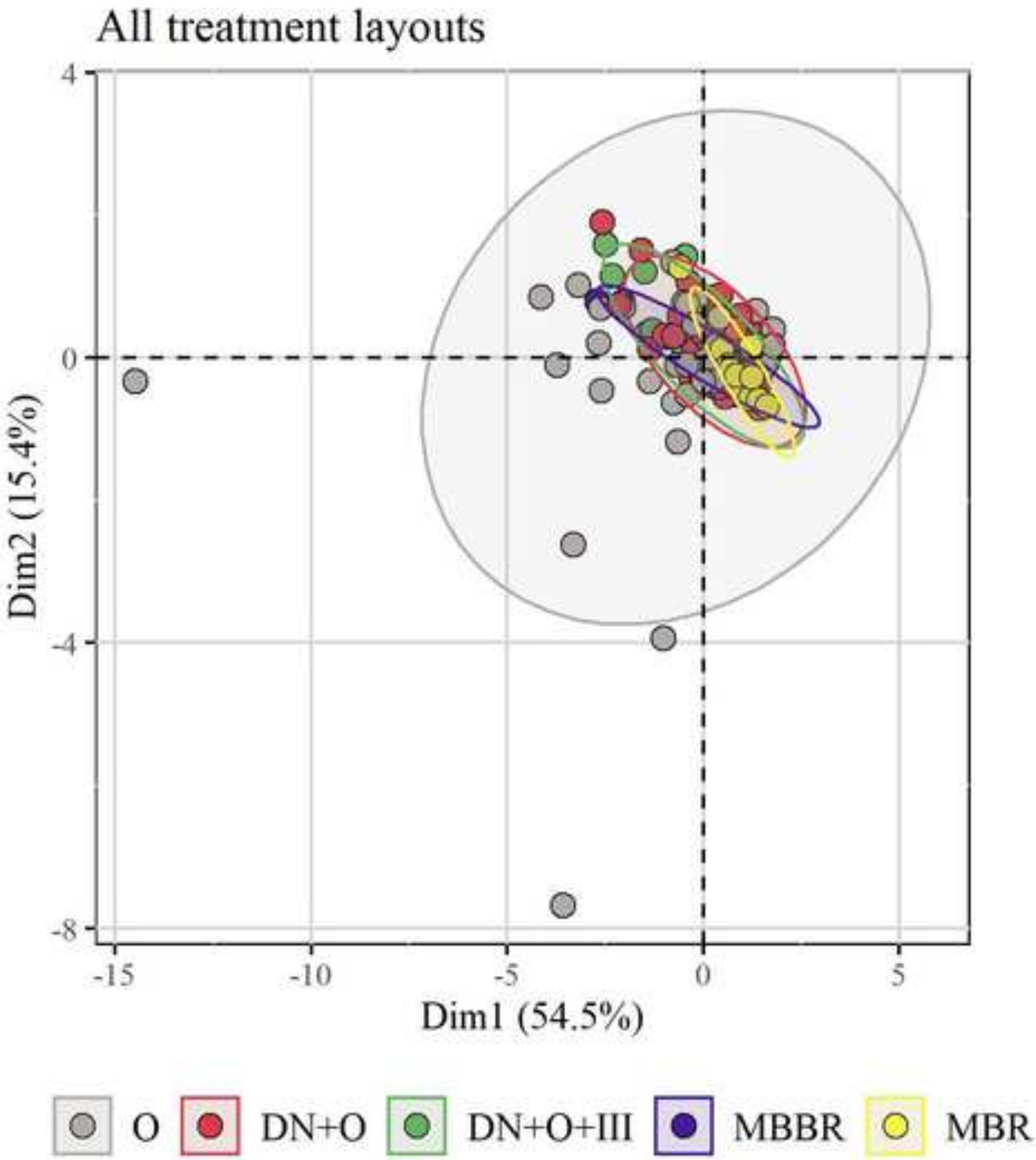
Table S.M. 3 PNEC values used for the Environmental Risk Assessment.

Table S.M. 4 Minimum, median and maximum CECs concentration (µg/L) measured in the influent and effluents to the WWTPs and the correspondent frequency of detection (reported between brackets).

Table S.M. 5 Median removal efficiencies of the water quality parameters.

Table S.M. 6 Values of the RQ obtained through the ERA, for the average-case and worst-case and considering both the site-specific dilution factor (D=S.S.) and the default value (D=10). The environmental risk was classified as follows: high risk (red), medium risk (yellow), low or negligible risk (green).


MET
SMX
TMT
SDZ
LCN
b abc ab ab abc a a c c
b ab ab b ab a a c c
d b ab b a a c c e e
ab b ab abc a c a c a c c
a a a a a a a a
100
50
0
-50
-100
Removal [%]
5 6 4 1 8 7 3 2
5 1 3 7 6 4 2 8
5 2 3 7 1 4 6 8
7 5 1 6 3 2 4 8
1 5 3 4 6 7 2 8
WWTPs


All treatment layouts
4
0
-4
-8
Dim2 (15.4%)
-15
-10
-5
0
5
Dim1 (54.5%)
O
DN+O
DN+O+III
MBBR
MBR

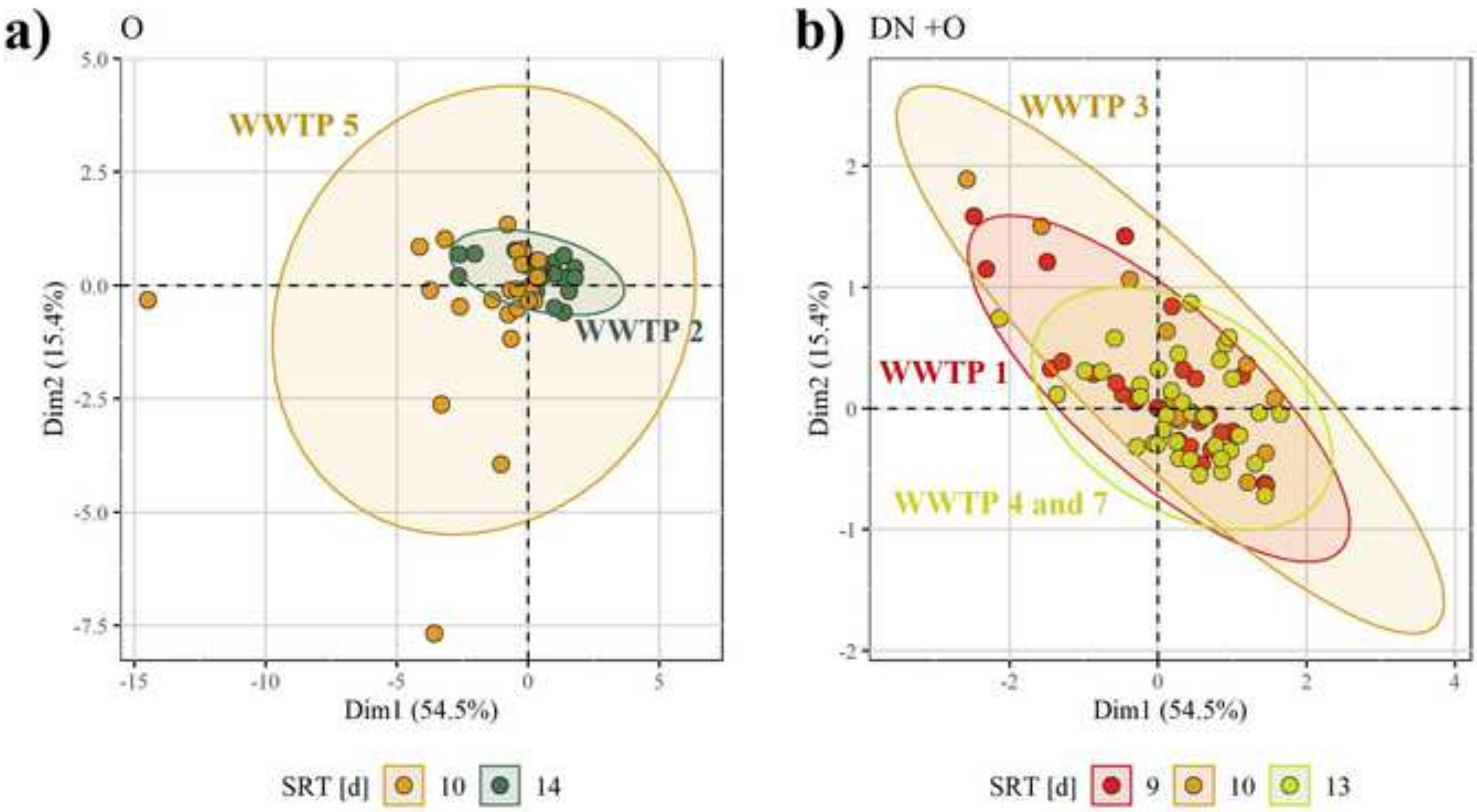

a)
O
WWTP 5
WWTP 2
Dim1 (54.5%)
Dim2 (15.4%)
5.0
2.5
0.0
-2.5
-5.0
-7.5
-15
-10
-5
0
5
SRT [d]
10
14
b)
DN +O
WWTP 3
WWTP 1
WWTP 4 and 7
Dim1 (54.5%)
Dim2 (15.4%)
2
1
0
-1
-2
-2
0
2
4
SRT [d]
9
10
13

Figure 4

Click here to access/download;Figure;Fig 4 _rev.jpg

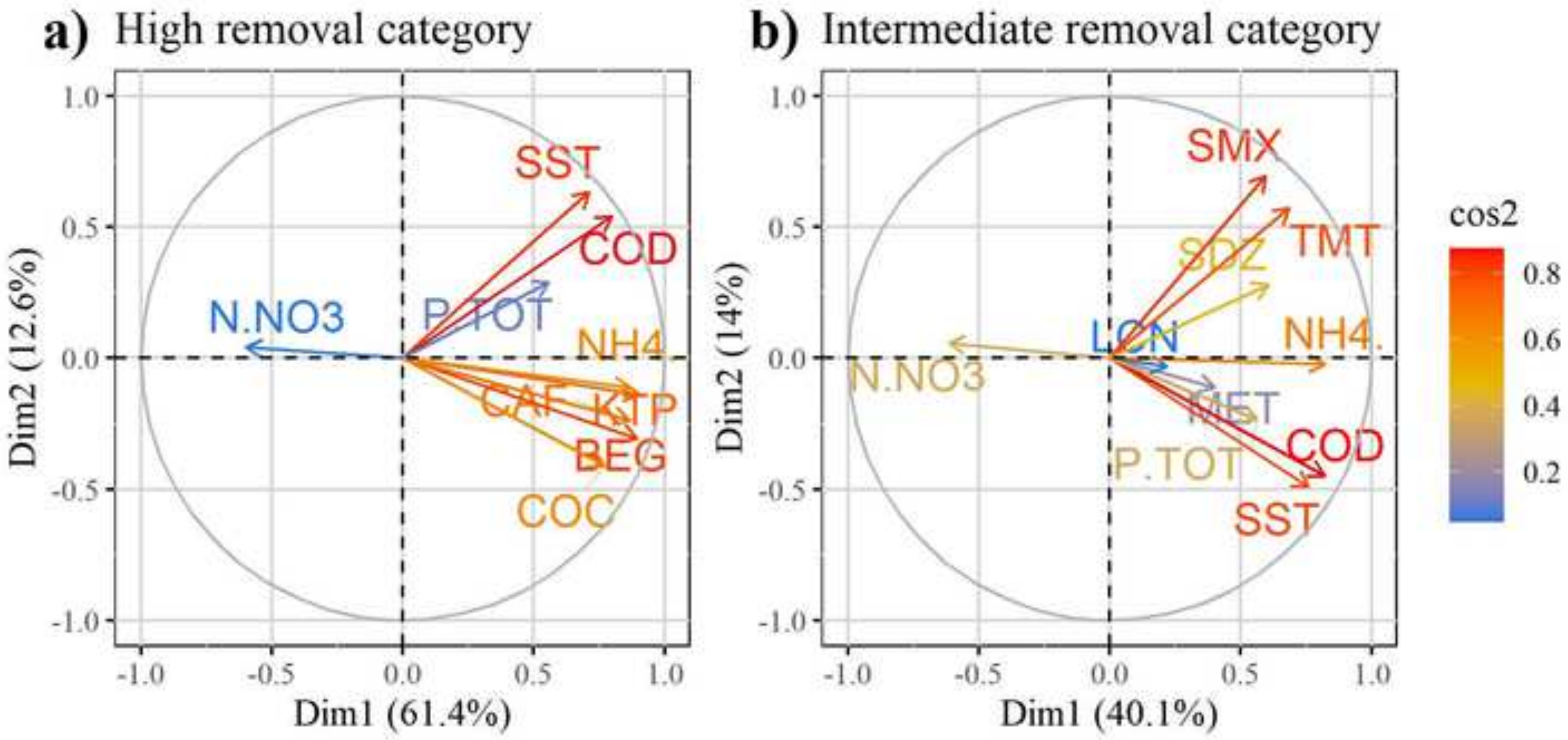


Figure 5

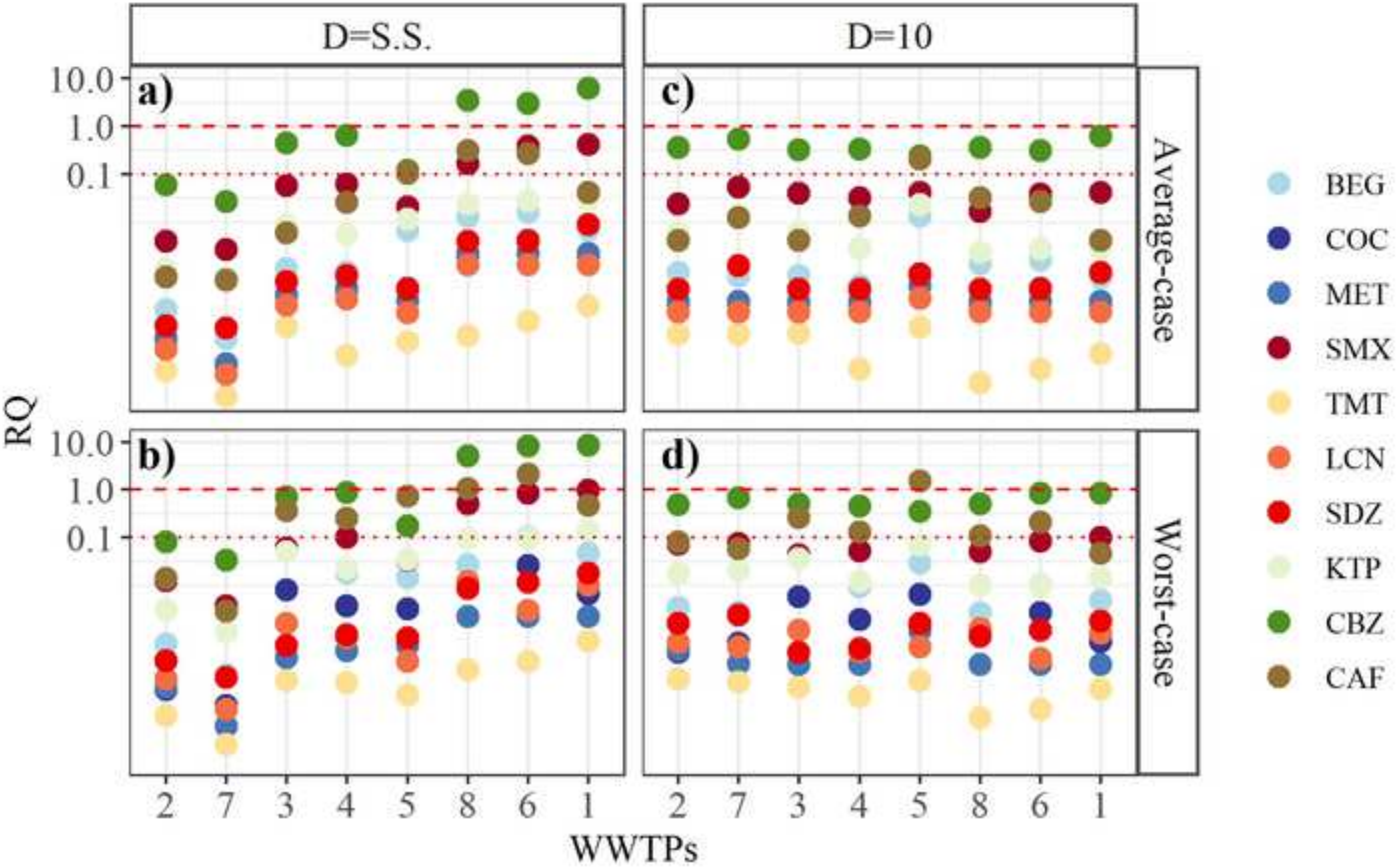

D=S.S.
D=10
a)
b)
c)
d)
Average-case
Worst-case
RQ
10.0
1.0
0.1
WWTPs
2
7
3
4
5
8
6
1
BEG
COC
MET
SMX
TMT
LCN
SDZ
KTP
CBZ
CAF

Table 1 Main characteristics of the monitored WWTPs and number of sampling days (Samples). Abbreviations: SRT= Sludge Retention Time, Q_{WWTP}= average flow rate of the WWTP, Q_{rec}= average flow rate of the receiving water body, Ca= sewage catchment area, PE_{au}= Authorized treatment capacity, BS=Bar Screening, DD=Degreasing-Degritting, PS=Primary Sedimentation, O=Aerobic activated sludge process (oxidation), DN=Anoxic activated sludge process (denitrification), SS=Secondary Sedimentation, MBR=Membrane Biological Reactor (ultrafiltration), MBBR=Moving Bed Biofilm Reactor, III=Sand filtration followed by UV disinfection, DC=Hypochlorite disinfection, DP=Peracetic acid disinfection.

WWTPs	**SRT [d]**	**Q_{WWTP} [mc/s]**	**Q_{rec} [mc/s]**	**Ca [sqkm]**	**PE_{au} [n.]**	**Samples [n.]**	**BS**	**DD**	**PS**	**DN**	**O**	**SS**	**MBBR**	**MBR**	**III**	**DC**	**DP**
1	9	0.22	0	22	90 000	31	•	•	•	•	•	•			•	•	
2	14	2.82	165	81	300 000	23	•	•	•		•	•				•	
3	10	1.22	7.5	44	600 000	11	•	•	•	•	•	•				•	
4	13	1.79	7.5	65	350 000	17	•	•	•	•	•	•				•	
5	10	9.2	177	195	780 000	24	•	•	•		•	•					•
6	-	0.16	0	14	1 090 000	18	•	•					•				•
7	13	0.93	188	53	90 000	20	•	•	•	•	•	•				•	
8	27	0.05	0	2	18 000	17	•	•		•	•	•		•			

Table 2 Median removal efficiencies for each CEC and WWTP: in italic the low removal (R ≤20%), in bold the high removal (R ≥80%) and underlined the intermediate removal (20%< R<80%).

WWTP	BEG	COC	THC-COOH	MET	APT	SMX	TMT	LCN	SDZ	SDM	KTP	CBZ	WRF	CAF
1	**98**	**97**	/	64	/	*9*	72	*-3*	50	/	**96**	*-12*	/	**100**
2	**98**	**97**	63	**83**	/	42	38	66	75	/	**88**	*-4*	78	**99**
3	**99**	**97**	/	79	/	*17*	43	50	71	/	**90**	*18*	/	**99**
4	**98**	**98**	50	54	/	40	**88**	50	75	/	**97**	*-13*	/	**99**
5	35	58	/	50	/	*-8*	*9*	*0*	36	/	38	*0*	/	33
6	**98**	**98**	64	50	/	23	**90**	50	63	/	**97**	32	69	**98**
7	**98**	**98**	58	75	/	*19*	45	50	32	/	**89**	*-15*	/	**98**
8	**98**	**98**	52	71	/	64	**94**	71	75	/	**98**	*18*	55	**97**

Table 3 Median removal efficiencies for each CEC and WWTP: in italic the low removal (R ≤20%), in bold the high removal (R ≥80%) and underlined the intermediate removal (20%< R<80%).

WWTP	BEG	COC	THC-COOH	MET	APT	SMX	TMT	LCN	SDZ	SDM	KTP	CBZ	WRF	CAF
1	**98**	**97**	/	64	/	*9*	72	*-3*	50	/	**96**	*-12*	/	**100**
2	**98**	**97**	63	**83**	/	42	38	66	75	/	**88**	*-4*	78	**99**
3	**99**	**97**	/	79	/	*17*	43	50	71	/	**90**	*18*	/	**99**
4	**98**	**98**	50	54	/	40	**88**	50	75	/	**97**	*-13*	/	**99**
5	35	58	/	50	/	*-8*	*9*	*0*	36	/	38	*0*	/	33
6	**98**	**98**	64	50	/	23	**90**	50	63	/	**97**	32	69	**98**
7	**98**	**98**	58	75	/	*19*	45	50	32	/	**89**	*-15*	/	**98**
8	**98**	**98**	52	71	/	64	**94**	71	75	/	**98**	*18*	55	**97**

A step forward on site-specific environmental risk assessment and insight into the main influencing factors of CECs removal from wastewater

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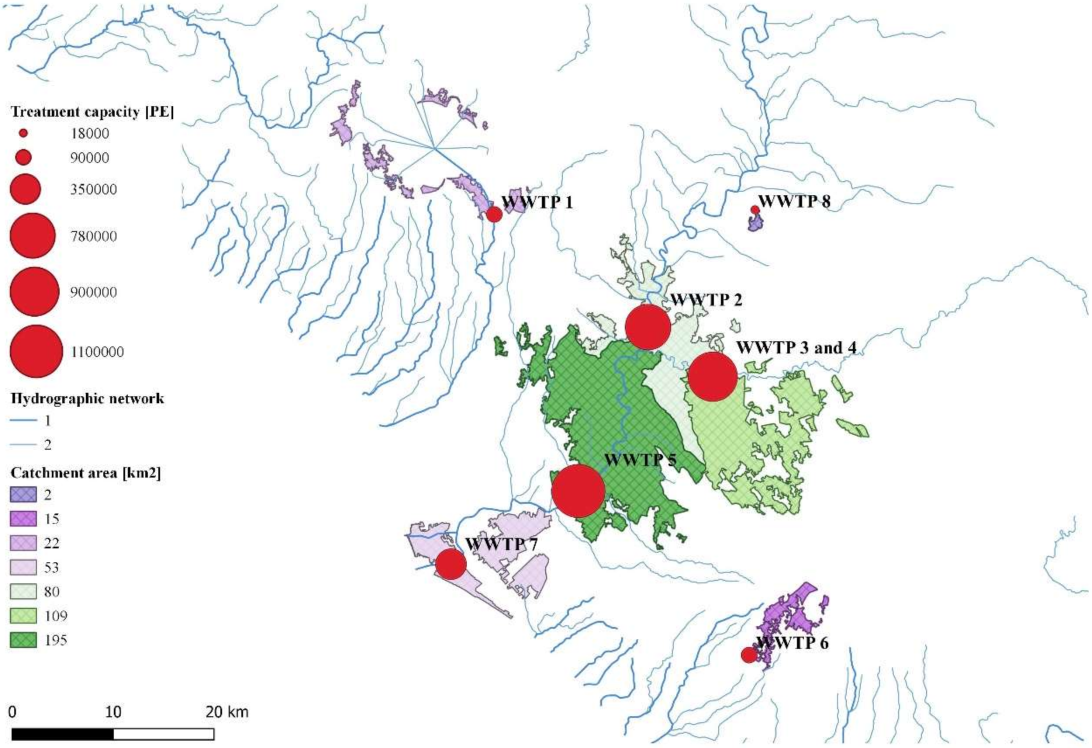

Figure S.M. 1 Map of the WWTPs with respect to the correspondent sewage catchment areas and the main hydrographic network according to bottom up hierarchy of stream (i.e. order 1 and 2 of the Hack stream order)

Table S.M. 1 Characterization of the influent to the WWTPs: Minimum, median and maximum concentration (mg/L) of COD, SST, Ptot, NH4+-N.

WWTP	**min- (median)- max [mg/L]**			
	SST	**COD**	**Ptot**	**$NH4^+$-N**
1	33- (165) -558	88- (288) -746	1.6- (4) -8.78	9.6- (21) -43.8
2	58- (174) -1546	36- (257) -2220	0.6- (4) -7.44	2.3- (22) -45
3	20- (96) -142	47- (103) -440	1.2- (2) -3.2	8.3- (16) -27.9
4	55- (109) -255	42- (179) -453	1.5- (2) -4.4	4.8- (16) -26.5
5	8- (69) -302	37- (107) -538	<0.05- (2) -5.58	7.1- (12) -27.2
6	24- (124) -260	100- (293) -513	2.3- (6) -7.47	27.1- (42) -52.7
7	31- (145) -592	96- (284) -1204	5- (7) -38.4	0.25- (28) -43.5
8	45- (100) -445	104- (233) -488	1.6- (4) -6.7	9.2- (32) -45.2

Table S.M. 2 Main chemical-physical characteristics of the target CECs: CAS n.=CAS number; Formula=Chemical formula; MW=Molecular Weight; pK_a=-log of acid dissociation constant; Log K_{ow}=log of octanol-water partition coefficient; K_H=Henry's law constant; Log K_{oc}=log of organic carbon-water partition coefficient; S=water solubility; p_v= vapour pressure ("NORMAN Database System," 2020; Williams et al., 2017).

CECs	**CAS n.**	**Formula**	**MW**	**pKa**	**Log Kow**	**K_H**	**Log K_{OC}**	**S 25°C**	**pv 25 °C**
	/	/	**[g/mol]**	/	/	**[atm·m³/mol]**	**[L/kg]**	**[mg /L]**	**[mmHg]**
COC	50-36-2	$C_{17}H_{21}NO_4$	303.35	8.61	2.30	$4.24\cdot10^{-11}$	3.276	1298	$1.91\cdot10^{-7}$
BEG	519-09-5	$C_{16}H_{19}NO_4$	289.33	3.15	-1.32	$1.03\cdot10^{-13}$	2.548	1605	$5.17\cdot10^{-8}$
THC-COOH	56354 -06-4	$C_{21}H_{28}O_4$	344.40	4.21	1.74	$3.87\cdot10^{-12}$	2.794	711.9	$3.73\cdot10^{-9}$
MET	537-46-2	$C_{10}H_{15}N$	149.23	9.87	2.07	$2.37\cdot10^{-6}$	3.207	$1.33\cdot10^{4}$	$5.4\cdot10^{-3}$
APT	300-62-9	$C_9H_{13}N$	135.21	10.1	1.76	$1.08\cdot10^{-6}$	3.045	$2.81\cdot10^{4}$	0.24
KTP	22071-15-4	$C_{16}H_{14}O_3$	254.28	4.5	3.12	$2.12\cdot10^{-11}$	2.459	51 (22°C)	$6.81\cdot10^{-7}$
CBZ	298-46-4	$C_{15}H_{12}N_2O$	236.27	13.9	2.45	$1.08\cdot10^{-10}$	3.588	17.7	$1.84\cdot10^{-7}$
SMX	723-46-6	$C_{10}H_{11}N_3O_3S$	253.28	6.16	0.89	$9.56\cdot10^{-13}$	3.185	3942	$3.79\cdot10^{-6}$
TMT	738-70-5	$C_{14}H_{18}N_4O_3$	290.32	7.12	0.91	$2.39\cdot10^{-14}$	2.957	2334	$5.13\cdot10^{-7}$
LCN	154-21-2	$C_{18}H_{34}N_2O_6S$	406.54	7.6	0.2	$3.0\cdot10^{-23}$	1.768	927	$1.34\cdot10^{-17}$
SDZ	68-35-9	$C_{10}H_{10}N_4O_2S$	250.28	6.36	-0.09	NA	NA	77	NA
SDM	122-11-2	$C_{12}H_{14}N_4O_4S$	310.33	6.91	1.63	NA	NA	343	NA
WRF	81-81-2	$C_{19}H_{16}O_4$	308.33	5	2.7	NA	NA	17 (20°C)	$1.125\cdot10^{-8}$
CAF	58-08-2	$C_8H_{10}N_4O_2$	194.19	10.4	-0.07	$1.1\cdot10^{-11}$	NA	$2.16\cdot10^{4}$	$9.0\cdot10^{-7}$

Table S.M. 3 PNEC values used for the Environmental Risk Assessment.

CECs	**PNEC [µg/L]**	**References**
BEG	2.33	NORMAN network
CBZ	0.05	NORMAN network
COC	2.46	NORMAN network
KTP	2.1	NORMAN network
LCN	3.95	NORMAN network
MET	2.3	(van der Aa et al., 2013)
SMX	0.6	NORMAN network
TMT	120	NORMAN network
THC-COOH	0.005	(Fernández-Rubio et al., 2019)
APT	24.8	NORMAN network
CAF	1.2	NORMAN network
SDZ	1.27	NORMAN network
WRF	0.45	NORMAN network
SDM	1.21	NORMAN network

Table S.M. 4 Minimum, median and maximum CECs concentration (µg/L) measured in the influent and effluents to the WWTPs and the correspondent frequency of detection (reported between brackets).

CECs	Sample	WWTP_1	WWTP_2	WWTP_3	WWTP_4	WWTP_5	WWTP_6	WWTP_7	WWTP_8	All WWTPs
APT	IN	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.1-<0.1-<0.1 (0)
	OUT	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.1-<0.1-<0.1 (0)
THC-COOH	IN	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-0.2 (9)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-0.1 (6)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-0.2 (17)	<0.10-<0.10-0.2 (20)	<0.10-<0.10-0.11 (12)	<0.1-<0.1-0.2 (7)
	OUT	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.10-<0.10-<0.10 (0)	<0.1-<0.1-<0.1 (0)
MET	IN	<0.01-<0.01-0.02 (13)	<0.01-0.03-0.11 (83)	<0.01-0.01-0.03 (64)	<0.01-<0.01-0.02 (35)	<0.01-0.02-0.13 (88)	<0.01-<0.01-0.01 (11)	<0.01-0.02-0.04 (75)	<0.01-<0.01-0.02 (6)	<0.01-<0.01-0.13 (47)
	OUT	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-0.01 (17)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-0.01-0.04 (71)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-0.01 (5)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-0.03 (14)
BEG	IN	<0.01-1.32-<0.01 (97)	0.09-1.61-0.09 (100)	1.1-2.02-1.1 (100)	<0.01-2.19-<0.01 (94)	<0.01-0.64-<0.01 (96)	<0.01-3.23-<0.01 (94)	0.03-2.06-0.03 (100)	0.57-1.98-0.57 (100)	<0.01-1.62-6.57 (98)
	OUT	<0.01-0.02-<0.01 (74)	<0.01-0.02-<0.01 (70)	<0.01-0.02-<0.01 (55)	<0.01-0.01-<0.01 (65)	<0.01-0.31-<0.01 (96)	<0.01-0.04-<0.01 (94)	<0.01-0.02-<0.01 (85)	<0.01-0.03-<0.01 (94)	<0.01-0.02-1.74 (80)
COC	IN	<0.01-0.17-<0.01 (87)	<0.01-0.14-<0.01 (87)	0.09-0.4-0.09 (100)	<0.01-0.35-<0.01 (88)	<0.01-0.12-<0.01 (67)	<0.01-0.38-<0.01 (89)	<0.01-0.27-<0.01 (80)	<0.01-0.43-<0.01 (94)	<0.01-0.22-1.38 (85)
	OUT	<0.01-<0.01-<0.01 (10)	<0.01-<0.01-<0.01 (9)	<0.01-<0.01-<0.01 (27)	<0.01-<0.01-<0.01 (41)	<0.01-0.02-<0.01 (63)	<0.01-0.01-<0.01 (61)	<0.01-<0.01-<0.01 (20)	<0.01-<0.01-<0.01 (29)	<0.01-<0.01-0.27 (31)
LCN	IN	<0.01-<0.01-0.06 (35)	<0.01-0.02-0.04 (78)	<0.01-0.01-0.08 (64)	<0.01-0.01-0.04 (65)	<0.01-<0.01-0.03 (42)	<0.01-<0.01-0.17 (22)	<0.01-0.01-0.04 (75)	<0.01-<0.01-0.17 (47)	<0.01-0.01-0.17 (52)
	OUT	<0.01-<0.01-0.05 (35)	<0.01-<0.01-0.04 (35)	<0.01-<0.01-0.06 (36)	<0.01-<0.01-0.04 (18)	<0.01-0.01-0.03 (54)	<0.01-<0.01-0.02 (11)	<0.01-<0.01-0.03 (45)	<0.01-<0.01-0.12 (41)	<0.01-<0.01-0.12 (35)
SDM	IN	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)
	OUT	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)
SDZ	IN	<0.01-0.02-0.07 (77)	<0.01-0.02-0.05 (70)	<0.01-<0.01-0.04 (45)	<0.01-<0.01-0.03 (41)	<0.01-0.01-0.02 (50)	<0.01-0.01-0.06 (56)	<0.01-0.03-0.08 (95)	<0.01-0.02-0.08 (71)	<0.01-0.01-0.078 (65)
	OUT	<0.01-0.01-0.03 (55)	<0.01-<0.01-0.02 (26)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-0.01 (6)	<0.01-0.01-0.04 (54)	<0.01-<0.01-0.03 (33)	<0.01-0.02-0.03 (65)	<0.01-<0.01-0.01 (12)	<0.01-<0.01-0.04 (36)
SMX	IN	0.07-0.25-2.84 (100)	0.04-0.33-0.78 (100)	0.11-0.24-0.69 (100)	0.04-0.34-0.89 (100)	0.11-0.23-0.44 (100)	0.09-0.28-1.04 (100)	0.14-0.38-0.68 (100)	0.08-0.32-0.88 (100)	0.04-0.31-2.84 (100)
	OUT	<0.01-0.25-0.65 (97)	0.05-0.14-0.51 (100)	<0.01-0.24-0.26 (91)	0.05-0.19-0.32 (100)	0.13-0.25-0.79 (100)	0.03-0.23-0.53 (100)	0.19-0.32-0.48 (100)	0.02-0.1-0.32 (100)	<0.01-0.23-0.78 (99)
TMT	IN	<0.01-0.1-0.82 (97)	0.02-0.1-0.22 (100)	0.07-0.1-0.19 (100)	0.03-0.09-0.21 (100)	0.03-0.07-0.15 (100)	0.03-0.14-0.47 (100)	0.04-0.09-0.14 (100)	0.05-0.11-0.25 (100)	<0.01-0.09-0.81 (99)
	OUT	<0.01-0.02-0.12	0.01-0.05-0.13	<0.01-0.05-0.09	<0.01-0.01-0.06	0.04-0.07-0.28	<0.01-0.01-0.03	<0.01-0.05-0.12	<0.01-<0.01-	<0.01-0.03-0.27

		(77)	(100)	(82)	(59)	(100)	(61)	(95)	0.02 (24)	(77)
WRF	IN	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-0.03 (9)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-0.02 (11)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-0.01 (12)	<0.01-<0.01-0.02 (4)
	OUT	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)	<0.01-<0.01-<0.01 (0)
KTP	IN	0.31-1.82-5.06 (100)	0.2-1.23-3.45 (100)	0.4-1.66-3 (100)	<0.05-1.64-2.99 (94)	0.43-0.82-3.47 (100)	0.35-2.48-4.62 (100)	0.65-2.48-4.2 (100)	0.81-2.35-5.15 (100)	<0.05-1.73-5.15 (99)
	OUT	<0.05-0.06-0.62 (58)	<0.05-0.13-0.49 (87)	<0.05-0.13-1.17 (91)	<0.05-0.06-0.39 (59)	0.16-0.49-2.43 (100)	<0.05-0.06-0.31 (67)	<0.05-0.28-0.47 (95)	<0.05-0.05-0.32 (53)	<0.05-0.11-2.42 (76)
CBZ	IN	0.04-0.27-0.69 (100)	0.01-0.17-0.28 (100)	0.07-0.17-0.24 (100)	0.05-0.13-0.29 (100)	0.05-0.12-0.21 (100)	0.01-0.25-0.63 (100)	0.06-0.22-0.33 (100)	0.04-0.18-1.26 (100)	0.01-0.18-1.26 (100)
	OUT	0.07-0.31-0.45 (100)	0.02-0.18-0.28 (100)	<0.01-0.16-0.29 (91)	0.04-0.17-0.26 (100)	0.02-0.12-0.33 (100)	0.02-0.15-1.32 (100)	0.09-0.27-0.44 (100)	0.02-0.18-0.27 (100)	<0.01-0.18-1.32 (99)
CAF	IN	<0.10-24-89 (90)	<0.10-15.88-53.69 (91)	5.83-16.11-34.73 (100)	0.03-20.06-52.8 (100)	<0.10-7.16-55.72 (71)	0.1-31.17-62 (100)	0.02-23.04-50.3 (100)	<0.10-24-60.24 (94)	<0.1-24.1-9.5 (92)
	OUT	0.03-<0.10-3 (35)	<0.10-<0.10-1.63 (35)	<0.10-<0.10-5.66 (36)	<0.10-0.16-3.5 (53)	0.03-2.55-30.93 (67)	0.1-0.33-5.61 (100)	0.03-0.15-0.99 (95)	<0.10-0.38-2.1 (76)	<0.1-0.13-8.5 (61)

Table S.M. 5 Median removal efficiencies of the water quality parameters.

WWTP	**SST**	**COD**	**Ptot**	**NH_4^+-N**
1	100	96	70	99
2	94	94	52	97
3	93	90	12	97
4	91	93	-9	98
5	73	61	-10	38
6	99	95	80	99
7	98	95	80	91
8	99	96	71	99

Table S.M. 6 Values of the RQ obtained thought the ERA, for the average-case and worst-case and considering both the site-specific dilution factor (D=S.S.) and the default value (D=10). The environmental risk was classified as follow: high risk (red), medium risk (yellow), low or negligible risk (green).

		WWTP	BEG	COC	MET	SMX	TMT	LCN	SDZ	KTP	CBZ	CAF
D= S.S.	Average-case	1	0.0068	0.0020	0.0022	0.4100	0.0002	0.0013	0.0087	0.0281	6.2000	0.0413
		2	0.0001	0.0000	0.0000	0.0039	0.0000	0.0000	0.0001	0.0010	0.0598	0.0007
		3	0.0011	0.0003	0.0003	0.0563	0.0001	0.0002	0.0006	0.0086	0.4475	0.0058
		4	0.0009	0.0004	0.0004	0.0617	0.0000	0.0002	0.0008	0.0055	0.6551	0.0255
		5	0.0065	0.0004	0.0002	0.0204	0.0000	0.0001	0.0004	0.0114	0.1189	0.1041
		6	0.0159	0.0041	0.0022	0.3891	0.0001	0.0013	0.0039	0.0276	3.0600	0.2691
		7	0.0000	0.0000	0.0000	0.0026	0.0000	0.0000	0.0001	0.0007	0.0262	0.0006
		8	0.0129	0.0020	0.0022	0.1667	0.0000	0.0013	0.0039	0.0238	3.5345	0.3157
	Worst-case	1	0.0471	0.0066	0.0022	0.9917	0.0007	0.0099	0.0178	0.1421	8.6143	0.4716
		2	0.0006	0.0001	0.0001	0.0124	0.0000	0.0001	0.0003	0.0030	0.0822	0.0137
		3	0.0547	0.0080	0.0003	0.0601	0.0001	0.0016	0.0006	0.0499	0.7037	0.3623
		4	0.0180	0.0036	0.0004	0.1000	0.0001	0.0008	0.0009	0.0226	0.8785	0.2517
		5	0.0144	0.0032	0.0005	0.0339	0.0000	0.0003	0.0008	0.0342	0.1764	0.7430
		6	0.1006	0.0262	0.0022	0.8338	0.0003	0.0029	0.0116	0.0952	8.3830	2.1001
		7	0.0001	0.0000	0.0000	0.0037	0.0000	0.0000	0.0001	0.0010	0.0329	0.0029
		8	0.0270	0.0089	0.0022	0.4998	0.0002	0.0121	0.0085	0.0983	5.0901	1.0744
D=10	Average-case	1	0.0007	0.0002	0.0002	0.0410	0.0000	0.0001	0.0009	0.0028	0.6200	0.0041
		2	0.0009	0.0002	0.0002	0.0233	0.0000	0.0001	0.0004	0.0061	0.3561	0.0041
		3	0.0008	0.0002	0.0002	0.0403	0.0000	0.0001	0.0004	0.0062	0.3198	0.0041
		4	0.0005	0.0002	0.0002	0.0320	0.0000	0.0001	0.0004	0.0029	0.3400	0.0132
		5	0.0132	0.0008	0.0005	0.0413	0.0001	0.0003	0.0008	0.0231	0.2407	0.2107
		6	0.0016	0.0004	0.0002	0.0389	0.0000	0.0001	0.0004	0.0028	0.3060	0.0269
		7	0.0007	0.0002	0.0002	0.0526	0.0000	0.0001	0.0012	0.0135	0.5330	0.0124
		8	0.0013	0.0002	0.0002	0.0167	0.0000	0.0001	0.0004	0.0024	0.3535	0.0316
	Worst-case	1	0.0047	0.0007	0.0002	0.0992	0.0001	0.0010	0.0018	0.0142	0.8614	0.0472
		2	0.0035	0.0004	0.0004	0.0736	0.0001	0.0006	0.0016	0.0181	0.4891	0.0818
		3	0.0391	0.0058	0.0002	0.0429	0.0001	0.0011	0.0004	0.0357	0.5030	0.2589
		4	0.0094	0.0019	0.0002	0.0519	0.0000	0.0004	0.0005	0.0117	0.4559	0.1306
		5	0.0291	0.0064	0.0011	0.0687	0.0001	0.0005	0.0016	0.0692	0.3570	1.5037
		6	0.0101	0.0026	0.0002	0.0834	0.0000	0.0003	0.0012	0.0095	0.8383	0.2100
		7	0.0027	0.0006	0.0002	0.0755	0.0001	0.0005	0.0024	0.0206	0.6692	0.0590
		8	0.0027	0.0009	0.0002	0.0500	0.0000	0.0012	0.0009	0.0098	0.5090	0.1074

CRediT author statement

Di Marcantonio: Conceptualization, Methodology, Formal analysis, Visualization, Writing - Original Draft**.** **Chiavola**: Conceptualization, Validation, Writing - Review & Editing. **Gioia**: Investigation. **Leoni:** Methodology. **Cecchini**: Project administration. **Frugis***:* Review & Editing**.** **Ceci**: Resources. **Spizzirri**: Project administration. **Boni:** Supervision.

Declaration of Interest Statement

Declaration of interests

☒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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: