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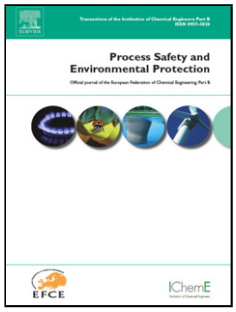

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Evaluation of removal of illicit drugs, pharmaceuticals and caffeine in a wastewater reclamation plant and related health risk for non-potable applications

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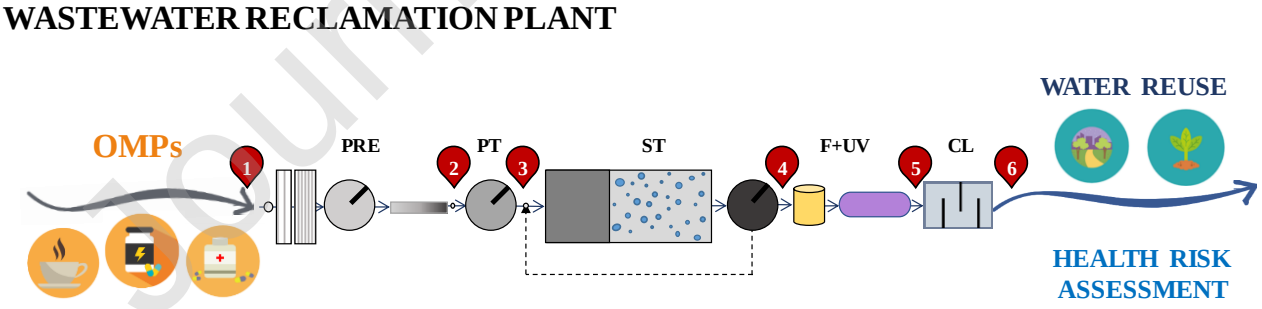
Graphical Abstract



Abstract

The present study aimed at determining the presence and removal rate achieved through the main treatment stages of a full-scale wastewater reclamation plant for some classes of Organic Micropollutants. Furthermore, the human health risk due to the reuse of the final effluent containing residual concentrations of these pollutants for non-potable applications was assessed.
The 8-months monitoring campaign on the influent and effluent of the treatment stages of the plant highlighted that the main removal took place in the bioreactor, reaching median removal of 99%, 97%, 60% 76%, 71%, 96% and 100%, for benzoylecgonine, cocaine, methamphetamine, trimetoprim, sulfadiazine, ketoprofene and caffeine, respectively. This result was also confirmed by the application of the principal component analysis. A further abatement, although slight, occurred in the tertiary compartment (made up by filtration, UV disinfection and chlorination) for sulfamethoxazole, trimethoprim and ketoprofen, determining a final median removal of 50%, 94% and 98%, respectively. A significant correlation between the removal processes of the investigated organic micropollutants and the traditional water quality parameters was also found out. The human health risk for incidental ingestion and dermal contact resulted to be always below 1 under average and worst scenarios, which indicates that the risk can be considered acceptable.

Keywords: contaminants of emerging concern; human health risk; organic micropollutants; reclamation; wastewater reuse; wastewater treatment plant

1 Introduction

Prescription drugs, illicit drugs and pharmaceuticals belong to the wide class of Organic Micropollutants (OMPs), also referred to as Contaminants of Emerging Concern (CEC) (Dulio et al., 2018). These substances are widely dispersed in the sewage systems due to the release from different sources, mainly as a consequence of human consumption, internal adsorption and metabolization. Therefore, beside original molecules, also their metabolites are often present. Through the sewage networks, the OMPs reach the wastewater treatment plants (WWTPs) where they go through a series of process units. Previous research highlights the limited capability of these treatment steps to achieve a complete removal of OMPs because they are not specifically designed and operated to this purpose. Therefore, residual concentrations of OMPs or their metabolites remain in the treated effluent, which is released to the environment or transferred to any of the available reuse options (Martín-Pozo et al., 2019; Martínez-Alcalá et al., 2017; Wilkinson et al., 2017). Indeed, the effluents are considered one of the primary sources of OMPs contamination of surface water and groundwater, thus representing a potential threat for ecosystems and human health due to their toxicity (Luo et al., 2019). In recent years, several stakeholders, such as research groups, water service managers, administrators and legislators, have posed increasing attention to the risk related to the presence of OMPs in

the water sources and enhanced their efforts in searching solutions to address this crucial environmental issue (Couto et al., 2019; Rizzo et al., 2019).

Main stages of municipal WWTPs usually include screening, degritting, primary sedimentation, secondary treatment and, when the treated water reuse is foreseen, also tertiary treatments (Metcalf & Eddy, 2015). The capability of each of these treatment compartments to remove OMPs has not been fully elucidated yet (Pawel Krzeminski et al., 2019). Most of the past studies was carried out at a small scale or focused on the overall performance of the plants (i.e. considering only the concentration change between the influent and the effluent of the plant). By contrast, less information is available on the fate and removal occurring in each stage of full-scale WWTPs; Gao et al. (2012) found a negligible or negative effect of pre-treatment compartment for pharmaceuticals. Wang et al. (2014) proved that primary treatment is not effective for the removal of pharmaceuticals and personal care products whereas an anaerobic/anoxic/aerobic activated sludge treatment can provide a relevant removal of some OMPs but also negative or negligible abatement for some others. About illicit drugs, Cosenza et al. (2018) obtained a removal efficiency above 65% considering a plant composed by traditional activated sludge treatment. Even less is known on the effects of the tertiary treatment implemented in the wastewater reclamation plants (WWRP) with the aim to enhance the effluent quality and allow its reuse. Particularly, the effect of UV was studied by a few authors and all found an improvement of the removal in case of pharmaceuticals and personal care products (Behera et al., 2011; Estrada-Arriaga et al., 2016; Salgado et al., 2012; Wang et al., 2014). However, in the cited studies, the UV treatment was not coupled with a previous filtration step which is usually present in order to ensure the required effluent quality for the optimal UV treatment. Another aspect of interest, which has not been fully addressed yet, is represented by a possible correlation between the removal processes of OMPs and of the water quality parameters usually monitored on a routine basis in the WWTPs (i.e., chemical oxygen demand (COD), total suspended solids (TSS), nitrogen and phosphorus) (Dong et al., 2016; Matamoros et al., 2016). Indeed, it would be interesting to know if operation of the plants to enhance e.g. ammonia nitrogen oxidation can also affect concentration, transformation and removal of OMPs.

In order to reduce the potential negative impacts due to OMPs release with the treated effluent, an improvement of the treatment plant removal capabilities becomes the first requirement (Jones et al., 2004). To this purpose, it is necessary to firstly define the actual performance achieved by the process units of the WWTPs. Secondly, it must be assessed which is the required efficiency to be guaranteed, and therefore the maximum allowable concentration in the treated effluent, in relation to its final destination, i.e., release to the environment or reuse (Bailey et al., 2018; Tiedeken et al., 2017).

It is now internationally recognized that the most suitable approach to address environmental problems (e.g., the contaminated sites) consists of determining the maximum permissible concentration on the basis of the acceptable relative risk for ecosystem and human health. This approach has been also followed by the new European Regulation on minimum requirements for water reuse 2020/741/EU (The European Parliament and the Council of the European Union, 2020). Several risk assessment studies have been conducted to evaluate the potential human health risk due to the use of OMPs-containing water for potable purpose by following

official guidelines such as the one provided by WHO (World Health Organization, 2017), or new approaches such as the quantitative chemical risk assessment proposed by Cantoni et al. (2021). By contrast, limited information is available regarding the risk due to non-potable applications and to standardized procedures for this type of assessment (Deviller et al., 2020). The health risk associated to agricultural field irrigation with wastewater was reviewed by Prosser and Sibley (2015) considering the accumulation in edible tissues of plants. A potential health risk from dietary intake of irrigated crops was obtained for sulfamethoxazole and 17a-ethinylestradiol in an Italian crop filed study (Delli Compagni et al., 2020a). A safe exposure to 10 pharmaceuticals due to landscape irrigation was demonstrated by Semerjian et al. (2018). About non-potable applications, no studies were found about the risk associate to illicit drugs residues in reclaimed water.
Considering the above lacks of knowledge, the present study was carried out with the aim to provide more information on the following issues regarding the removal processes of OMPs in a full-scale wastewater reclamation plant: (1) the effect of each treatment stage; (2) any possible correlation existing between the removal of the main water quality parameters and that of OMPs; (3) the human health risk due to effluent reuse for park irrigation and ornamental fountain feeding, considering different groups of receptors and exposure pathways. To achieve these purposes, the full-scale WWRP was monitored for 8 months, collecting samples in different points of the water treatment line.
Within the wide class of OMPs, the followings were selected for the study based on a previous investigation carried out in the same geographical area, which demonstrated that these compounds were present in the influent wastewater at a higher concentration (Di Marcantonio et al., 2020b). Some of the selected OMPs are included in EU legislation (e.g., trimethoprim, sulfamethoxazole) (European Commission, 2020), whereas others are considered as anthropogenic markers (such as carbamazepine and caffeine) (Buerge et al., 2003; Hai et al., 2018). Cocaine (COC), methamphetamine (MET) and amphetamine (APT) belong to the class of illicit drugs, whereas benzoylecgonine (BEG) and 11-nor-9carboxy-Δ9-THC (THC-COOH) are human metabolites of illicit drugs. Lincomycin (LCN), trimethoprim (TMT), sulfamethoxazole (SMX), sulfadiazine (SDZ) and sulfadimethoxin (SDM) are commonly used antibiotics; carbamazepine (CBZ) is an antiepileptic, ketoprofen (KTP) is an analgesic, warfarin (WFR) is an anticoagulant and caffeine (CAF) is a psychoactive drug also used as a pharmaceutical adjuvant.

2 Materials and Methods

2.1 Wastewater treatment plant

The investigated WWRP is located in the central area of Italy (Lazio region). The plant has a treatment capacity of 90,000 population equivalents (PE), corresponding to an average dry weather flow rate Q=18,700 m^3/d. The layout of the water treatment line is shown in **Fig. 1**. After the initial pumping station, the influent of the plant along with the supernatants from the sludge treatment line enter the pre-treatment compartment made up by medium and fine screens, three in-parallel circular degritting tanks followed by three

longitudinal degreasing tanks. Then, the wastewater is split into two sections, named as Section 1 and Section 2, respectively, which have a similar layout: The present experimental study was carried out in Section 2, which includes the following main units: two in-parallel primary settlement tanks, two in-parallel activated sludge process lines each one made up by pre-denitrification (total volume, V_D=1400 m^3) followed by organic matter oxidation-nitrification (with fine bubble aeration and total volume, V_N=2800 m^3, and average Sludge Retention Time, SRT=13 d) and two secondary settlement tanks. The effluents from Section 1 and 2 are mixed and sent to the tertiary treatment stage which consists of: three in-parallel rapid sand filter units (filtration media composed by monocrystalline sand and anthracite, specific flowrate equal to 2.8 m/h) a UV disinfection tank (contact time equal to 40 min), a chlorination tank (contact time equal to 40 min and sodium hypochlorite dosage equal to 3.5 mg/L). The characteristics of the UV system are reported in **Table S.M. 1** of Supplementary materials. The chlorination unit is in operation only during the bathing season (i.e., from May to September) according to the plant's permit.

2.2 Sampling campaign

The sampling campaign was conducted from May 2020 to December 2020 for a total number of 14 days, with a temporal interval between two consecutive sampling days in the range 10 d-30 d. The following sampling points (as indicated by the numbers reported in **Fig. 1**) were selected along the water treatment line with the aim to assess the removal achieved in each treatment stage: 1) influent to the plant (IN); 2) effluent of pre-treatments (PRE); 3) effluent of primary treatments (PT); 4) effluent of secondary treatments (ST); 5) effluent of tertiary treatments (F+UV); 6) effluent of chlorination (CL). The latter sampling point, being chlorination in operation only from May to September as reported above, was available only for 7 out of 14 sampling days. The samples were collected on Wednesday, since a preliminary investigation showed that the highest OMPs concentrations at the inlet of the plant occurred in the middle of the week (data not here reported).

Due to the long Hydraulic Retention Time of the plant (average HRT=18 h), wastewater sample collection was carried out through grab sampling; the data obtained were then statistically processed to provide representative results. The grab samples were manually collected using a 1 L Nalgene bottle, then transferred to the laboratory where they were pre-treated and finally stored at T=4°C until the analyses. The following 14 OMPs 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), sulfadimethoxin (SDM), carbamazepine (CBZ), ketoprofen (KTP), warfarin (WFR) and caffeine (CAF). Furthermore, the following water quality parameters were also determined in each sample: total suspended solids (TSS), chemical oxygen demand (COD), ammonia, nitrite and nitrate nitrogen (NH_4^+-N, NO_2^--N and NO_3^--N, respectively) and total phosphorous (P_{tot}).

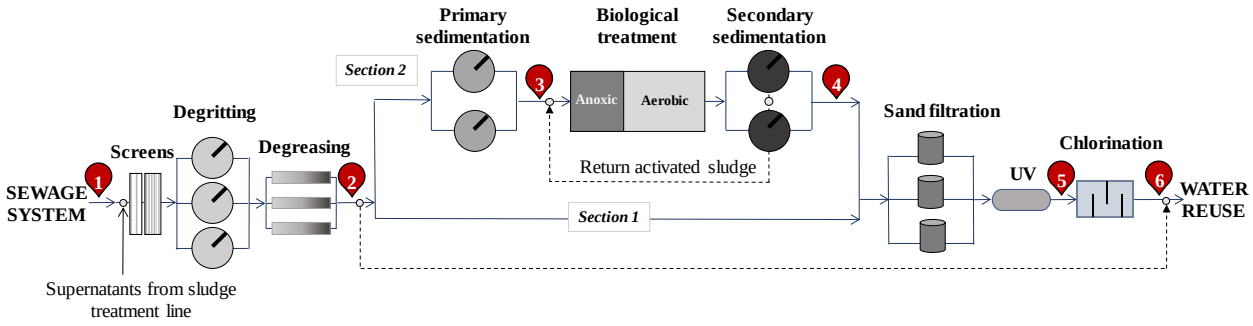


Fig. 1 Wastewater Reclamation Plant (WWRP) layout and sampling points: 1) IN, 2) PRE, 3) PT, 4) ST, 5) F+UV, 6) CL.

2.3 Chemicals

Standard solutions of OMPs (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), each one at a concentration of 100 µg/mL in methanol solution. Main chemical-physical characteristics of the contaminants are reported in **Table S.M. 2** ("NORMAN Database System," 2020; Williams et al., 2017).

2.4 Analytical methods

The water quality parameters were measured by following 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 determinations were validated according to ISO Standards. The quantitative analysis of OMPs was performed by applying the Ultra-Performance Liquid Chromatography coupled to tandem Mass Spectrometry (UHPLC–MS/MS). The analytical method is based on EPA 538 and on previous studies by the same research group; it was also accredited by ACCREDIA for most of the analytes in 2020 (U.S. EPA, 2009; Di Marcantonio et al., 2020b). A detailed description of the OMPs analytical method as well as the acceptance criteria are reported in Supplementary Materials (**Table S.M. 3**).

2.5 Health risk assessment for wastewater reuse

A further aim of the present study was to assess the value of the human health risk due to the reuse for non-potable purposes of the treated effluent containing residual OMPs concentration as determined in the sampling campaign. The assessment was conducted considering the reuse options actually practised in the

WWRP, i.e., irrigation of parks, gardens and green areas and feeding of ornamental fountains; besides, different exposure scenarios were included in the analysis based on a conservative approach.

For the reuse as ornamental fountain feeding, the maintenance workers were identified as the most exposed receptors (referred to as *Workers* in the following sections). It was assumed a work schedule of 250 days per year (exposure frequency, EF), corresponding to 5 days/week including holidays, 8 h/day (exposure time, ET), 30 years of activity (exposure duration, ED) and 70 kg as body weight (BW). Regarding the reuse for park, gardens and green areas irrigation, children were identified as the most exposed receptors (referred to as *Children* in the following sections). It was assumed that a 15 kg child (BW) plays for 6 years (ED) at a frequency of once per week for 1 hour throughout a duration of 6 months (EF) on areas freshly irrigated with the treated effluent (Semerjian et al., 2018).

For each receptor group, incidental ingestion and dermal contact were identified as the exposure pathways. Specifically, the incidental ingestion by *Workers* was estimated to occur at a rate of 4 mL/h (ingestion rate, IR). For dermal contact, it was assumed a 10% exposed skin area (SA = 3300 cm^2) at any given moment during the work day (U.S. EPA, 2004). In the case of *Children*, incidental ingestion was estimated to occur at a rate of 10 mL/h (IR) and it was supposed that the entire hands, forearms and lower legs (SA = 1400 cm^2) could get wet (U.S. EPA, 2004). The exposure due to inhalation was not taken into account since the selected OMPs are non-volatile and unlikely to be released by aerosols.

The risk assessment, summarized below, followed the procedure proposed by previous studies (Semerjian et al., 2018; Watts et al., 2007). Particularly, the acceptable concentration (AC) in the treated effluent for each exposure scenario was calculated through the following equation (Eq. 1):

$$AC\left[\frac{\mu g}{L}\right] = \frac{ADI}{Exp} \quad (1)$$

where ADI and Exp stand for the acceptable daily intake [µg/(kg·day)] and exposure rate [L/(kg·day)], respectively.

The ADI represents the toxicological benchmark, that is the daily intake of the compound that is unlikely to result in adverse health effects to humans (Semerjian et al., 2018). The ADI values of the pharmaceutical compounds, listed in **Table 1,** were calculated by the ratio of the therapeutic dose (in µg/(kg·d, (assuming 70 kg as body weight for adults) to a default uncertainty factor posed equal to 3000 (Watts et al., 2007). Identification of the therapeutic dose for illicit drugs was not possible because of the lack of the required information within the technical literature; therefore, the ADI values reported in **Table 1** for illicit drugs were calculated assuming a very precautionary minimum therapeutic dose equal to 1 mg, as suggested by Watts et al. (2007).

Table 1 ADI values used for the acceptable concentration calculation.

OMPs	**ADI [µg/(kg·d)]**	**References**
COC	0.005	(Watts et al., 2007)

BEG	0.005	(Watts et al., 2007)
THC-COOH	0.005	(Watts et al., 2007)
MET	0.005	(Watts et al., 2007)
APT	0.005	(Watts et al., 2007)
KTP	100	(Watts et al., 2007)
CBZ	0.3	(Leung et al. 2013; Snyder et al. 2010)
SMX	3.8	(Semerjian et al., 2018)
TMT	2.7	(Leung et al., 2013)
LCN	25	(Snyder et al., 2010)
SDZ	9.5	(Semerjian et al., 2018)
SDM	NA	-
WRF	0.16	(Schwab et al., 2005)
CAF	150	(Leung et al., 2013)

Eqs. 2 and. 3 were used to calculate the exposures for the different scenarios as previously detailed (Semerjian et al., 2018):

$$Exp_{Ingestion}\left[\frac{L}{kg-day}\right] = \frac{IR \cdot EF \cdot ED}{BW \cdot AT} \quad (2)$$

$$Exp_{Dermal}\left[\frac{L}{kg-day}\right] = \frac{SA \cdot PC \cdot ET \cdot EF \cdot ED}{BW \cdot AT \cdot 1000} \quad (3)$$

where IR is the ingestion rate [L/day], EF is the exposure frequency [days/year], ED is the exposure duration [years], BW is the body weight [kg], AT is the averaging time equal to 365·ED [days], SA is the exposed skin surface area [cm^2], PC is the chemical specific permeability constant [cm/h] and ET is the exposure time per day [h/day].

The PC value of OMPs was estimated using the following equation (Eq. 4), as a function of the octanol/water coefficient (K_{ow}) and molecular weight (MW) (US EPA, 2007):

$$PC\left[\frac{cm}{h}\right] = -2.80 + 0.66 \cdot logK_{ow} - 0.0056 \cdot MW \quad (4)$$

Finally, the human health risk was assessed by calculating the risk quotient, RQ, for each contaminant and all the considered exposure pathways (Eq. 5):

$$RQ[\%] = \frac{MEC}{AC} \quad (5)$$

The RQ represents the ratio between the measured concentration (MEC) in the treated effluent and the calculated acceptable concentration (AC, see Eq. 1): if RQ ≥ 1, the water reuse is likely to determine

negative effects, whereas for RQ < 1 it does not pose any risk under the established conditions (Semerjian et al., 2018).

The risk assessment was carried out for two different scenarios (i.e., *average* and *worst*) depending on the effluent concentrations assumed as MECs: the median value for the average scenario and the 99th percentile for the worst scenario.

2.6 Calculation methods

The frequency of detection (F_D) was calculated based on Eq. 6:

$$F_D[\%] = \frac{n}{N} \cdot 100 \quad (6)$$

where N is the total number of samples and n is the number of samples with a concentration above the Minimum Reporting Levels (MRL), for a given contaminant. The values of MRL for each contaminant are reported in Supplementary Materials (**Table S.M. 3**).

All the boxplot graphs presented in this study displaying different statistical elements, were built using the R software, as described by Di Marcantonio et al. (2020b).

When OMPs concentration resulted to be below the MRL, the value was set to half of the MRL in the calculation of statistical descriptor and removal efficiency (European Commission, 2009).

The percentage removal efficiency (R) achieved by each treatment stage was calculated as below:

$$R\ [\%] = \frac{C_{in} - C_{sp}}{C_{in}} \cdot 100 \quad (7)$$

where C_{in} and C_{sp} stand for the concentrations of each contaminant measured in the influent of the plant (i.e. sampling point number 1 (IN) of **Fig. 1**) and the effluent of each stage, respectively. The removal was not calculated if the influent and effluent concentration were both equal to MRL.

In order to evaluate the statistical difference between the removal efficiencies achieved by the different treatment stages for each class of OMPs and for all pollutants grouped together, Wilcoxon test was applied to the removal efficiency data. This test is a non-parametric test used for assessing whether two independent and unpaired groups have significantly different median (p-value below 0.05); it is considered as a valid test for data that are not normally distributed, as in the present case. The normality of the data-sets was checked through Shapiro-Wilk normality test (Conover, 1999). The analysis was carried out thought the R package "stats" (R Core Team, 2019).

The whole data set (i.e. the concentrations of OMPs and water quality parameters) 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 applying the R package "FactoMineR" (Lê et al., 2008). More details about PCA interpretation are reported in supplementary materials (see **Fig. S.M. 1**).

3 Results and discussions

3.1 OMPs occurrence in the influent and effluent

Concentrations of OMPs measured in the influent (IN) and effluent (OUT) of the WWRP, along with the frequency of detection (F_D), are reported in **Fig. 2**.

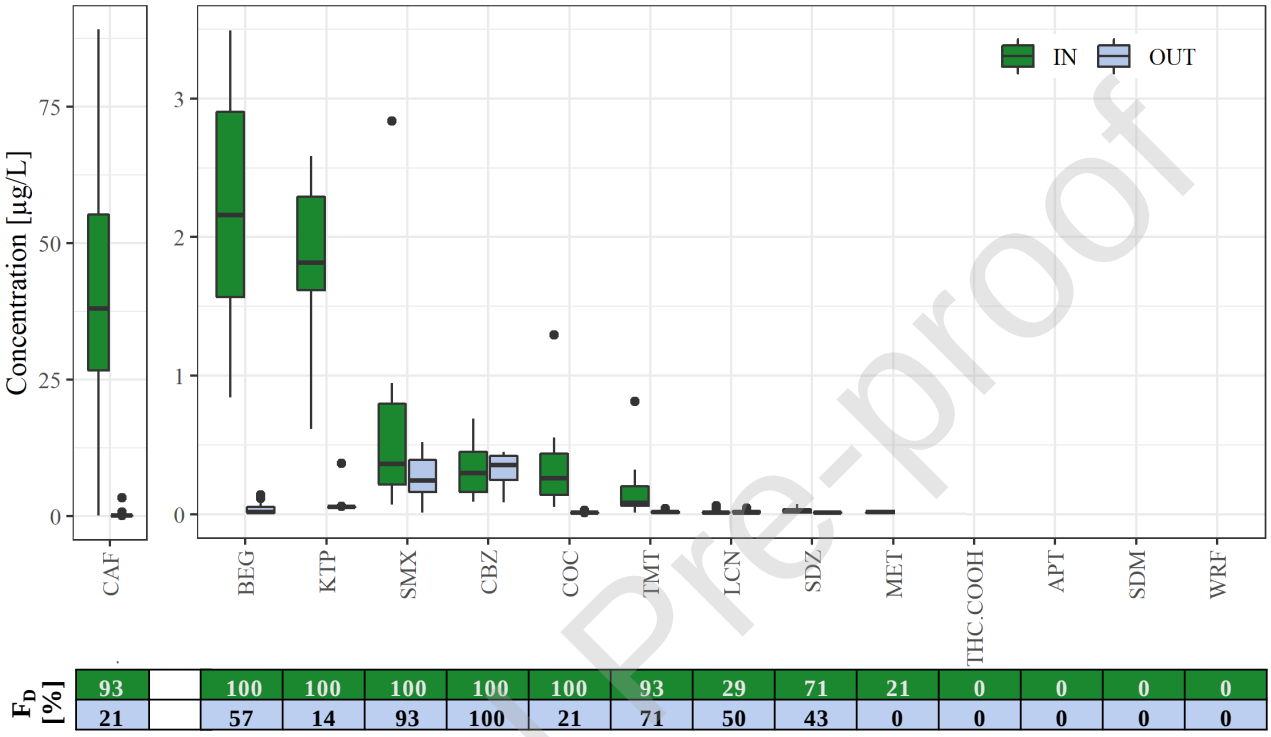


Fig. 2 Statistical representation of OMPs concentrations in the influent (IN) and effluent (OUT) and corresponding frequency of detection (F_D).

The F_D values highlight that APT and THC-COOH (drugs of abuse), WRF (anticoagulant) and SDM (antibiotic) were always below the MRL in both the influent and effluent samples, whereas MET (illicit drug) only in the effluent. BEG (human metabolite of illicit drugs), COC (illicit drug), SMX (sulfonamide bacteriostatic antibiotic), CBZ (antiepileptic) and KTP (analgesic) were detected in all the influent samples (100%). CBZ was also detected in all the effluent samples (100%) and SMX in most of them (93%).
The following observations can be drawn by looking more in details at the concentrations of each class of OMPs.

Illicit drugs

BEG and COC were detected in the influent at a very high F_D, and with 2.47 µg/L and 0.26 µg/L as median and 4.94 µg/L and 1.29 µg/L as maximum concentrations, respectively. The BEG values fall within the range of data reported by similar scientific studies, as shown in **Table 2**, whereas maximum value of COC was far above the upper limit of this range. Repice et al. (2013) and Cosenza et al. (2018) found lower values of BEG in the influent of WWTPs located in Veneto and Sicily (i.e. 0.48 µg/L and 0.19 µg/L as average concentration, respectively). Those data are related to samples collected in 2010 in the former study and 2015 in the latter one. This can be one of the reasons which can motivate the discrepancy with the values measured in 2020 in the present WWRP. BEG was found at a higher concentration in the influent as compared to COC. This can be explained by the fact that the former is the product of the human metabolism of the latter one: particularly, it is reported that for each COC dose, only 1-9% is excreted in the urine as unchanged compound, while 35-54% is released as BEG (Ratola et al., 2012).

As far as the effluent is concerned, the F_D as well as the concentrations of BEG and COC were much lower than the corresponding values measured in the influent: particularly, 0.14 µg/L and 0.03 µg/L were the maximum for BEG and COC, respectively, whereas the median was below MRL for both compounds.

Antibiotics

SMX and TMT were the most frequently detected among the antibiotics; for SMX, the relative frequency of detection did not change appreciably between the influent and effluent. The influent medians were 0.36 µg/L and 0.08 µg/L, whereas the maximum of 2.84 µg/L and 0.82 µg/L, for SMX and TMT, respectively; the values found in the effluent were 0.24 µg/L and 0.01 µg/L as median, and 0.52 µg/L and 0.04 µg/L as maximum, respectively. TMT was also monitored by Verlicchi et al.(2014) in the influent and effluent of a WWTP located in Emilia Romagna region (Italy); the concentrations detected (i.e. 0.08 µg/L and 0.04 µg/L, respectively) are comparable with those reported in the present study. This conformity suggests that the consumption of this pharmaceutical compound did not change significantly with the years and the geographical areas. This behavior differs from that observed for BEG.

SDZ was the following antibiotic in terms of F_D and median and maximum values in the influent (0.02 µg/L and 0.07 µg/L, respectively). Its median effluent concentration was below the MRL, whereas the maximum was equal to 0.02 µg/L. All these values are rather in accordance with those referred by other studies.

Since TMT is usually consumed in association with SMX, Thiebault et al. (2020) proposed a theoretical ratio of SMX/TMT as a tool to characterize raw wastewaters and their origin: they reported a ratio ranging from 1.1 to 3.3, with median value equal to 2. It is interesting to notice that in the present study, the SMX/TMT ratio ranged from 1.2 to 5.0, with a median value equal to 3.4. The upper values herewith founded are therefore higher than the theoretical ratio in raw wastewater proposed by Thiebault et al. (2020). This difference is likely due to the presence of farming activities in the area served by the WWRP, which release into the sewage network livestock wastewater containing high concentrations of SMX.

LCN was detected in the influent with median concentration below MRL and maximum equal to 0.06 µg/L, respectively. Besides, an increase of its F_D was observed after the treatments (i.e. from 29% to 50%). This observation was also found by other authors. A proposed hypothesis to explain this phenomenon is that

conjugated groups of lincomycin metabolites could be broken and converted into lincomycin, causing an increase of the detection frequency and the median concentration in the effluent of the plant (i.e. median effluent concentration equal to 0.01 µg/L and maximum of 0.02 µg/L) (Chen et al., 2020a).

Other pharmaceuticals and Caffeine

KTP and CBZ were both detected in all the influent samples (F_D =100%). CBZ showed a F_D equal to 100% also in the effluent and changed only slightly its concentration during the treatments, in accordance with the recalcitrant nature as reported by several authors (Dey et al., 2019; Hai et al., 2018). For KTP, the median and maximum influent concentrations were 2.11 µg/L and 5. 06 µg/L, respectively. The values of KTP concentration detected by Patrolecco et al., (2015), during a sampling campaign carried out in 2011 in four WWTPs located in the Lazio region, were below the detection limit both in the influents and effluents. Differently, Di Marcantonio et al. (2020b), during a campaign conducted between March 2017 and December 2019, found an average concentration of KTP in influents of 76 WWTPs in the same Lazio region equal to 1.42 µg/L. This trend seems to suggest that consumption of this anti-inflammatory drug has been increasing. Values of F_D and KTP concentration in the effluent were lower (i.e., 14% and 0.37 µg/L as maximum, respectively), thus showing a removal by the treatments.

The median value of CBZ detected in influent and effluent of the WWRP were 0.30 µg/L and 0.35 µg/L, respectively. Similarly, other studies conducted in Italian plants measured average concentrations ranging from 0.20 µg/L to 0.57 µg/L in the influents and from 0.19 µg/L and 0.39 µg/L in the effluents (Di Marcantonio et al., 2020b; Patrolecco et al., 2015; Repice et al., 2013b; Verlicchi et al., 2014).

Among the investigated OMPs, CAF was that one detected in the influent at the highest concentration and in most of the samples (F_D=93%). The median and maximum concentrations were 38.02 µg/L and 89.19 µg/L, respectively. CAF was detected in 21% of the effluent samples and at a lower concentration than in the influent (i.e. 3.35 µg/L as maximum and below the MRL as median).

Table 2 shows influent and effluent concentrations and removal efficiencies provided by some scientific studies performed on treatment plants having similar characteristics as the present WWRP. Comparing the data found in this study with the ranges of **Table 2** shows a good agreement for all the classes of OMPs.

Table 2 OMPs concentrations in the influent and effluent and removal efficiencies reported by similar studies.

OMPs	**Concentrations**			**Removal efficiencies**	
	IN [µg/L]	**OUT [µg/L]**	**References**	**[%]**	**References**
COC	0.0007 – 0.2915	0.0002 – 0.0997	(Cosenza et al., 2018; Senta et al., 2013a; Skees et al., 2018)	72 -100	(Kasprzyk-Hordern et al., 2009; Pal et al., 2013; Subedi and Kannan, 2014; Zuccato and Castiglioni, 2009)
BEG	0.005 – 10.55	0.0008 – 3.42	(Balakrishna et al., 2017; Bijlsma et al., 2014; Castiglioni, 2006; Cosenza et al., 2018; Di Marcantonio et al., 2020b; Pal et al., 2013; Petrie et al., 2015; Repice et al., 2013a; Senta et al., 2013a; Skees et al., 2018)	83 -100	(Chiavola et al., 2017; Yadav et al., 2019a; Zuccato and Castiglioni, 2009)

THC-COOH	0.015 – 0.10	0.001 – 0.044	(Cosenza et al., 2018; Senta et al., 2013a)	11 - 99	(Chiavola et al., 2017; Zuccato and Castiglioni, 2009)
MET	0.001 – 0.39	0.0002 – 0.50	(Balakrishna et al., 2017; Cosenza et al., 2018; D'Alessio et al., 2018; Petrie et al., 2015; Senta et al., 2013a)	60 - 98	(Chiavola et al., 2017; Zuccato and Castiglioni, 2009)
APT	0.002 – 4.72	0,0006 – 2.24	(Balakrishna et al., 2017; Petrie et al., 2015; Senta et al., 2013a)	85 - 99	(Chiavola et al., 2017; Zuccato and Castiglioni, 2009)
KTP	0.00013 – 11.24	0.00034 – 1.77	(Behera et al., 2011; Couto et al., 2019; Deblonde et al., 2011; Di Marcantonio et al., 2020b; Lishman et al., 2006; Palli et al., 2019)	31- 100	(Behera et al., 2011; Deblonde et al., 2011; Di Marcantonio et al., 2020b; Salgado et al., 2012; Tiwari et al., 2017; Watts et al., 2007)
CBZ	0.043 – 2.59	0.00037 – 3.117	(Balakrishna et al., 2017; Behera et al., 2011; D'Alessio et al., 2018; Deblonde et al., 2011; Di Marcantonio et al., 2020b; Pawel Krzeminski et al., 2019; Palli et al., 2019; Petrie et al., 2015; Repice et al., 2013a; Tran and Gin, 2017)	-110 - 50	(Behera et al., 2011; Couto et al., 2019; Estrada-Arriaga et al., 2016; P. Krzeminski et al., 2019; Palli et al., 2019; Verlicchi et al., 2012; Yang et al., 2017)
SMX	0.00029 – 5.49	0.02 – 2.07	(Balakrishna et al., 2017; Behera et al., 2011; D'Alessio et al., 2018; Deblonde et al., 2011; Di Marcantonio et al., 2020b; Petrie et al., 2015)	36 - 68	(Behera et al., 2011; Couto et al., 2019; Watts et al., 2007)
TMT	0.033 – 3.44	0.013 – 1.152	(Balakrishna et al., 2017; Behera et al., 2011; D'Alessio et al., 2018; Di Marcantonio et al., 2020b; Petrie et al., 2015; Senta et al., 2013b)	-17 -69	(Behera et al., 2011; P. Krzeminski et al., 2019; Verlicchi et al., 2012)
LCN	0.015 – 19.40	0.043 – 9.089	(Balakrishna et al., 2017; Behera et al., 2011; Verlicchi, 2012)	-11 - 57	(Behera et al., 2011; Blair et al., 2015; Verlicchi, 2012)
SDZ	0.00039 – 0.254	0.00009 – 0.129	(Couto et al., 2019; García-Galán et al., 2011; Verlicchi, 2012)	32 - 98	(Couto et al., 2019; Verlicchi, 2012)
SDM	0.0001 – 0.213	0.00005 – 0.07	(García-Galán et al., 2011; Santos et al., 2010; Verlicchi, 2012)	50 - 100	(García-Galán et al., 2011; Verlicchi, 2012)
WRF	0.0001 – 0.33	0.00002 – 0.447	(Couto et al., 2019; Gómez-Canela et al., 2014; Kostich et al., 2014)	82 - 100	(Couto et al., 2019; Gómez-Canela et al., 2014)
CAF	1.6 - 118	0 – 51.7	(Balakrishna et al., 2017; Behera et al., 2011; Deblonde et al., 2011)	96 - 100	(Behera et al., 2011; Blair et al., 2015; Buerge et al., 2003; Deblonde et al., 2011; Estrada-Arriaga et al., 2016; Sousa et al., 2017)

3.2 Effect of the treatment stages on the OMPs removal

Fig. 3 shows the median concentrations measured at the outlet of the different treatment stages and the relative standard deviation. The minimum, maximum and median concentrations determined in the same points are reported in **Table S.M. 4**. The corresponding removal efficiency calculated with respect to the concentration measured in the influent to the plant, for each class and all OMPs grouped together, are shown in **Fig. 4** whereas the median values are summarized in **Table 3**. Contaminants showing a F_D always equal to 0 were excluded from the following discussion (i.e., THC-COOH, APT, SDM, WRF).

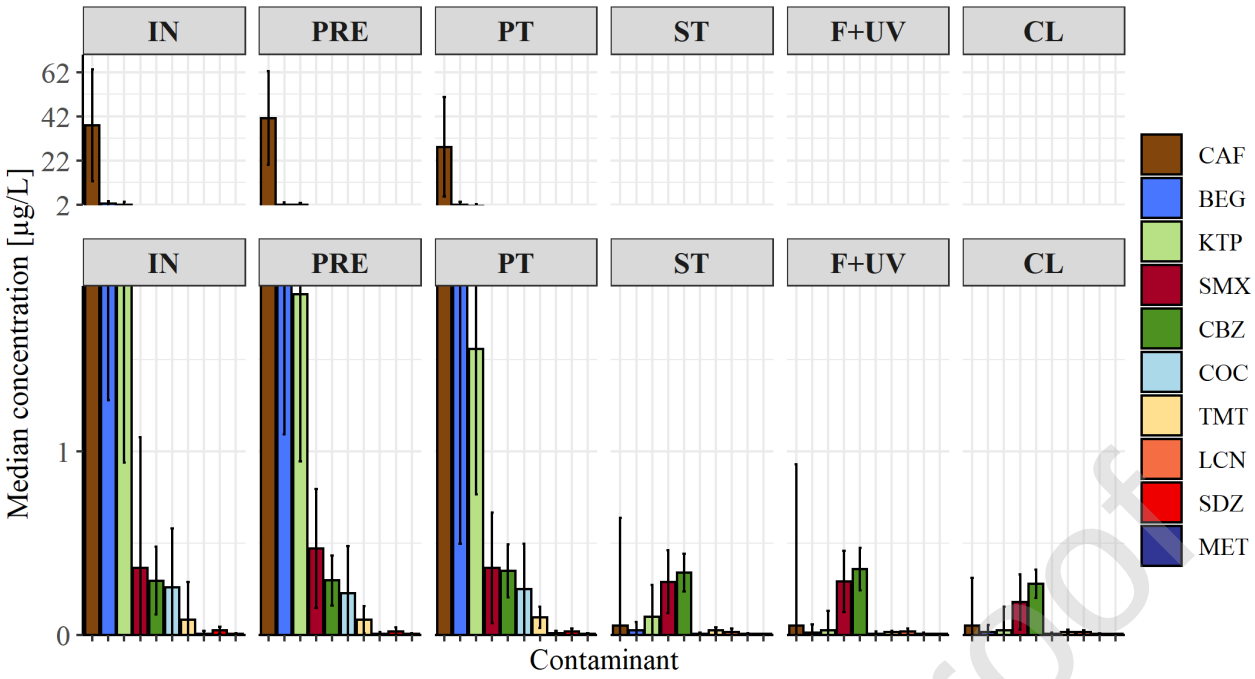


Fig. 3 Median concentration of each contaminant measured in the influent to the plant and in the effluent of each treatment stage. The error bar represents the standard deviation.

Table 3 Median removal efficiency after each treatment stage calculated with respect to the concentration measured in the influent to the plant and the effluent of each treatment stage.

OMPs	PRE	PT	ST	F+UV	CL
	%	%	%	%	%
BEG	13	17	99	100	99
COC	7	9	97	97	98
MET	10	1	60	60	60
SMX	2	-22	25	33	50
TMT	17	17	76	87	94
LCN	23	-34	-172	-264	-224
SDZ	19	21	71	65	64
KTP	13	33	96	99	98
CBZ	-3	-23	-10	-21	-28
CAF	8	22	100	100	100
All OMPs	8	17	84	87	90

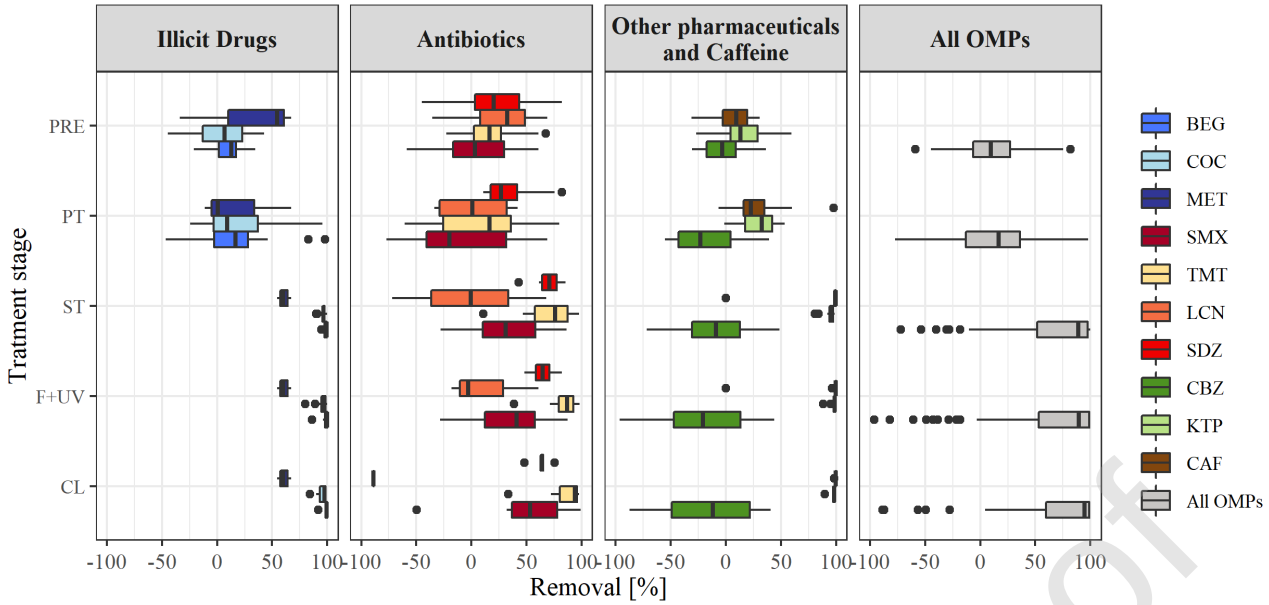


Fig. 4 OMPs removal efficiency after the different treatment stages. The data are grouped based on the class of contaminants and considering all OMPs grouped together.

Illicit drugs

The plant achieved a very high removal of COC and BEG (up to 98 and 99%, respectively), in agreement with the results shown by other studies (**Table 2**). Regarding BEG and the effect of each treatment unit, a low concentration reduction was observed due to PRE and PT (17% as total), whereas the main removal took place in the ST. The effluent from this stage reached the MRL and the tertiary treatment did not change significantly the concentration. The high removal, also referred by other authors (Chiavola et al., 2019; Yadav et al., 2019b), can be ascribed to the chemical-physical characteristics of the molecule, i.e., the high water solubility (S=1605 mg/L) and the low value of the octanol-water partition coefficient (Log K_{ow} = 2.30) (**Table S.M. 2**). These properties lead to suppose that BEG molecules were slightly adsorbed on the solid phases in the primary treatment, giving rise to the limited removal above mentioned; then, they were extensively biodegraded in the following activated sludge process due to high biodegradability.

COC behaved very similarly to BEG, which represents its main metabolite. Indeed, effects of PT and PRE were very low (total removal of 9%), whereas the secondary treatment provided the main removal rate. The median concentration in the effluent from this stage was below the corresponding MRL, and contribution of the tertiary treatment was negligible. Due to the high solubility (1298 mg/L at T=25°C) and the values of the partition coefficients (LogK_{ow} < 3 and pKa = 8.61) (listed in **Table S.M. 2**), COC was mainly removed by biodegradation in the activated sludge process, in accordance with other studies (see **Table 2**). Subedi and Kannan (2014) found similar removal by the ST (>95%); however, they also observed a higher reduction in the PT (efficiency falling in the range 51-75%). These differences are likely to be ascribed to the different wastewater composition and treatment conditions of the investigated plants. It might be present a higher

solid content in the influent to the PT which favored the adsorption of COC molecules with the following removal by settling.

MET was slightly removed in the PRE and PT stages, whereas the main reduction (up to 60%) was observed in the ST; the removal did not change in the following stages. These results agree with the high solubility and the hydrophilic characteristics of MET (K_{OW} = 2.07, S = $1.33 \cdot 10^4$ mg/L); moreover, Boni et al. (2018) proved that nitrifying bacteria can provide a contribution to the removal of MET.

Antibiotics

Removal of SMX through PRE and PT was negligible. Then, it increased progressively to 25%, 33% and 50%% through ST, F+UV and CL, respectively. These ranges of values are in accordance with other studies (Yang et al., 2017). The lower removal observed in the biological stage with respect to that measured for other OMPs can be explained by the pH value: indeed, it is reported that higher removal rate can take place when SMX is present in its hydrophobic form, which occurs under acidic conditions (Couto et al., 2019). However, the wastewater treatment plants and particularly the secondary treatment process are usually operated at pH values close to neutrality, which do not favor higher removal rate (Metcalf & Eddy, 2015). Nevertheless, the ST was capable to improve the removal significantly as compared to the PT. Moreover, it must be taken into account that 15% of SMX dose is excreted from the human body as unaltered drug, whereas about 50% is metabolized into N 4-acetylsulfamethoxazole which can be re-transformed into SMX during the biological treatment process (Gao et al., 2012; Göbel et al., 2005). This process can give rise to a subsequent increase of SMX concentration, thus reducing the overall value of removal. It is noteworthy the higher SMX removal observed after F+UV and after CL with respect to the negligible contribution provided by these processes versus the other investigated OMPs. The monitoring activity of 36 Italian WWTPs equipped with tertiary treatment stage showed comparable median removal efficiency (i.e. above 60%) (Di Marcantonio et al., 2020b).

Similarly, also in the case of TMT a good contribution to the overall removal was provided by the tertiary treatments. Particularly, the effect due to PRE accounted for 17% as median value, whereas PT did not provide any additional contribution; the highest removal increase was achieved by the ST (values up to 76%). This finding can be explained by the low value of $LogK_{ow}$ (i.e., 0.73) which makes adsorption process not to be a relevant removal mechanism, as also reported in the scientific literature (Tran et al., 2016). The activated sludge was indeed capable of TMT biodegradation/biotransformation to a wide extent, favoured by the nitrifying microorganisms activity under aerobic conditions and the relatively long Sludge Retention Time (13 d as average), in accordance with other studies (Michael et al., 2013). Removal of TMT also occurred in the F+UV and CL treatments: indeed, its value increased up to 87% after the first stage and to 94% after the second stage. This observation is consistent with a previous study of the same research group where an improvement of TMT removal after tertiary treatments was also observed (Di Marcantonio et al., 2020b). Other studies report similar findings. For instance, trimethoprim was reported to be degraded (removal above 75%) in dual media or sand biofilters (Zhang et al., 2017); a moderate reduction of TMT concentration was also observed through UV radiation by Wang et al. (2014). Characteristics and operating

conditions of the chlorination unit, such as contact time and disinfectant dose, are likely suitable to spur SMX chemical oxidation (Michael et al., 2013). Removals of LCN were null or negative in all the treatment stages. It must be remembered that the median concentration in the influent remained close to MRL; furthermore, a recombination of the parent compound might have occurred from their conjugates and metabolites through the different treatment processes, thus increasing the concentration in the outlet which determined high negative removal efficiency, as reported by other authors (Behera et al., 2011; Blair et al., 2015; Chen et al., 2020b; Di Marcantonio et al., 2020b; Verlicchi, 2012).

Concerning SDZ, PRE and PT provided removal percentage of 19% and 21%, respectively, whereas ST increased it to 71%, which is in agreement with the reference data of **Table 2**. The removal slightly decreases through F+UV (to 64%) and remained constant in CL (65%). It is likely that UV caused re-formation of the parent sulfonamide due to photo-processes, which determined an increased concentration in the outlet and correspondingly a reduction in the removal percentage (Bahnmüller et al., 2014).

Other pharmaceuticals and caffeine

KTP was efficiently removed by the plant with the main contribution provided by the biological process, which is in accordance with other studies (**Table 2**). A progressive increase was observed along the water treatment line: from 13% in the PRE to 33% in the PT to 96% in the ST and to 98-99% after F+UV. Based on the value of $LogK_{ow}$ (equal to 3.12), it can be assumed that adsorption was the mechanism responsible of the removal observed in the PT (Metcalf & Eddy, 2015). Moreover, biodegradation in the activated sludge process prevailed as removal mechanism due to biodegradable nature of the KTP molecule (removal equal to 96%). Chlorination, sand filtration and UV did not determine any significant change in the final concentration (the removal achieved after these treatment stages were 99% and 98%, respectively).

Low or negative removals were observed for CBZ throughout the water treatment line. The increased concentration observed in the outlet of PRE and PT might be also due to the release from the solid particles (i.e., faeces) present in the wastewater. It must be highlighted that CBZ is characterized by low values of the solid-liquid and octanol-water partitioning coefficients (K_D = 1.2 L/kg TSS and LogKow 2.45, respectively) which make the molecule to be refractory to any treatment process and particularly to biological oxidation, as reported by several authors (Martínez-Alcalá et al., 2017; Min et al., 2018; Tran and Gin, 2017). Moreover, a transformation of the conjugated forms into the original parent compound can occur. Therefore, it is expected that the processes usually implemented in the plants treating the domestic sewage are unable to achieve any removal from the liquid phase (Hai et al., 2018; Jelic et al., 2011; Tran et al., 2016). The tertiary treatments did not provide an improvement to the removal efficiency. The efficacy of the single tertiary treatment technologies of the monitored WWRP was also evaluated by other authors: sand filtration was proved not to be really effective for CBZ removal from wastewater (removal ranging from -52% to 22% (Nakada et al., 2007)) as well as from water for human consumption (removal below 10% (D'Alessio et al., 2015; Di Marcantonio et al., 2020a)). Wang et al. (2016) observed a positive synergistic effect due to a combination of UV and chlorine: the simultaneous CL and UV processes result in the formation of hydroxyl and chlorine radicals which makes them as an advanced oxidation process, which were proved to be effective

for CBZ removal. By contrast, the application of the two treatments separately is not expected to form those radicals, which made the treatment less effective for CBZ abatement (Di Marcantonio et al., 2020a; Nakada et al., 2007). Moreover, direct UV irradiation at disinfection doses was observed not to be effective on micropollutants removal (Yang et al., 2014).

Removal of caffeine was achieved in the first treatment stages: the lowest value took place in PRE and PT (8% and 22%, respectively), whereas the highest contribution was due to the biological process where it reached 100%. These results are in accordance with the main caffeine's properties, such as the high water solubility (2.16 10^4 mg/L), the low octanol-water partition coefficient (Log K_{ow} = -0.07) and the ready biodegradability (Ahmed et al., 2017; Behera et al., 2011; Warner et al., 2019). The aptitude of this contaminant to dissociate in water rather than to be adsorbed on the solid particles explains the efficient removal achieved in the biological process, as also referred by a high number of studies (see **Table 2**).

The above data highlight that among the selected OMPs, BEG, COC, KTP, TMT and CAF were removed by 100% or very closely in the WWRP. Lower removals were observed for MET (60%), SMX (50%) and SDZ (64%). CBZ and LCN were not affected by all the treatment stages.

The main contribution was always provided by the biological process in the ST. However, high removal from the liquid phase in the biological treatment could also not correspond only to a degradation of the contaminants but also to their adsorption onto the sludge flocs. This mass transfer is likely to occur for the compounds characterized by poor solubility and good affinity with the solid phase (i.e. activated sludge flocs) as described by the solid-liquid partition coefficient (K_D). To comprehensively estimate the effectiveness of WWTPs and WWRPs, it is of a paramount importance to consider the presence of OMPs also on the wasted sludge. Nevertheless, the present study focused on the liquid effluent of the plant being only this phase intended for reuse. PRE and PT achieved removals from the liquid phase in the range 7-33% depending on the specific compound: since biodegradation does not take place in these stages, the observed removal percentages were ascribed to the adsorption of the contaminants on the suspended solids followed by their co-sedimentation. Tertiary treatments were only capable of a limited removal and for a few OMPs. Particularly, a relevant difference in the median removal achieved by ST and F+UV or CL was present only in the cases of SMX, TMT and KTP. The same conclusion can be drawn by considering the data regarding all OMPs grouped together (**Fig. 4**).

A statistical analysis was performed to estimate the significance of the differences observed between the removal efficiencies achieved after each treatment stage. The Wilcoxon test (as described in section 2.6) was applied to this purpose, which allowed to compare two by two all treatment stages. The results obtained for the p-values are reported in **Table S.M. 5**. The statistical analysis provided a p-value below 0.05 for the comparison of PT vs ST and of PRE vs ST; this value is representative of a relevant statistical difference. Therefore, it is confirmed that there was a significant improvement of the removal efficiency passing from the primary to the secondary treatment process. By contrast, the differences for ST vs F + UV, ST vs CL and F+UV vs CL cannot be considered statistically significant since the p-values were always above 0.05.

Therefore, it is confirmed that the following stages downward the ST did not further enhance the removal efficiency. It is worth of noting that, due to the high performance achieved by the ST, the residual concentration received by the following stages was very low thus not allowing a further removal. The p-values obtained through the Wilcoxon test are reported in **Table S.M. 5**. The p-value for ST vs PT resulted to be below 0.05 for all groups of contaminants and also all OMPs grouped together: this confirms that the highest contribution to the overall removal was provided by the secondary process.

Furthermore, the differences for ST vs F + UV, ST vs CL and F+UV vs CL cannot be considered statistically significant (i.e., the p-value was always above 0.05). It is also worth of noting that the following treatment stages could operate only against very low residual concentrations since main removal had already occurred in the previous stages.

3.3 PCA and correlation among the treatment process variables

Through the PCA, the number of measured variables was reduced to two principal components, which explains the 56.9% of the variability observed. The first and second principal components (Dim1 and Dim2, respectively) accounted for 42.8% and 14.1% of the variance, respectively (see **Fig. S.M. 1**). **Fig. 5a** shows the individuals coloured on the basis of the sampling points.

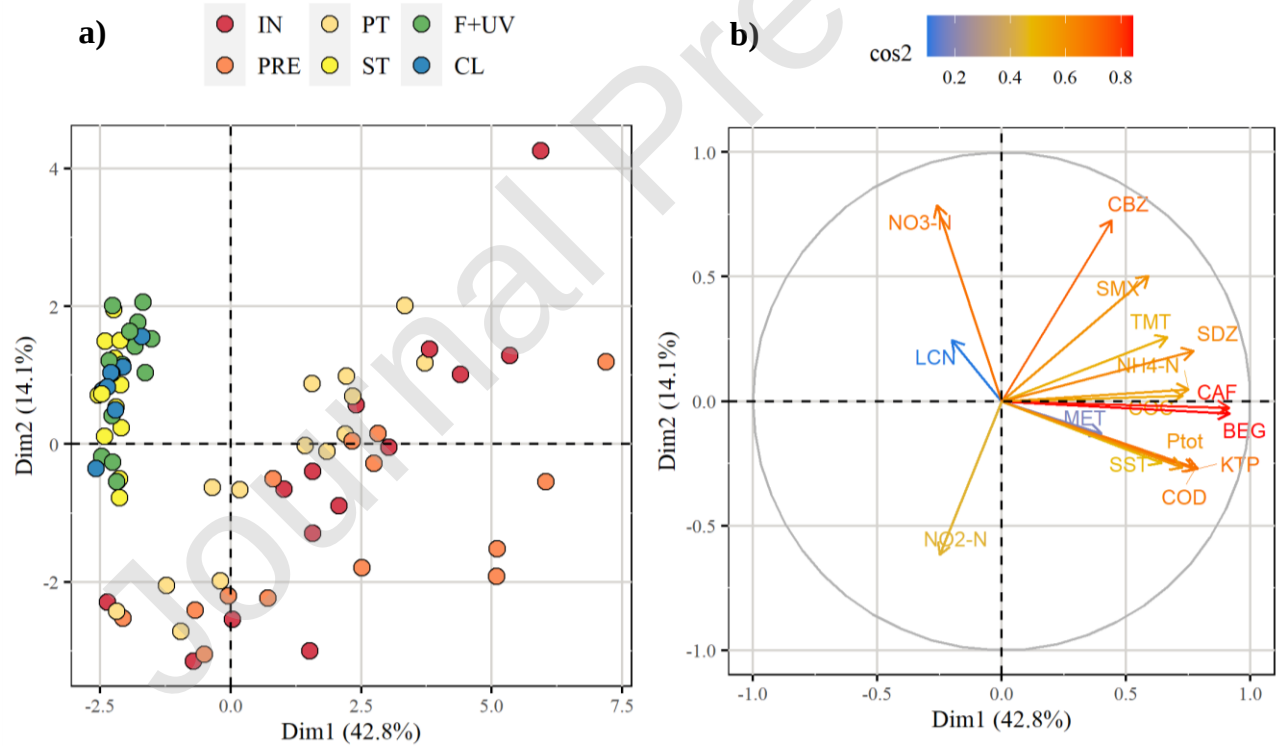


Fig. 5 a) PCA score plot. Samples are coloured according to the sampling point. b) PCA loading plot. The variables are coloured based on the quality of the representation (cos2).

The plot divides all the samples into two groups. The first group, consisting of samples collected in IN, PRE and PT, arranged heterogeneously within the right and low parts of the graph and included the lower removal efficiency. On the contrary, the second group, represented on the left-hand side of the plot, referred to the units where a higher removal efficiency was observed (i.e., ST, F+UV and CL). Since this representation of the statistical units considers all the available information, it can be highlighted that the parameters related to the samples collected in the sections of the second group had lower overall variations than those belonging to the first group. The reduced variability proves that these compartments, and particularly the ST, were capable of pretty constant performance although the wide changes of the influent characteristics.

The results of the correlation analysis between the concentrations of OMPs and water quality parameters are shown in **Fig. 5b**. BEG and CAF were the best represented variables, having cos2 equal to 0.8; a quality slightly lower though still high was found in the representation of CBZ, KTP, NO_3^--N, COD, SDZ, SMX, P_{tot}, NO_4^+-N, COC, TMT, which gave cos2 values between 0.8 and 0.5. Quite the opposite, SST, NO_2^--N, MET and LCN were not well represented by the performed analysis, and therefore they will not be further discussed. Compounds that have been reported to be removed by biodegradation showed to be strongly correlated with those water quality parameters which are known to be removed by the same process. Particularly CAF, BEG and COC were directly correlated with NH_4^+-N, whereas KTP with SST, COD and P_{tot}. Therefore, CAF, BEG and COC should be degraded through nitrification, whereas KTP should better follow the carbon removal process. Indeed, this hypothesis is supported by their chemical structure: KTP is made up by carbon, hydrogen and oxygen, whereas CAF, BEG and COC include nitrogen also in their molecule. These results suggest that improving the rate of reactions of nitrification and carbon oxidation will likely increase also the removal of these compounds. CBZ, considered as a recalcitrant compound (Valdés et al., 2016), did not show any correlation with the water quality parameters (Matamoros et al., 2016). For SMX, TMT and SDZ, the principal component analysis did not provide significant results.

3.4 Health risk assessment

The health risk assessment was carried out with the aim to evaluate whether the presence of OMPs in the treated effluent of the plant may pose a risk to human health. The risk quotient (RQ) was calculated using Eq. 5 for each OMP present in the effluent and for the different exposure pathways, as described in section 2.5. The results obtained are shown in **Fig. 6.**

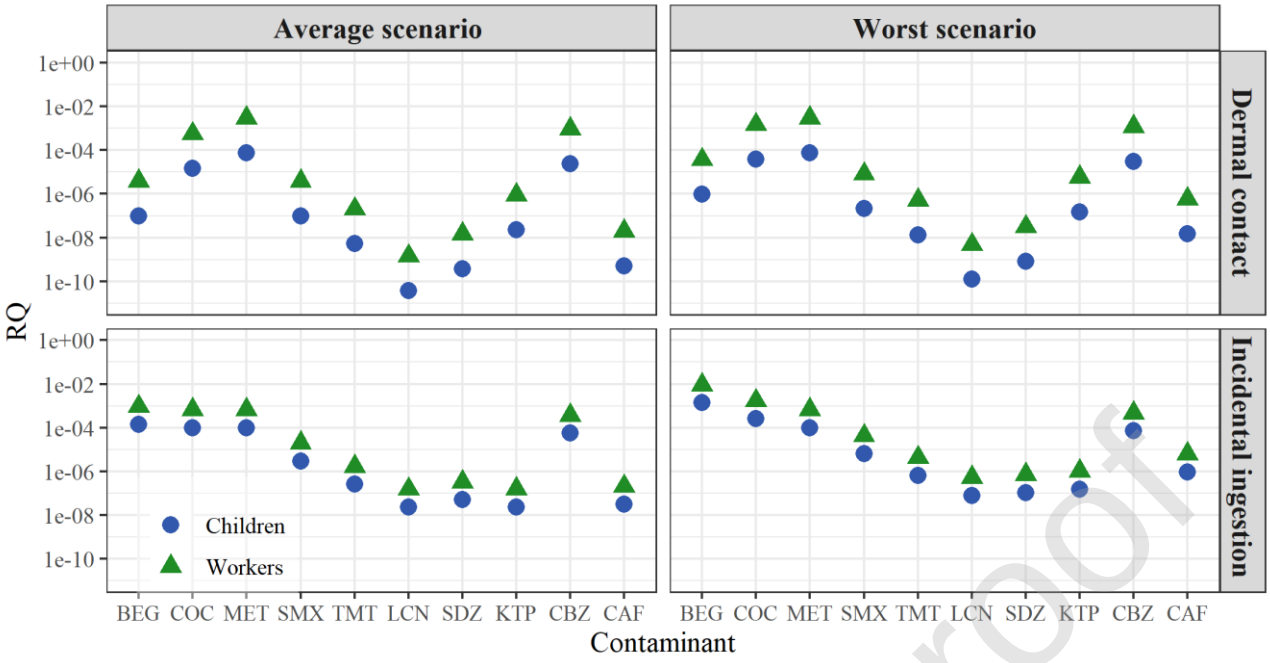


Fig. 6 Results of the health risk assessment for dermal contact and incidental digestion and the average and worst scenarios.

It can be noted that the RQ values were always lower than one: this indicates that, under the investigated conditions, there was no risk for the receptors due to incidental ingestion or dermal contact with the treated effluent. As expected, the RQs values calculated for the average scenario were lower than those related to the worst conditions (where the 99th percentile of the effluent concentration was used as MEC).

It is also highlighted a higher risk for the landscape workers as compared to that for the children, because of the longer exposure time (30 years for workers and 6 years for children).

For incidental ingestion, BEG, COC and CBZ were the compounds with higher RQs, due to the low ADIs values (0.005 µg/kg·d for illicit drugs and 0.3 µg/kg·d for CBZ). However, it must be recalled that the ADIs used for illicit drugs were calculated using a precautionary approach (Watts et al., 2007). In the present study, CBZ was always present in the effluent of the plant due to the null removal. Being recognized as a hazardous compound, its release to the environment can pose a risk, since it can accumulate in algae, fish, invertebrates and birds organs/tissues.(Valdés et al., 2016). However, the related risk measured in the present case was assessed to be negligible.

LCN, SDZ, KTP and CAF showed the lower RQs values; in accordance with the above considerations, these contaminants were characterized by higher ADI values.

For dermal contact, CBZ was the compound determining the highest RQ, followed by COC, BEG and SMX, which were also characterized by high values of the chemical specific permeability constant which is used to calculate the AC (as reported in **Table S.M. 4**). By contrast, LCN, SDZ and CAF showed lower RQ values.

Although the studies on the health risk assessment for water reuse are very few, these results are in a good agreement with the few findings reported by other scientific works (Delli Compagni et al., 2020b; Schwab et al., 2005; Semerjian et al., 2018).

It is worth noting that the present risk assessment analysis, as well as most of those found in the scientific literature, was carried out referring to only individual contaminants without considering the potential effect of the different substances present at the same time in the same reclaimed water. It is difficult to assess the risk due to the exposure to a mixture of OMPs because of the complexity in the prediction of the potential additive, antagonistic or synergistic effects (Drakvik et al., 2020; Kumari and Kumar, 2020).

4 Conclusions

Among the selected OMPs, BEG, COC, KTP, TMT and CAF were removed by 100% or very closely from the liquid phase in the WWRP. Lower removals were observed for MET (60%), SMX (50%) and SDZ (64%). CBZ and LCN were not affected by all the treatment stages.

The main contribution was always provided by the ST, i.e. the biological process, whereas PRE and PT achieved removals in the range 7-33%, depending on the specific compound. Tertiary treatments were only capable of a limited removal and for a few OMPs. Particularly, a difference in the removal achieved by ST and F+UV or CL was present only in the cases of SMX, TMT and KTP.

Since it is reported that UV disinfection can affect differently the OMPs concentration depending on the applied dose (Michael et al. 2013), therefore it would be interesting to investigate if removal could be enhanced by properly modifying the operating conditions.

The high removal observed for some OMPs was well correlated to the efficient abatement of the water quality parameters which are traditionally under control in the wastewater treatment plants. Therefore, an efficient plant is likely to achieve also a high removal of these OMPs.

The risk for human health due to the treated effluent reuse resulted to be negligible, even in the worst contamination scenario and for the OMPs not being removed by the plant. This result indicates that the final effluent of the plant can be reused for the non-potable applications actually operated by the plant without posing a risk for human health.

More studies are required to determine the risk generated under exposure conditions other than those considered in the present study, and particularly for a mixture of different OMPs which more closely to real cases.

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.

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Supplementary materials

Table S.M. 1 UV system characteristics.

Table S.M. 2 Main chemical-physical characteristics of the target OMPs: 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 Details of the analytical method for OMPs detection in wastewater.

Table S.M. 4 Minimum, maximum and median OMPs concentration effluents from the different treatment units and the correspondent the number of measurements (reported between brackets).

Table S.M. 5 Results of the Wilcoxon test. Significance difference if p-value <0.05 (highlighted in italics).

Fig. S.M. 1 Screen plot of the PCA dimensions.