Advanced processes for the removal of organic micropollutants from wastewater by the addition of powdered activated carbon to membrane bioreactor

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ADVANCED PROCESSES FOR THE REMOVAL OF ORGANIC MICROPOLLUTANTS FROM WASTEWATER BY THE ADDITION OF POWDERED ACTIVATED CARBON TO MEMBRANE BIOREACTOR

INTERNATIONAL DUAL DOCTORATE

Ferrara, 2023

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NAPREDNI PROCESI ZA UKLANJANJE ORGANSKIH MIKROZAGAĐIVALA IZ OTPADNIH VODA DODATKOM PRAŠKASTOGA AKTIVNOGA UGLJENA U MEMBRANSKI BIOREAKTOR

MEĐUNARODNI DVOJNI DOKTORAT

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ABSTRACT IN ENGLISH

Activated carbon coupled to a membrane bioreactor (MBR) is a novel hybrid system able to potentially enhance the removal of organic micropollutants (OMPs) in wastewater. In a context in which wastewater treatment plants (WWTPs) effluents have been declared as the major sources of OMPs into the aquatic environment, hospital wastewater is a growing concern as a point source of these contaminants, especially of pharmaceuticals. The combination of the great adsorption capacity of the activated carbon with the biological degradation and membrane separation of the MBR results in a promising option to obtain a high-quality effluent. That being said, the numerous influencing factors and mechanisms by which OMP removal is enhanced are yet not fully understood. In addition, few research studies in full-scale hybrid MBRs have been reported in literature.

In this thesis, an in-situ hybrid MBR coupled to powdered activated carbon (PAC) has been proposed to remove OMPs from wastewater and reduce the impact of the effluent on the receiving water body. The experiments were conducted in a full-scale MBR treating mainly hospital wastewater with 0.1 and 0.2 g/L of PAC added inside the biological reactor. The occurrence and removal efficiencies of a vast selection of OMPs (232 individual compounds) were reported, compared and discussed in a MBR and a hybrid MBR over a year time. Based on the results obtained, PAC addition was proved to enhance the removal of several OMPs, especially antibiotics and psychiatric drugs. The increase of the PAC concentration from 0.1 g/L to 0.2 g/L showed to further improve the quality of the effluent by reducing the total OMP loads and the environmental risk in the receiving water body.

In addition to that, a systematic review and a meta-analysis were conducted about the state-of-the-art of MBRs coupled to activated carbon to treat urban and domestic wastewater. Collected data on the removal efficiencies, the effluent concentrations, the physicochemical properties of the OMPs, the system configuration and the operational conditions applied were discussed and subjected to statistical analysis. Consequently, a detailed assessment of the factors affecting the removal of the OMPs in presence of activated carbon was carried out.

Finally, the adsorption of three pharmaceuticals (i.e., diclofenac, sulfamethoxazole and trimethoprim) onto PAC was studied using mathematical models applied to batch experiments at laboratory-scale. The PAC adsorption capacity, mechanisms and kinetics were investigated under controlled conditions. In particular, four water matrices of increasing complexity were used: Milli-Q water, humic acid solution, permeate and mixed liquor of an MBR. The adsorption was proved to be an overall fast kinetic process dependent on the initial concentration of the pharmaceutical and the adsorbent. A competitive effect was observed when compounds occur in a mixture, causing a decrease in the overall PAC adsorption capacity. Additionally, the composition of the water matrix proved to have a major effect on the adsorption of the selected compounds. Decreased adsorption was found in the mixed liquor for all tested pharmaceuticals, whereas the humic acids were proven to enhance the adsorption of certain compounds, namely diclofenac and sulfamethoxazole.

Keywords: activated carbon, adsorption, membrane bioreactor, organic micropollutants, wastewater treatment.

ABSTRACT ESTESO IN ITALIANO

La presenza di contaminanti organici di origine antropica nell'ambiente acquatico è motivo di preoccupazione negli ultimi decenni. Sebbene i loro carichi siano bassi, il rilascio continuo può promuovere effetti negativi continui ma inosservati sull'ambiente e sulla vita umana. Negli ecosistemi acquatici, si trovano comunemente a livello di tracce e sono quindi indicati come microinquinanti organici (OMP). A causa della crescente consapevolezza degli effetti potenzialmente dannosi, le metodologie analitiche per la determinazione delle concentrazioni di OMPs hanno registrato un maggiore sviluppo. L'applicazione della cromatografia liquida-spettrometria di massa (LC-MS) per l'analisi degli OMP in campioni ambientali complessi come le acque reflue ha consentito di tracciare queste sostanze nel ciclo dell'acqua.

Gli impianti di trattamento delle acque reflue (*wastewater treatment plants,* WWTP) sono una delle principali fonti di OMP, dove decine a centinaia ne sono trovati contemporaneamente nelle acque reflue urbane. Attualmente nessuna normativa vigente ne disciplina la loro rimozione o la loro concentrazione nell'effluente finale. L'inefficacia dei sistemi di trattamento convenzionali per rimuovere gli OMP e ridurre i potenziali effetti dannosi derivati dal loro rilascio hanno favorito lo sviluppo di trattamenti avanzati e ibridi. In questo contesto, i reattori biologici a membrana (*membrane bioreactors*, MBRs) hanno conosciuto uno straordinario sviluppo negli ultimi due decenni. La combinazione del trattamento biologico con la separazione a membrana garantisce un effluente di migliore qualità rispetto ai sistemi convenzionali. Tuttavia, gli MBR non sono stati progettati per la rimozione degli OMP perciò sono necessari upgrading con tecnologie innovative per ottenere una maggiore qualità degli effluenti.

L'utilizzo di carbone attivo accoppiato ad un MBR è un nuovo sistema ibrido in grado di promuovere la rimozione di contaminanti attraverso diversi meccanismi. La combinazione di processi biologici di degradazione e assorbimento può causare effetti sinergici che contribuiscono alla rimozione di OMP dalle acque reflue. Il carbone attivo è un adsorbente poroso con una superficie specifica molto elevata che consente l'adsorbimento di più composti contemporaneamente. La sua applicazione al trattamento delle acque reflue

presenta numerosi vantaggi rispetto ad altre tecnologie innovative (es. ozonizzazione, fotocatalisi), come il miglioramento del funzionamento del reattore e la diminuzione della tossicità dell'effluente. Questo adsorbente è disponibile in commercio in diverse forme e la sua aggiunta nel sistema MBR offre un design semplice e condizioni operative di facile mantenimento, che possono essere condotte mediante diverse configurazioni di trattamento. Infatti, questo adsorbente è particolarmente conveniente per gli MBR già operativi che cercano un upgrading nella loro linea di trattamento delle acque reflue esistente, poiché può essere aggiunto all'interno del reattore biologico o in un serbatoio di contatto per trattare l'effluente secondario.

I benefici della combinazione della grande capacità di adsorbimento del carbone attivo con la degradazione biologica che avviene all'interno dell'MBR sono stati ampiamente riportati nella letteratura scientifica. Nonostante ciò, i fattori che influenzano la rimozione e i meccanismi che determinano il grado di rimozione non sono ancora del tutto chiari. Risulta perciò importante comprendere in quale misura questi fattori possono influenzare questo tipo di trattamento in modo che possa essere progettato con una ridotta pressione antropica sull'ambiente. Il carbone attivo è caratterizzato dalla presenza di un elevato numero di micropori che fungono da siti attivi per l'adsorbimento degli OMP. La capacità di questo adsorbente dipende quindi dalle sue proprietà superficiali (area superficiale specifica, volume dei pori, gruppi chimici funzionali). Le proprietà fisico-chimiche (gruppi funzionali, idrofobicità, carica, peso molecolare) dei numerosi OMP presenti nelle acque reflue definiscono invece la loro biodegradabilità e la loro affinità verso la superficie del carbone attivo. Inoltre, le acque reflue sono caratterizzate da una matrice complessa con un elevato contenuto di sostanza organica disciolta (DOM) con concentrazioni di almeno tre o sei ordini di grandezza superiori alla concentrazione di OMP. Il DOM è costituito da frazioni di diverse dimensioni che interagiscono con il carbone attivo e con gli OMP in differenti modi. I risultati di queste interazioni possono effettivamente migliorare o diminuire la rimozione di OMP, a seconda dei composti e delle condizioni testati. Ad esempio, è ben noto che la presenza di DOM e solidi sospesi può limitare l'adsorbimento di OMP ostruendo i pori del carbone attivo o competendo direttamente per i siti attivi. D'altra parte, alcuni costituenti del DOM, come

sostanze umiche, possono influenzare positivamente l'adsorbimento di alcuni OMP.

Infine, anche la configurazione del trattamento e le condizioni operative di questi sistemi ibridi possono influenzare la rimozione degli OMP. All'interno del serbatoio biologico, il carbone attivo viene aggiunto esclusivamente sotto forma di polvere (carbone attivo in polvere, PAC), mentre se utilizzato come post-trattamento può essere aggiunto come PAC in un serbatoio di contatto o sotto forma di granuli (granulare attivato carbonio, GAC) in una letto filtrante. In questo scenario, è noto che la rimozione dei composti che si basano esclusivamente sull'adsorbimento sul carbone attivo è altamente dipendente dal grado di saturazione dell'adsorbente. Ad esempio, se il PAC viene aggiunto all'MBR, la dose e la frequenza in cui ciò avviene possono influenzare la rimozione di composti recalcitranti come il diclofenac o la carbamazepina.

In questa tesi, l'aggiunta di PAC a un MBR per la rimozione di OMP nelle acque reflue è stata studiata attraverso diversi approcci. In primo luogo, è stata effettuata una revisione sistematica della letteratura scientifica sullo stato dell'arte dei sistemi ibridi MBR accoppiati al carbone attivo per la rimozione degli OMP dalle acque reflue urbane e domestiche. La revisione della letteratura mirava a fornire un'istantanea delle efficienze di rimozione di un'ampia selezione di OMP che sono state presentate e discusse in base al carbone attivo selezionato (cioè PAC o GAC), alla configurazione del trattamento e alle condizioni operative utilizzate. Lo stesso è stato fatto per le concentrazioni degli OMP nell' effluente. I dati di rimozione sono stati raccolti e analizzati in base alla dose e al tempo di contatto a letto vuoto per PAC e GAC, rispettivamente. I risultati degli studi raccolti hanno indicato che la presenza di carbone attivo migliora la rimozione della maggior parte degli OMP testati favorendone l'assorbimento sulla superficie adsorbente potenziandone la biodegradazione.

Sulla base delle lezioni apprese dagli studi raccolti, è stato svolto un successivo approfondimento sui fattori che influenzano la rimozione degli OMP in presenza di carbone attivo. Nel caso in cui il PAC venga aggiunto al reattore biologico, i principali parametri di influenza identificati e descritti sono stati: il punto di dosaggio, il tempo di ritenzione del fango, il tempo di ritenzione idraulica e il contenuto di sostanza organica disciolta. Per il GAC, le condizioni operative adottate (ad esempio, velocità di filtrazione, EBCT) sono i parametri

che hanno influenzato il trasporto di OMP dalla fase liquida alla superficie adsorbente. Il DOM ha dimostrato di essere un forte concorrente per i siti di adsorbimento sulla superficie del carbone attivo, ma anche di favorire la trasformazione del carbone attivo in un carbone biologicamente attivo cosi da promuovere tutti i processi di degradazione. Inoltre, è stato discusso il potenziale miglioramento del funzionamento dell'MBR per quanto riguarda i parametri convenzionali (materia organica, composti di azoto e fosforo) nonché la mitigazione del fouling della membrana. I risultati hanno indicato che una presenza di carbone attivo all'interno del reattore aumenta leggermente la rimozione degli inquinanti convenzionali dalle acque reflue, così come aumenta la forza del fiocco di fango e migliora le sue caratteristiche di sedimentazione, riducendo così l'incrostazione della membrana.
Poiché i sistemi ibridi sono caratterizzati per la promozione di diversi meccanismi di rimozione durante il trattamento delle acque reflue, è stata prestata particolare attenzione all'interazione dinamica tra l'adsorbente, la materia organica e gli OMP negli MBR ibridi. In particolare, sono stati discussi approfonditamente i processi di adsorbimento, ovvero adsorbimento e assorbimento, e la degradazione biologica a seconda delle condizioni in cui il carbone attivo è incluso nel trattamento delle acque reflue.

La revisione della letteratura ha sottolineato la complessità dei fenomeni coinvolti nella rimozione degli OMP negli MBR ibridi. L'interazione di più fattori consente di trarre conclusioni immediate, ed è quindi necessario un approccio più rigoroso per elaborare e interpretare i risultati ottenuti in letteratura. A tal fine, i dati raccolti sono stati sottoposti ad una meta-analisi al fine di far luce sui parametri che influenzano maggiormente la rimozione delle OMP. A tal fine, le caratteristiche fisico-chimiche degli OMP, le efficienze di rimozione e le condizioni operative degli MBR ibridi accoppiati al PAC aggiunto all'interno del reattore sono stati sottoposti ad un’analisi statistica. I parametri operativi (dosaggio PAC, tempo di ritenzione PAC e tempo di ritenzione fanghi) e le proprietà fisico-chimiche degli OMP (coefficiente di distribuzione ottanolo-acqua (D_{ow}), carica e peso molecolare) sono stati selezionati come variabili indipendenti nella fase di screening dedicata. Quindi, sono state condotte analisi statistiche basate su metodi esplorativi, cioè analisi dei cluster e analisi delle componenti principali, nonché analisi di

regressione, per confrontare e discutere le efficienze di rimozione ottenute nella letteratura scientifica. È emerso che nel dataset raccolto non sono state riscontrate correlazioni significative tra condizioni operative ed efficienze di rimozione. La variazione delle condizioni operative definite non implicava una migliore efficienza di rimozione di un ampio spettro di OMP. Tuttavia, una gestione precisa delle condizioni operative può migliorare significativamente la rimozione di alcuni contaminanti. Al contrario, alcune caratteristiche fisico-chimiche dei composti sembrano influenzare maggiormente il comportamento degli OMP. In particolare, la carica si è dimostrata significativamente correlata alle efficienze di rimozione, presumibilmente a causa delle interazioni elettrostatiche tra sostanze caricate positivamente e PAC e DOM caricate negativamente contenute nelle acque reflue. D'altra parte, $logD_{ow}$ si è dimostrato esclusivamente correlato alla rimozione di composti anionici e neutri, suggerendo che in assenza di interazioni elettrostatiche favorevoli, l'idrofobicità determina il grado di affinità verso il PAC.

Una volta predisposte le basi teoriche della tesi, ovvero la revisione della letteratura e l'analisi statistica, è stato realizzato l'obiettivo principale della presente tesi. In un contesto in cui gli WWTP sono stati dichiarati come le principali fonti di OMP nell'ambiente, le acque reflue ospedaliere hanno suscitato maggiore preoccupazione come fonte puntuale di OMP nelle acque reflue, in particolare di farmaci. In questa tesi è stato proposto un trattamento avanzato delle acque reflue in situ al fine di ridurre l'impatto delle strutture ospedaliere nel rilascio di OMP nei corpi idrici. La rimozione di un'ampia selezione di OMP è stata studiata in un MBR full-scale che tratta principalmente acque reflue ospedaliere (75% del flusso influente),accoppiato con PAC aggiunto all'interno del serbatoio biologico. Sulla base della revisione di letteratura e le analisi statistiche, si è deciso di testare il PAC dosi (0.1 e 0.2 g/L). Inoltre, la frequenza di rilevamento e occorrenza degli OMP target è stata valutata nelle acque reflue ospedaliere, nell'influente e nell'effluente dell'impianto di trattamento delle acque reflue nell'arco di un anno. Gli OMP sono stati determinati e quantificati mediante UHPLC-QTOF-MS, utilizzando il metodo dell'iniezione diretta, che ha permesso di determinare le concentrazioni di 232 OMP target. Inoltre, altri 83 OMP sono stati rilevati durante l'analisi "non-target" utilizzando lo stesso metodo analitico. È stata

inoltre condotta una valutazione del rischio ambientale per determinare l'impatto dell'effluente finale del WWTP nelle acque riceventi. Infine, è stato effettuato un ampio monitoraggio dell'MBR e dell'MBR accoppiato al funzionamento del PAC per avere un'istantanea completa dei trattamenti testati.
I risultati presentati nella tesi indicano che l'aggiunta di PAC ha dimostrato di migliorare la rimozione di diversi OMP, in particolare per gli antibiotici (l'efficienza di rimozione è aumentata tra il 33 e l'89%) e gli psicofarmaci (tra il 12 e il 67%). Al contrario, alcuni composti (es. iopromide, atenolol) e classi terapeuche (es. analgesici/antinfiammatori) non hanno mostrato alcun miglioramento significativo nella loro rimozione a causa dell'aggiunta di PAC, poiché elevate efficienze di rimozione erano già state raggiunte dal sistema MBR. L'aumento della dose di PAC da 0.1 g/L a 0.2 g/L ha migliorato la qualità dell'effluente diminuendo i carichi totali di OMP nel comparto dell'acqua ricevente e riducendo il rischio per l'ambiente. Ciò è particolarmente rilevante considerando che alcune delle sostanze analizzate erano altamente recalcitranti (ad es. diclofenac, ciprofloxacin, carbamazepine) e/o potevano potenzialmente causare lo sviluppo di batteri resistenti agli antibiotici (ad es. antibiotici). Infine, l'aggiunta di PAC ha leggermente migliorato il funzionamento dell'MBR per quanto riguarda alcuni inquinanti convenzionali (es. azoto totale).

L'approccio finale affrontato nella Tesi è lo studio del processo di adsorbimento attraverso l'applicazione di modelli matematici a esperimenti batch condotti in laboratorio. L'adsorbimento di tre farmaci (diclofenac, sulfamethoxazole e trimethoprim) è stato studiato in diverse matrici acquose e differenti concentrazioni di PAC. In studi precedenti, l'applicazione dei modelli di adsorbimento è stata di grande importanza per la comprensione dei meccanismi di adsorbimento degli adsorbenti porosi. Tuttavia, solo alcuni hanno indagato la capacità, i meccanismi e la cinetica di adsorbimento del PAC in circostanze che emulano i fenomeni che si verificano negli WWTP. In questo modo, le proprietà farmaceutiche e le concentrazioni, la dose di PAC e la matrice acquosa vengono studiate a fondo in condizioni controllate che consentono la precisa quantificazione dell'effetto di questi fattori di influenza nel processo complessivo di adsorbimento. In particolare, l'approccio

innovativo di questo studio è stato l'utilizzo di matrici acquose di crescente complessità per confrontare il processo di adsorbimento. Le matrici acquose utilizzate erano: acqua MilliQ, soluzione di acido umico, permeato MBR e liquido misto proveniente dall'impianto di trattamento delle acque reflue utilizzato nelle indagini precedenti.

I risultati ottenuti indicano che l'adsorbimento dei prodotti farmaceutici è fortemente dipendente dalle proprietà fisico-chimiche dei composti. La carica dei composti sotto le condizioni studiate, seguita dall'idrofobicità, hanno determinato la velocità e l'entità dell'adsorbimento in tutte le matrici acquose testate. Il trimethoprim, un composto cationico nelle condizioni testate, ha dimostrato di avere la maggiore affinità di rimozione e adsorbimento nei confronti del PAC. Invece, l'entità della rimozione per diclofenac e sulfamethoxazole, due composti trovati anionici nelle stesse condizioni testate, è stata determinata dalla loro idrofobicità. Per conseguenza, sulfamethoxazole è stato il composto meno adsorbito in tutte le matrici acquose testate. Inoltre, l'adsorbimento si è dimostrato dipendente dalla concentrazione iniziale di farmaco e PAC. Le più alte capacità di adsorbimento del PAC sono state osservate con la più bassa concentrazione di PAC (0.1 g/L) così come con la più bassa concentrazione farmaceutica testata (5 mg/L). Al contrario, l'adsorbimento si è dimostrato essere un processo cinetico complessivamente veloce governato dal numero di siti disponibili per l'adsorbimento (cinetica di pseudo-secondo ordine, $R^2 > 0.98$). Infatti, il 50% della massima efficienza di rimozione è stata raggiunta entro i primi 10 minuti nella maggior parte delle condizioni e dei composti testati. Quando i prodotti farmaceutici si presentavano simultaneamente in soluzione, le velocità cinetiche non differivano significativamente ($p < 0.05$). Tuttavia, si è osservata una diminuzione della capacità di assorbimento del PAC nella soluzione miscelata, indicando la esistenza di un effetto competitivo tra i composti.

Gli esperimenti batch in laboratorio hanno dimostrato che il processo di adsorbimento è fortemente influenzato dalla matrice acquosa. Le più basse capacità di adsorbimento del PAC sono state osservate nel liquido misto, presumibilmente a causa della presenza di solidi sospesi che interferivano nell'interazione tra particelle di PAC e prodotti farmaceutici. Inoltre, la natura complessa del liquido misto è stata spiegata sperimentalmente con l'isoterma di Freundlich ($R^2 > 0.94$). I meccanismi di adsorbimento si sono dimostrati

dipendenti non solo del composto testato ma anche dalla matrice acquosa. Ciò confermato dal fatto che l'adsorbimento sugli acidi umici ha seguito un'isoterma di Langmuir per tutti i composti testati e la sua presenza è sembrata essere benefica per l'adsorbimento di alcuni prodotti farmaceutici, vale a dire il diclofenac anionico e il sulfamethoxazole ($R^2 > 0.98$).

Parole chiave: assorbimento, carbone attivo, microinquinanti organici, reattore di membrana, trattamento delle acque reflue.

PROŠIRENI SAŽETAK NA HRVATSKOM

Prisutnost organskih zagađivala antropogenog podrijetla u vodenom okolišu posljednjih desetljeća izaziva veliku zabrinutost. Iako su prisutni u niskim koncentracijama, njihov kontinuirani unos na dnevnoj bazi može uzrokovati stalne, ali nezapažene štetne učinke na okoliš i ljudski život. Budući se u vodenim ekosustavima, obično nalaze u tragovima ubrajamo ih u skupinu organskih mikrozagađivala (engl. *organic micropollutants*, OMP). Zbog sve veće svijesti o potencijalno štetnim učincima, u posljednjih nekoliko godina razvoj analitičkih metoda za određivanje koncentracija OMP-a doživljava veliki uspon. Tu je najveću ulogu odigrala primjena tekućinske kromatografije vezane na spektrometriju masa (LC-MS) za analizu OMP-ova u složenim uzorcima okoliša poput otpadne vode.

Do sada su postrojenja za obradu otpadnih voda (engl. *wastewater treatment plant*, WWTP) proglašena jednim od glavnih izvora ovih zagađivala, pri čemu se u urbanim otpadnim vodama u isto vrijeme nalazi više stotina OMP-a. Trenutno ne postoji zakonska regulativa o njihovom ispuštanju u okoliš kao niti o dozvoljenim koncentracijama u vodi nakon procesa obrade. Neučinkovitost konvencionalnih sustava obrade voda za uklanjanje OMP-a kao i njihovi potencijalni štetni učinci njihovog ispuštanja u vodotokove potaknuli su razvoj naprednih i hibridnih postupaka za pročišćavanje otpadnih voda. U tom su kontekstu membranski bioreaktori (engl. *membrane bioreactors*, MBRs) doživjeli izniman razvoj u posljednja dva desetljeća. Kombinacija biološke obrade s membranskim procesima jamči kvalitetniji efluent u usporedbi s konvencionalnim sustavima. Međutim, MBR-ovi nisu dizajnirani za uklanjanje OMP-ova, te su potrebne nadogradnje koje kombiniraju inovativne tehnologije s MBR-ovima kako bi se postigla što veća kvaliteta otpadnih voda.

Korištenje aktivnog ugljena povezanog s MBR-om novi je hibridni sustav koji može pospješiti uklanjanje zagađivala primjenom različitih mehanizama. Kombinacija procesa biološke razgradnje i sorpcije može izazvati sinergijske učinke koji pridonose uklanjanju OMP iz otpadne vode. Aktivni ugljen je porozni adsorbens s vrlo visokom specifičnom površinom koji omogućuje

adsorpciju više komponenti u isto vrijeme. Njegova primjena u postupku obrade otpadnih voda ima nekoliko prednosti u usporedbi s drugim inovativnim tehnologijama (npr. ozonizacija, fotokataliza), poput poboljšanja rada reaktora i smanjenja toksičnosti efluenta. Ovaj adsorbens komercijalno je dostupan u različitim oblicima, a njegova ugradnja u MBR sustav nudi jednostavan dizajn i blage radne uvjete, koji se mogu postići primjenom nekoliko konfiguracija. Doista, ovaj adsorbens je posebno prikladan za postojeće MBR-ove koji traže nadogradnju postojeće linije za obradu otpadnih voda, budući da se može dodati unutar biološkog reaktora ili u kontaktni spremnik za obradu sekundarnog efluenta.

Korisni učinci kombinacije velikog kapaciteta adsorpcije aktivnog ugljena s biološkom razgradnjom koja se odvija unutar MBR-a već su objavljeni u velikom broju znanstvenih publikacija. Unatoč tome, brojni faktori utjecaja te mehanizmi kojima dolazi do poboljšanja uklanjanja mikrozagađivala još uvijek nisu u potpunosti razjašnjeni. Razumijevanje opsega u kojem ovi čimbenici mogu utjecati od iznimne je važnosti jer se na osnovu njih mogu osmisliti posebni postupci obrade otpadnih voda kojima bi se smanjio antropogeni utjecaj na okoliš. Aktivni ugljen je karakteriziran prisutnošću velikog broja mikropora koje djeluju kao aktivna mjesta za adsorpciju OMP-a. Kapacitet ovog adsorbensa stoga ovisi o njegovim površinskim svojstvima (tj. specifičnoj površini, volumenu pora, funkcionalnim kemijskim skupinama). S druge strane, fizikalno-kemijska svojstva (npr. funkcionalne skupine, hidrofobnost, naboj, molekulska masa) širokog spektra OMP-ova koji se pojavljuju u otpadnim vodama definiraju do određenog stupnja njihovu biorazgradivost i njihov afinitet prema površini aktivnog ugljena. Nadalje, otpadnu vodu karakterizira složena matrica s visokim udjelom otopljene organske tvari (engl. *dissolved organic matter*, DOM) koja je prisutna u koncentraciji barem tri do šest puta većoj od koncentracije OMP-a. DOM se sastoji od frakcija različitih veličina koje na nekoliko načina stupaju u interakciju s aktivnim ugljenom i OMP-ovima. Te interakcije mogu doista poboljšati ili umanjiti uklanjanje OMP-a, ovisno o ispitivanim komponentama i uvjetima. Na primjer, dobro je poznato da prisutnost DOM-a i suspendiranih krutih tvari može ograničiti adsorpciju OMP-a blokiranjem pora aktivnog ugljena ili izravnim natjecanjem za aktivna mjesta. S druge strane, neki sastojci DOM-a, poput humusnih tvari, mogu pozitivno utjecati na adsorpciju pojedinih OMP-ova.

Konačno, sama konfiguracija postrojenja za obradu otpadnih voda i radni uvjeti ovih hibridnih sustava također mogu utjecati na uklanjanje OMP-ova. Unutar biološkog spremnika aktivni ugljen se dodaje isključivo u obliku praha (engl. *powdered active carbon*, PAC), dok se kod upotrebe kao naknadni tretman može dodati kao PAC u kontaktni spremnik ili u obliku granula (engl. *granular activated carbon*, GAC) u napunjenoj koloni. U ovom scenariju, poznato je da komponente koje se oslanjaju isključivo na adsorpciju na aktivni ugljen jako ovise o stupnju zasićenja adsorbensa. Na primjer, ako se PAC doda u MBR, količina i učestalost dodavanja mogu utjecati na uklanjanje postojanih spojeva poput diklofenaka ili karbamazepina.

U ovoj disertaciji istraženo je dodavanje PAC-a MBR-u za uklanjanje OMP-ova iz otpadne vode. U tu svrhu prvo se pristupilo sustavnom pregledu literature najsuvremenijih hibridnih MBR-ova vezanih s aktivnim ugljenom za uklanjanje OMP-a iz gradskih i komunalnih otpadnih voda. Cilj tog pregleda bio je dobiti uvid u učinkovitost uklanjanja OMP-ova različitih fizikalno-kemijskih svojstava. Učinkovitost uklanjanja OMP te njihove koncentracije u efluentu nakon obrade prikazane su i diskutirane u skladu s primijenjenim aktivnim ugljenom (tj. PAC ili GAC), konfiguracijom postrojenja za obradu otpadnih voda i primijenjenim radnim uvjetima. Podaci o uklanjanju prikupljeni su i analizirani prema količini i vremenu kontakta za PAC odnosno GAC. Rezultati prikupljenih studija pokazali su da prisutnost aktivnog ugljena poboljšava uklanjanje većine ispitivanih OMP-ova pogodujući njihovoj sorpciji na površinu adsorbensa čime se naknadno poboljšava njihova biorazgradnja.

Na temelju saznanja dobivenih pregledom literature, provedena je i naknadna detaljna analiza čimbenika koji utječu na uklanjanje OMP-a u prisutnosti aktivnog ugljena. U slučaju dodavanja PAC u biološki reaktor, glavni identificirani parametri utjecaja bili su mjesto doziranja, vrijeme zadržavanja mulja, hidrauličko vrijeme zadržavanja i sadržaj otopljene organske tvari. U slučaju GAC-a, glavni parametar koji utječe na transport OMP-a iz tekuće faze na površinu adsorbensa je brzine filtracije, EBCT. DOM se pokazao jakim konkurentom za adsorpcijska mjesta na površini aktivnog ugljena, ali bez obzira na to može pospješiti transformaciju aktivnog ugljena u biološki aktivni ugljen čime se pospješuju svi procesi razgradnje. Dodatno, analizirano je i potencijalno poboljšanje rada MBR-a s obzirom na konvencionalne parametre

(organska tvar, dušikovi i fosforni spojevi) kao i smanjenje onečišćenja membrane. Rezultati su pokazali da prisutnost aktivnog ugljena unutar reaktora neznatno povećava uklanjanje konvencionalnih zagađivala iz otpadne vode, kao i da povećava čvrstoću pahuljica mulja i poboljšava njegove karakteristike taloženja, čime se smanjuje onečišćenje membrane.

Budući da su hibridni sustavi karakterizirani promicanjem različitih mehanizama uklanjanja tijekom pročišćavanja otpadnih voda, poseban fokus stavljen je na dinamičku interakciju između adsorbensa, organske tvari i OMP-ova u hibridnim MBR-ovima. Osobito su detaljno obrađeni sorpcijski procesi, odnosno adsorpcija, te biološka razgradnja ovisno o uvjetima u kojima se aktivni ugljen uključuje u postupke obrade otpadnih voda.

Završetak pregleda naglasio je složenost fenomena uključenih u uklanjanje OMP-ova u hibridnim MBR-ovima. Budući da interakcija nekoliko čimbenika istovremeno dopušta donošenje jednostavnih zaključaka, potreban je rigorozniji pristup. Iz tog razloga pristupilo se drugoj fazi istraživanja koja je uključivala statističku analizu. U tu svrhu prikupljeni podaci o fizikalno-kemijskim karakteristikama OMP-a, učinkovitosti uklanjanja i radnim uvjetima hibridnih MBR-ova povezanih s PAC-om dodanim unutar reaktora podvrgnuti su meta-analizi kako bi se rasvijetlili parametri koji najviše utječu na uklanjanje OMP-a. Radni parametri poput doziranja PAC-a, vrijeme zadržavanja PAC-a i vrijeme zadržavanja mulja te fizikalno-kemijska svojstva OMP-a (koeficijent razdijeljenja oktanol-voda (*Dow*), naboj i molekulska masa) izabrani su kao neovisne varijable. Primijenjene su statističke analize temeljene na istraživačkim metodama, poput klaster analize, analize glavnih komponenti, kao i regresijske analize, s ciljem uspoređivanja učinkovitosti uklanjanja dobivenih iz znanstvene literature. Pokazalo se da u prikupljenom skupu podataka nisu pronađene značajne korelacije između radnih uvjeta i učinkovitosti uklanjanja. Varijacija definiranih radnih uvjeta nije implicirala bolju učinkovitost uklanjanja OMP-ova različitih fizikalno-kemijskih svojstava. Međutim, promišljeno upravljanje radnim uvjetima može značajno poboljšati uklanjanje određenih zagađivala. Naprotiv, čini se da određene fizikalno-kemijske karakteristike komponenata najviše utječu na ponašanje OMP-ova. Konkretno, pokazano je da je naboj značajno povezan s učinkovitošću uklanjanja, vjerojatno zbog elektrostatskih interakcija između pozitivno

nabijenih tvari i negativno nabijenih PAC i DOM sadržanih u otpadnoj vodi. S druge strane, pokazano je da je logD_{ow} isključivo povezan s uklanjanjem anionskih i neutralnih spojeva, što sugerira da u nedostatku povoljnih elektrostatskih interakcija, hidrofobnost određuje stupanj afiniteta prema PAC-u.

Nakon pregleda znanstvene literature i statističke analize, pristupilo se ostvarivanju glavnog cilja disertacije. Budući da su uređaji za obradu otpadnih voda proglašeni glavnim izvorima OMP-ova u okolišu, bolničke otpadne vode izazivaju povećanu zabrinutost kao točkasti izvor ulaska OMP-ova posebice farmaceutika u otpadne vode. U ovoj disertaciji predloženo je napredno pročišćavanje otpadnih voda na licu mjesta kako bi se smanjio utjecaj bolničkih objekata na ispuštanje OMP-a u vodena tijela. Uklanjanje OMP-ova različitih fizikalno-kemijskih svojstava proučavano je u velikom MBR-u koji je uglavnom tretirao bolničku otpadnu vodu (75% ukupnog dotoka) zajedno s PAC-om dodanim unutar biološkog spremnika. Na temelju pregleda literature i statističke analize odlučeno je da se u bioreaktor dodaje PAC i to u dvije različite koncentracije 0.1 g/L i 0.2 g/L. Istraživanja vezana uz dodavanje PAC-a provedena su unutar godine dana pri čemu su redovito uzimani uzorci na četiri mjesta uzorkovanja (bolnička otpadna voda, mješavina gradskih i bolničkih otpadnih voda na ulazu u postrojenje-UPOV, MBR permeat i konačni efluent nakon izlaska iz UV reaktora). Svi prikupljeni uzorci su analizirani UHPLC-QTOF-MS metodom izravnog ubrizgavanja pri čemu su određene koncentracije 232 poznata OMP-a iz otpadnih voda. Osim toga „*non-target*" analizom na istom instrumentu identificirano je još 83 OMP-a. Na osnovu dobivenih rezultata provedena je i procjena rizika za okoliš kako bi se utvrdio utjecaj konačnog efluenta UPOV-a na prijemne vode. Naposljetku, provedeno je opsežno praćenje MBR-a i MBR-a vezanog s PAC-om kako bi se dobio potpuni uvid u primijenjene postupke.

Rezultati predstavljeni u disertaciji pokazuju da se dodavanjem PAC-a poboljšava uklanjanje nekih ispitivanih mikrozagađivala, posebice antibiotika (učinkovitost uklanjanja se povećala između 33 i 89%) i psihijatrijskih lijekova (između 12 i 67%). Suprotno tome, određeni spojevi (npr. jopromid, atenolol) i skupine farmaceutika (analgetici/protuupalni lijekovi) nisu pokazali nikakvo značajno poboljšanje u uklanjanju uslijed dodatka PAC-a, budući da je visoka

učinkovitost uklanjanja već postignuta MBR sustavom. Povećanje koncentracije PAC-a u bioreaktoru s 0.1 g/L na 0.2 g/L dodatno je poboljšalo kvalitetu efluenta smanjujući njegovo ukupno opterećenje mikrozagađivalima ispuštenim u prihvatno vodno tijelo, čime se smanjuje rizik za okoliš. Ovo je posebno važno s obzirom na to da su neke od analiziranih tvari bile vrlo postojane (npr. diklofenak, ciprofloksacin, karbamazepin) i/ili su potencijalno mogle uzrokovati razvoj otpornosti bakterija prema antibioticima. Osim toga, dodavanje PAC-a je generalno unaprijedilo MBR-obradu s obzirom na neka konvencionalna zagađivala (npr. ukupni dušik).

Naposljetku, u disertaciji je proučavan procesa adsorpcije kroz primjenu matematičkih modela na šaržne eksperimente provedene u laboratoriju. Proučavana je adsorpcija tri farmaceutika, diklofenaka, sulfametoksazola i trimetoprima, u različitim vodenim matricama i koncentracijama dodanog PAC-a. U dosadašnjim istraživanjima primjena adsorpcijskih modela bila je od velike važnosti za razumijevanje adsorpcijskih mehanizama poroznih adsorbensa. Međutim, samo je nekoliko studija istraživalo adsorpcijski kapacitet, mehanizme i kinetiku PAC-a pod okolnostima koje oponašaju fenomene koji se odvijaju u uređajima za pročišćavanje otpadnih voda. Na ovaj način, ispitan je utjecaj fizikalno-kemijskih svojstva i koncentracije farmaceutika, koncentracije PAC-a i vodene matrice u kontroliranim uvjetima koji omogućuju preciznu kvantifikaciju učinka navedenih čimbenika utjecaja u ukupnom procesu adsorpcije. Konkretno, inovativni pristup ove studije bila je uporaba vodenih matrica sve veće složenosti za usporedbu procesa adsorpcije. Korištene vodene matrice bile su MilliQ voda, otopina huminskih kiselina, MBR permeat i miješana tekućina iz uređaja za pročišćavanje otpadnih voda korištenog u ranijim istraživanjima.

Dobiveni rezultati pokazuju da je adsorpcija farmaceutika uvelike ovisila o fizikalno-kemijskim svojstvima ispitivanih komponenti. Naboj ispitivanih komponenti u ispitivanih uvjetima, praćen hidrofobnošću, odredio je brzinu i opseg adsorpcije u svim testiranim vodenim matricama. Trimetoprim, koji se pri ispitivanim uvjetima nalazio u kationskom obliku, dokazano ima najveći afinitet uklanjanja i adsorpcije prema PAC. Pri istim ispitivanim uvjetima, diklofenak i sulfametoksazol su se nalazili u anionskom obliku, tako da je za njih presudnu ulogu u stupnju uklanjanja, odredila njihova hidrofobnost.

Sulfametoksazol je tako pokazao najmanji afinitet za sorpciju na PAC u svim testiranim vodenim matricama. Osim toga, adsorpcija se pokazala ovisnom o početnoj koncentraciji ispitivanog farmaceutika i PAC-a. Najveći kapaciteti adsorpcije PAC-a uočeni su pri najnižoj koncentraciji PAC-a (0.1 g/L), kao i pri najnižoj ispitivanoj koncentraciji farmaceutika (5 mg/L). S druge strane, dokazano je da je adsorpcija sveukupno brz kinetički proces kojim upravlja broj dostupnih mjesta za adsorpciju (kinetika pseudo-drugog reda, $R^2 > 0.98$). Zapravo, 50% maksimalne učinkovitosti uklanjanja postignuto je unutar prvih 10 minuta za ispitivane farmaceutike u većini eksperimentalnih uvjeta. Kada su se ispitivani farmaceutici nalazili zajedno u smjesi, njihove brzine kinetike nisu se značajno razlikovale ($p < 0.05$). Ipak, s obzirom da je u smjesi primijećeno smanjivanje njihovog kapaciteta prema PAC-u u odnosu na eksperimente kada je svaki od ispitivanih farmaceutika bio u pojedinačnoj otopini, potvrđen je kompetitivni učinak među ispitivanim farmaceuticima u smjesi za aktivna mjesta na PAC-u.

Tim ispitivanjima je također potvrđeno da sastav vodene matrice ima veliki utjecaj na adsorpciju OMP-a. Najniži adsorpcijski kapaciteti PAC-a primijećeni su u mješavini tekuće faze i aktivnog mulja (eng. *mixed liquor*), vjerojatno zbog prisutnosti suspendiranih krutih tvari koje su ometale interakciju između čestica PAC-a i ispitivanih farmaceutika. Osim toga, složena priroda te najkompleksnije vodene matrice (miješane tekućine) najbolje je opisana primjenom Freundlichove izoterme ($R^2 > 0.94$). Tim je pokazano da mehanizmi adsorpcije ovise ne samo o ispitivanoj komponenti već i o vodenoj matrici. Tome u prilog ide i činjenica da je adsorpcija u prisutnosti huminskih kiselina najbolje opisana Langmuirovom izotermom za sve ispitivane farmaceutike što pokazuje da je prisutnost huminskih kiselina korisna za adsorpciju određenih komponenti, poput diklofenaka i sulfametoksazola ($R^2 > 0.98$).

Ključne riječi: aktivni ugljen, adsorpcija, membranski bioreaktor, organska mikrozagađivala, obrada otpadnih voda.

List of acronyms

AC	Activated Carbon
AGMBR	Aerobic Granular Sludge Membrane Bioreactor
AOP	Advanced oxidation process
BAC	Biologically Activated Carbon
BET	Brunauer–Emmett–Teller
CAS	Conventional Activated Sludge
C_e	Equilibrium concentration in the liquid phase
PDA	Photo-diode array
DCF	Diclofenac
DOC	Dissolved Organic Carbon
D_{ow}	Octanol-Water distribution coefficient
DOM	Dissolved Organic Matter
EBCT	Empty Bed Contact Time
EBV	Empty Bed Volume
EPS	Extracellular Polymeric Substance
FO-MBR	Forward Osmosis Membrane Bioreactor
GAC	Granular Activated Carbon
HA	Humic Acid
H_c	Henry's constant
HPLC	High-Performance Liquid Chromatography
HRT	Hydraulic Retention Time
HWW	Hospital wastewater
K_{biol}	Biodegradation rate constant
K_d	Distribution Coefficient
K_F	Freundlich adsorption constant
K_L	Langmuir adsorption constant
K_{ow}	Octanol-water partition coefficient
LC	Liquid chromatography
LC-MS	Liquid chromatography – mass spectrometry

LC-MS/MS	Liquid chromatography – tandem mass spectrometry
LOD	Limit of Detection
LOQ	Limit of Quantification
MBR	Membrane Bioreactor
MDMBR	Membrane Distillation Membrane Bioreactor
MF	Microfiltration
MLSS	Mixed Liquor Suspended Solids
MLVSS	Mixed Liquor Volatile Suspended Solids
MW	Molecular weight
NOM	Natural Organic Matter
NSAID	Non-steroidal anti-inflammatory drug
OMP	Organic Micropollutant
PAC	Powdered Activated Carbon
PCA	Principal Component Analysis
PE	Population Equivalent
pH_{pzc}	pH Point of zero charge
pK_a	Dissociation constant
PT	Post-Treatment
QQ	Quorum Quenching
q_m	Maximum adsorption capacity
RO-MBR	Reverse Osmosis Membrane Bioreactor
SMX	Sulfamethoxazole
SRT	Sludge Retention Time
TMP	Trimethoprim
TOF	Time-of-flight
UWW	Urban wastewater
v_f	Filtration Velocity
WWTP	Wastewater treatment plant

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Chapter 1

GENERAL INTRODUCTION

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1.1 Micropollutants in the environment

Intensive industrial and agricultural development in a continuously growing population, especially in urban areas, leads to the mass production of an uncountable amount of chemicals as well as severe pressure on water resources. In the context of climate change, many regions in the world already experience water scarcity, alteration in precipitation patterns, contamination of water resources as well as loss of ecological value of the aquatic environment (Eggen et al., 2014).

A healthy structure and functioning of the aquatic environment provide the ecosystem services that support human society and the economy. However, surface waters have been traditionally used as a waste disposal route for human activities. To deal with it, wastewater management has been subjected to improvement over the last century, namely with the wide implementation of sanitary sewers, biological wastewater treatment and nutrient elimination, which are today taken for granted (Eggen et al., 2014). Nonetheless, monitoring of the treatment efficiency is still limited nowadays to a certain number of macro-parameters due to the complex nature of wastewater.

In the last years, the advances in the analytical methods for environmental analysis have allowed the quantification and determination of contaminants that were previously unnoticed. Since they are commonly found at trace levels, they are usually referred to as organic micropollutants (OMPs) and the commonly regulated conventional parameters have proved to be useless in their monitoring. OMPs are not necessarily new substances, but since their occurrence has been unnoticed until the development of proper analytical techniques, and the potential effects they may have on the biota and human health are yet misunderstood, they are usually referred to as contaminants of emerging concern (CECs). In the European Union (EU), 30,000 to 70,000 substances are classified as chemicals of daily use (Schwarzenbach et al., 2006). Among them, there are pharmaceuticals and personal care products, fragrances, endocrine-disrupting compounds, surfactants, pesticides, herbicides, natural hormones, plastic additives and disinfection by-products (Besha et al., 2017). Many OMPs present complex chemical structures and low biodegradability, which lead to unknown behaviour in the environment. In some cases, depending on their bioavailability, their persistence and the susceptibility of the receiving water body, the effect of their release may be magnified (Bui et al., 2016). Among them, human and veterinary pharmaceuticals are designed to be biologically active. Once ingested, the contaminant (i.e., parent compound) undergoes partial or total metabolization, which results in intermediate or final products of the metabolism, called metabolites. The degree of metabolization may vary depending on the compound, being some pharmaceuticals metabolized to a large extent, whereas others may be only partially metabolized or non-metabolized at all. In this way, mixtures of parent compounds and their metabolites are commonly found in wastewater (Yin et al., 2017).

Although the treatment of many human and veterinary diseases relies on access to effective pharmaceuticals, the pollution caused by their continuous use is an

increasing concern, and the sources for their release in water bodies will differ depending on whether human or veterinary drugs are involved. For instance, wastewater treatment plants (WWTPs) effluents have been identified as the main point source of human pollution in water bodies, followed by industrial plants and storm overflow to a lesser degree. On the other side, the main driver of diffuse pollution of veterinary drugs is agriculture since their release is not connected to the sewage. In this context, parent compounds may be degraded during the wastewater treatment and in the environment from biotic (i.e., biodegradation) and abiotic processes (e.g., hydrolysis, photolysis, oxidation). In this way, a transformation product is a general term to define the compounds that are the result of any reaction which does not completely mineralize the parent compound (Zwiener, 2007). When considering the fate an OMP, and particularly a pharmaceutical, it should be expected to find in the environment either the parent compound or a transformation product of lesser or higher toxicity, thus attention must be paid to the risk of their release (Vallero, 2018).

Among the sources of wastewater arriving to WWTPs, hospital effluent has drawn the attention of the scientific community due to its microbiological (e.g., antibiotic resistance bacteria or genes) and chemical composition, which includes a wide variety of active principles of drugs, metabolites, detergents, disinfectants, and iodinated contrast media, among others (Daouk et al., 2015). OMPs related to hospital wastewater are characterized for presenting seasonal variations (i.e., annual disease outbreaks) and, on some occasions, be linked to extreme outbreaks such as SARS or COVID-19. Despite it, hospital effluent is still considered urban wastewater, and thus it is discharged into public sewage systems without undergoing any specific treatment (Verlicchi et al., 2015)

Currently, wastewater treatment trends are directed to create and upgrade WWTPs to minimise the impact of OMP discharge by the development of integrated methods to monitor and enhance their removal. Decentralized advanced treatments are a promising option to reduce specific on-point sources, such as hospital wastewater.

1.2 Legal framework

OMPs have been found worldwide in surface water, groundwater, soil and animal tissues at concentrations that vary depending on the compound's nature and the proximity to the source of contamination. In this regard, the 6th Sustainable Development Goal of the United Nations Agenda for 2030 and the Ministerial declarations of the 3rd and 4th UN Environmental Assemblies express the need for commitment to ensure the sustainability of water bodies, improve the monitoring systems and prevent/mitigate the water pollution (Tsalis et al., 2020; UNEP, 2018, 2017).

In Europe, the Water Framework Directive (WFD) 2000/60/EC is the first and main legislation including the totality of EU water bodies (Council of the European Union, 2000). Adopted on 23 October 2000, WFD introduced a new integrated water management approach at the river basin scale. Member states should aim to reach a good ecological and chemical status in surface waters and a good chemical and qualitative status for groundwater. Good ecological status is fundamental to ensure the long-term availability of good quality water resources to provide ecosystem services. Despite efforts made to reach WFD objectives set by 2015, at present many member states deal with severe pollution, hydro-morphological pressures and over-abstraction of water resources (EPA, 2018). According to River Basin Management Plans (RBMPs) set by the EU Commission (up to 2015, soon to be revised), only 38% of surface waters are in a good chemical status. Latest reports also indicate that chemical monitoring is insufficient and not all priority substances are regularly monitored. As a matter of fact, 16% of the EU water bodies present an unknown chemical status (EPA, 2018).

In order to ensure a good chemical status in European river basins, WFD approaches surface water pollutants in two ways, by identifying and monitoring those of great concern and by requiring Member States to identify specific contaminants affecting their river basins. In 2008, the EU Commission approved the Environmental Quality Standards Directive (2008/105/EC), also known as Priority Substances Directive, which established a list of 33 priority substances and their environmental quality standards (i.e., concentrations) in surface waters (European Commission, 2008). Among the priority substances, the most harmful are described as priority hazardous substances, and WFD intends to phase out their discharge into water bodies. The list was amended by Directive 2013/39/EU, which resulted in the inclusion of 12 new priority substances for a total of 45 (European Commission, 2013). It provided new environmental quality standards for biota, and it established a mechanism to improve the information available for some pollutants of emerging concern, the so-called Watch list.

The establishment of the Watch List aims to gather monitoring data that underlies the subsequent risk assessments for the inclusion of substances in the priority list. It includes highly toxic substances that are rarely monitored in water bodies and for

which the information available indicates that they may pose a risk. The Watch list promotes the creation of high-quality data on the compounds listed to better understand their occurrence, persistence and bioaccumulation in aquatic environments. The substances, therefore, are related to emerging contaminants not yet regulated, which once sufficient data is collected, are removed from the Watch List and evaluated for the next revision of Directive 2008/105/EC. The Watch List was introduced in 2015 (Decision 2015/495) and updated every 2 years since then (Decision EU 2018/840, Decision EU 2020/1161, Decision EU 2022/1307) (European Commission, 2022a, 2020, 2018a, 2015). The last version of the Watch List (2022) contains 26 substances grouped into 9 classes:

- Antibiotics sulfamethoxazole, trimethoprim, clindamycin and ofloxacin
- Antimycotics clotrimazole, fluconazole and miconazole
- Diabetes type 2 pharmaceutical metformin and its metabolite guanyl urea
- Pesticides imazalil, ipconazole, metconazole, penconazole, prochloraz, tebuconazole and tetraconazole
- Fungicides dimoxystrobin, azoxystrobin and famoxadone
- Herbicide diflufenican
- Insecticide and veterinary drug fipronil
- Sunscreen agents butyl methoxydibenzoylmethane, octocrylene and benzophenone-3

Many of the substances listed in the Watch List are pharmaceuticals. Indeed, Article 8c of the Directive 2013/39/UE requires the Commission to persuade a strategic approach regarding, specifically, the pollution of pharmaceutical substances in water. Member States are required to consider their potential environmental impacts and propose measures to reduce them while taking into account the cost-effectiveness of the actions and the public health needs. The European legislation for the regulation of medical products is compiled in the Directive 2001/83/EC, where an environmental risk assessment is mandatory to apply for marketing authorisation (Article 8) (European Commission, 2001). However, it should be noted that pharmaceuticals and active principles are exempt from most of the provisions under REACH legislation (Article 2, paragraph 5) (European Commission, 2006a), which aims at controlling chemicals in industry production in order to limit contamination in water bodies.

Approaches commented on in this section are complementary to other European initiatives as the European One Health Action Plan of the Commission (European Commission, 2017) which includes measures to address the presence of antimicrobial pharmaceuticals in water and soil, or the approaches to create a new EU framework for endocrine disruptors (European Commission, 2018b). At the same time, they align with other European legislations regarding the release of chemicals in industrial or agricultural activities, such as the Persistent organic pollutants Regulation (EU) 2019/1021 (European Commission, 2019a), the Directive on Plant Protection Products (91/414/EEC) (European Commission, 1991a), the Industrial Emissions Directive (2010/75/EU) (European Commission, 2010) or the Waste Framework Directive (2008/98/EC) (European Commission, 2008). In the same way, the EU

Bathing Water Directive (2006/7/EC) and EU Urban Wastewater Treatment Directive (UWWTD) (91/271/EEC) are legislations adopted to protect water bodies and human health from the adverse effects of pollution (European Commission, 2006b, 1991b). Regarding this latter, a proposal for a law revising the Directive was published on 26th October 2022 (European Commission, 2022b). The draft law revising the UWWTD, originally adopted in 1991, was written based on the assessment carried out by the Regulatory Fitness and Performance programme (REFIT), which concluded in 2019 (European Commission, 2019b). The REFIT evaluation confirmed that the implementation of the UWWTD led to a significant reduction of pollutant releases, which caused positive effects on the quality of EU lakes, rivers and seas. However, the evaluation also identified a set of remaining challenges, namely the pollution from urban sources, the alignment of the Directive with the European Green Deal and the insufficient and uneven level of governance. In this way, the UWWTD proposal aims to address them cost-effectively while keeping the Directive as simple as possible to ensure its implementation.

Among the new measures that will be progressively applied until 2040 in the upcoming UWWTD, new limit values will be established for micropollutants that will require additional treatment steps in the WWTPs. In particular, the growing evidence of the issue that is the presence of micropollutants in EU water bodies has led to the introduction of a new Article regarding the obligation of application of a quaternary treatment (Article 8) in WWTPs treating a load ≥ 100,000 PE (by December 2035) and between 10,000 and 10,000 PE in sensitive areas to micropollutant pollution by December 2040. To monitor the performance of the quaternary treatment, the removal of a limited set of representative OMPs will be measured (Table 3 of Annex 1 of the proposal). The indicator compounds are defined in two categories. Category 1 includes 7substances that can be easily treated, namely amisulpride, carbamazepine, citalopram, clarithromycin, diclofenac, hydrochlorothiazide, metoprolol and venlafaxine; whereas category 2 lists substances that can be easily disposed of, that is, benzotriazole, candesartan, irbesartan and the mixture of 4-methylbenzotriazole and 6-methyl- benzotriazole. The minimum removal of indicator substances is set at 80%, which should be calculated for at least 6 substances. In addition to that, the number of substances falling in category 1 shall be twice the number of compounds in category 2. The collection of samples is carried out at regular intervals throughout the year according to the size of the WWTP (i.e.,1 sample per month or two samples per week, Part D of Annex I of the proposal).

Beyond the European legislation, other regional, national and international guidelines and regulations have been the result of the global rising concern regarding the presence of MPs in the water sector. Bui et al. (2016) summarize a set of OMPs, their concentrations and the regulations adopted around the globe. The authors highlighted that most of the regulations regard drinking water supply, like the D.Lgl. 31/2001 in Italy and the National Primary Drinking Water Regulations of the USA (USEPA, 2009).

Switzerland is a pioneer country enforcing legal actions to limit the OMPs discharge from WWTPs effluents (Swiss Office for the Environment (FOEN), 2016, 201AD). The decision was approved by the Swiss parliament in 2011 with the aim to improve drinking water resources and water quality (Schweizer Bundesrat, 2016). The scientific basis was mainly gained through the multi-project "Strategy MicroPoll" (2006-2010) (www.micropoll.ch) that investigated the load and toxicity of multiple OMPs in WWTP effluents and assessed options to upgrade the existing WWTPs to enhance their removal. WWTPs have been thus required to upgrade their installations based on the foreseen OMP loads and the capacity of dilution in the receiving waters (Bui et al., 2016). For the selected WWTPs, the average removal efficiency is targeted at 80% over a year time (considering all indicator substances), on the basis of regular sampling that depends on the size of the WWTP (The Swiss Federal Council, 1998). The first indicator compounds set to monitor the treatment efficiency were benzotriazole, carbamazepine, diclofenac, and sulfamethoxazole (Eggen et al., 2014), which were then updated to 12 substances in 2015 (i.e., amisulpride, carbamazepine, citalopram, clarithromycin, diclofenac, hydrochlorothiazide, metoprolol, venlafaxine, benzotriazole, candesartan, irbesartan, methylbenzotriazole) (Götz et al., 2015; Schachtler and Hubaux, 2016). In any case, updates of the Swiss ordinance may modify the substances used to measure the removal efficiency and how efficiency is calculated. Note that the list of compounds proposed in 2015 is practically the same as the proposed for the new EU UWWTD (European Commission, 2022b). The preferred treatments are ozonation and PAC, used as a post-treatment after the biological reactor. In case PAC is used, the adsorbent particles are filtered before the discharge of the final effluent into the aquatic environment (Kovalova et al., 2013a; Margot et al., 2013). Both treatments have been considered technically feasible and cost-effective (Eggen et al., 2014).

Progress has been made thanks to the actions for monitoring and assessing the presence of pharmaceuticals in the aquatic environment. At the same time, regulations have been created to limit the indiscriminate disposal of waste from the pharmaceutical industry into the environment. However, the annual consumption rates of pharmaceuticals have increased over the years (OECD, 2013), and thus their presence in water bodies. Still, there are many knowledge gaps to deal with. Although at present pharmaceuticals are subjected to environmental risk assessments before their commercialization, many of them have been put into the market several years ago and were not subjected to them. Monitoring is still very limited to the selected substances under the WFD. There are pharmaceutical hotspot locations, such as those WWTP receiving hospital wastewater, which would need particular monitoring and assessment to regulate the impact of their effluent on the receiving waters (Verlicchi et al., 2015). In addition, the potential synergistic effects from the combination of many pharmaceuticals at the environmental level are still not contemplated in the WFD.

Following the case of Switzerland, other European States have started to implement innovation programs for the removal of OMPs, such as Germany, Poland, Lithuania,

Sweden, The Netherlands and Luxembourg. In Germany, although no legal thresholds for OMPs have been set do date, a common strategy is being developed at both regional and national levels (Kosek et al., 2020). So far, monitoring data on OMPs for several surface waters and small-scale research studies have been reported within the Federal States and, at a national level, the Federal Environmental Agency (i.e., UBA) has published a list of suggested limits for selected priority substances and has issued comprehensive reports on measures to reduce the discharge of micropollutants in the aquatic environment. Additionally, financial incentive systems have been created as economic policy instruments to foster the implementation of a German wastewater regulation (Luczkiewicz et al., 2019). The common strategy aims to harmonize the data obtained from both regional and national approaches as well as the data retrieved from finished research studies (Kosek et al., 2020). However, the UBA agency of North Rhine Westphalia has differentiated itself from the other regions by issuing a list of priority substances that includes pharmaceuticals such as benzotriazole, carbamazepine, diclofenac, metoprolol, clarithromycin and sulfamethoxazole. In the same way, both North Rhine Westphalia and Baden-Württemberg have already upgraded some WWTPs. The preferred advanced quaternary treatment stages are the ozonation, the adsorption onto PAC or GAC and the combination of these two technologies. Up to 2019, 16 full-scale WWTPs were upgraded with the fourth treatment stage, whereas 6 installations were under construction and 11 WWTPs were planned to be upgraded (Kosek et al., 2020). The implementation of these advanced treatments is fundamental to evaluate the treatment effectiveness and cost implementation in the country, especially along the Rhine-Ruhr catchment area, a densely populated region with a high wastewater ratio inflow into the surface water (Kosek et al., 2020). Likewise, the International Commission for Rhine Protection, composed of the nine countries from which the water of the Rhine River is abstracted has provided comprehensive studies regarding the OMP's release in the Rhine catchment area (ICPR, 2018) and helps to bridge the gap of the implemented measures for the development of a future action plan.

As a final example, the Netherlands has launched the Dutch Approach, based on "learning by implementation" (STOWA, 2021). The Dutch Government, together with regional water authorities and healthcare parties are working on a multibarrier approach for the removal of selected pharmaceuticals. The aim is to limit the manufacture and the use of medicines and to promote their removal by the implementation of specific treatments in WWTPs. Selected treatments must remain in operation for 10 years, reach a minimum removal of 70% for key OMPs and check the effectiveness of the treatment by periodical monitoring and, if needed, conduct a proper adjustment of the technology. The treatments chosen are mainly focused on PAC added inside the biological reactor and post-treatment with ozonation or GAC. Additionally, the multi-barrier approach addresses the analysis of hotspots, the severity of OMPs emissions and the effect of these contaminants on the water cycle.

1.3 Wastewater treatment

Until 1970, the main objectives of wastewater treatment were the removal of suspended solids, organic matter, and pathogens (Metcalf & Eddy, 2014). Since then, environmental awareness has expanded, and pollution and energy efficiency have become central issues in our current society. As scientific understanding has advanced, the scientific community has put efforts into the research of wastewater characterization while new analytical techniques have been developed. The knowledge about constituents that may cause long-term health and environmental effects, like OMPs, has fostered the need for the update and improvement of the existing treatment technologies to meet upcoming new water-quality objectives. The design of new advanced cost-effective treatments has resulted in the development of systems like the membrane bioreactor (MBR), which have become widely used since the 1990s (Judd, 2011). In the last years, promising insights have been obtained by combining advanced biological systems (MBRs) with innovative treatment technologies, leading to the development of the so-called hybrid MBRs or integrated MBRs (Qin et al., 2018). In this section, an overview of conventional wastewater treatment will be made, and focus will be put on the fundamentals of MBR technology.

1.3.1. Conventional wastewater treatment process

The most widespread wastewater treatment process is conventional activated sludge (CAS). The activated sludge process forms part of a complete scheme that comprises four stages (Figure 1.1). The first stage consists of a pre-treatment where coarse materials and floatable substances are removed by screening and grit removal chambers. The second stage consists of a primary clarifier where readily settleable solids are removed in what is called primary sedimentation. When needed, coagulants like ferric alum chloride are added to promote the coagulation/flocculation of suspended material. If efficiently operated and designed, primary settlers can remove 50 – 70% of the total suspended solids (Metcalf & Eddy, 2014). The third stage is the activated sludge process (described below) which involves the biological reactor and secondary clarifier. This stage is the crucial step in WWTPs, and it is usually controlled to maximize the microbiological activity and the quality of the effluent. Depending on the required quality of final effluent, tertiary treatment (optional) is carried out. This stage usually consists of disinfection with UV light or chlorine and/or advanced treatments to remove specific pollutants. Waste sludge from the primary and secondary clarifiers is removed from the system for further processing, potential reuse or ultimate disposal.

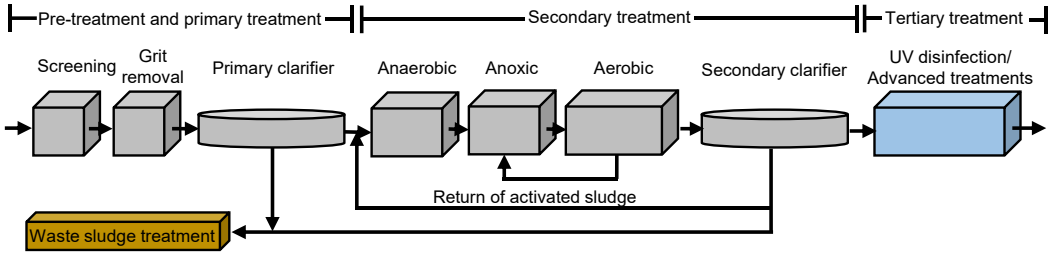

Figure 1.1. Diagram of conventional WWTP.

The activated sludge process is a wastewater treatment that involves the production of an activated mass of microorganisms capable of biologically oxidising organic waste under aerobic conditions (eq. 1). The main objective is to remove dissolved, colloidal and particulate (suspended) carbonaceous organic matter, nutrients (nitrogen and phosphorous) and to capture and incorporate suspended or non-settleable solids into sludge flocs. The microorganisms involved are mainly bacteria and protozoa, which are able to biodegrade the organic matter to simple end-products (mineralization).

$$\nu_1 \text{organic matter} + \nu_2 O_2 + \nu_3 NH_3 + \nu_4 PO_4^{-3} \xrightarrow{\text{microorg.}} \nu_5 \text{ microorg. growth} + \nu_6 CO_2 + \nu_7 H_2O \qquad \text{eq. 1}$$

A basic activated sludge treatment process consists of three main components: an aerated reactor where the microorganisms are kept suspended, a liquids-solid separation unit (sedimentation tank or second clarifier) and a recycling system that returns the solids from the separation unit to the aerated reactor. The aerobic conditions are obtained through mechanical aeration and mixing of the wastewater in the aeration tanks. The microbial suspension is normally referred to as mixed liquor suspended solids (MLSS) or mixed liquor volatile suspended solids (MLVSS). The suspended microorganisms tend to flocculate to create sludge flocs, with a density slightly superior to water and a size ranging from 50 to 200 mm (Metcalf & Eddy, 2014). In CAS processes, sludge flocs are separated by gravity settling in a secondary (final) clarifier. The settled biomass is partially returned to the aeration tank, while a portion is removed periodically to maintain a constant concentration of MLSS in the reactor. Conventional sludge systems have been optimized over the years to incorporate nitrification and denitrification chambers and biological phosphorous removal through different redox conditions used (anaerobic, anoxic and aerobic chambers) and precipitation.

Strict discharge limits lead to the emphasis and regulation of the removal of nutrients in CAS. Since the 1980s, the high effluent-quality demands and the simultaneous increment of energy costs have promoted the improvement of the design and operation of WWTPs. Technological advances in materials, manufacturing methods, process operation, and energy efficiency have led to the upgrade and improvement of activated sludge processes. Among the new solutions created, advanced biological systems (MBRs) started to be widely used in the late 1990s and early 2000s (Xiao et al., 2019).

1.3.2. Membrane bioreactor

The membrane bioreactor (MBR) combines the activated sludge process with membrane separation. Essentially, the role of the membranes is to substitute the second clarifier in CAS. A pressure-driven vacuum withdraws the water (permeate) through the membrane while retaining the solids inside the reactor (retentate). Membranes are characterized by a high specific surface and a fixed membrane pore size. In wastewater treatment, membrane pore size ranges from 0.01 to 0.1 μm in ultrafiltration membranes (UF) and from 0.1 to 10 μm in microfiltration (MF), thus the final effluent is free of suspended and colloidal materials (Figure 1.2).

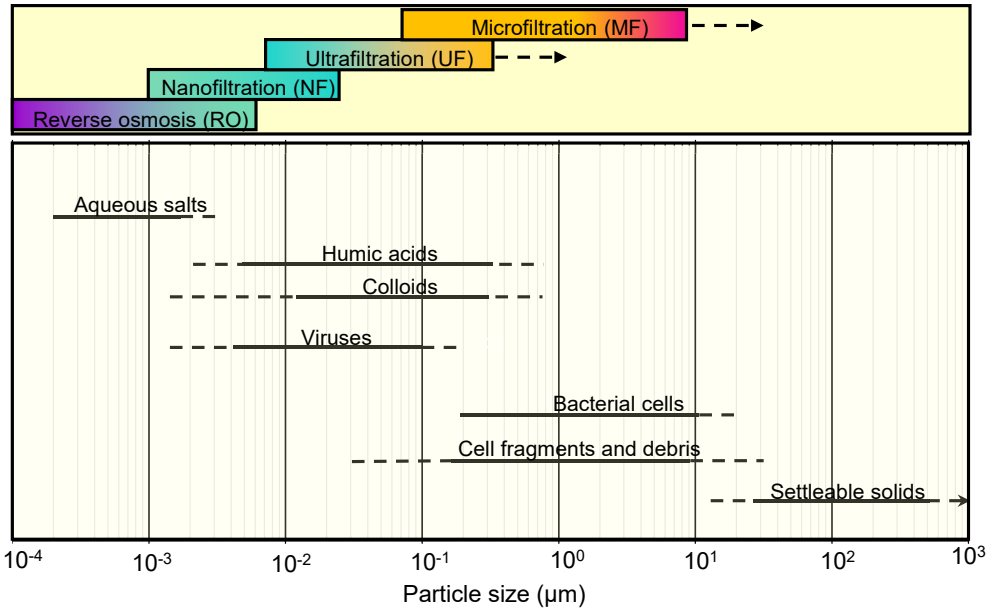

Figure 1.2. Size range of the constituents commonly found in wastewater and the operating size ranges for membrane technologies. Adapted from Metcalf and Eddy, (Metcalf & Eddy, 2014).

The common types of membranes used are hollow fiber and flat sheets, which are mounted in modules which support the structure. Hollow fiber configurations are usually designed to operate with lower MLSS concentration and higher flux, and they possess a higher specific surface area, which made them suitable for bigger WWTPs (Krzeminski et al., 2017). The membranes are commonly made up of polymers with high porosity as polyvinylidene difluoride (PVDF), polyethylene (PE), polyethylsulphone (PES) and polypropylene (PP) (Metcalf & Eddy, 2014). The filtration goes from the mixed liquor (outside) to collect the permeate inside the fiber/module. This type of filtration is denominated outside/in. Depending on the position of the membrane, two configurations are found in wastewater treatment: side stream, where the membrane is placed in a different chamber from the biological treatment or submerged, when it is directly immersed in the bioreactor (Figure 1.3).

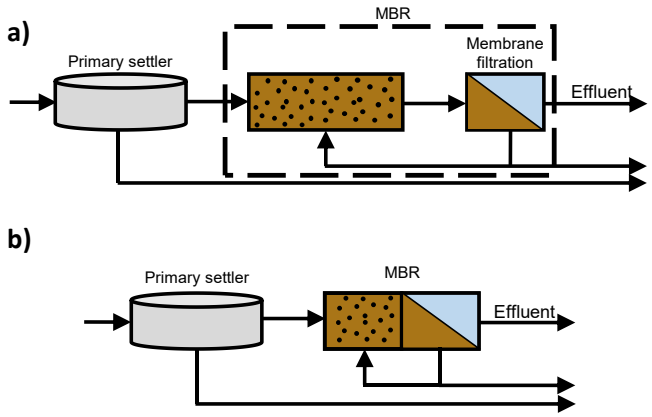

Figure 1.3. Configurations of MBR, a) side-stream and b) submerged.

Membranes placed in the biological reactor deal with a high concentration of MLSS, which usually range from 8 to 10 g/L. To avoid membrane fouling with retained materials, a coarse bubble air supply is provided to remove the embedded solids in the external membrane surface. In addition to air scouring periodical relaxation, maintenance cleaning (backpulsing) and recovery cleaning are common fouling control methods, which are applied depending on the degree of fouling. Membrane fouling is the deposition and accumulation of particulate and dissolved foulants on the membrane surface and pore structure, which can be caused by physical, chemical and biological agents. Mechanisms of fouling include membrane pore clogging, pore blocking and cake layer formation. Fouling results in an increase of the transmembrane pressure (TMP), thus reducing the permeability of the membrane and leading to more frequent membrane cleaning, an increase in the operation costs and a reduction of the membrane's lifespan (Krzeminski et al., 2017). Membrane fouling may be classified as biofouling and inorganic fouling. The major contributors to membrane fouling are organic substances such as polysaccharides, proteins, humic acids, and other organic biopolymers excreted by the microorganisms, which can lead to the development of a biofilm in the membrane's surface (cake layer formation). To deal with it, air scouring, membrane relaxation and maintenance cleaning are frequently used methods. Membrane relaxation refers to the period during which the permeate is not withdrawn (e.g., 1 min every 10 mins of filtration), while backpulsing is when the water flow is reversed to remove the particles attached to the surface of the membrane, sometimes in combination with a sodium hypochlorite or citric acid solution. When these three methods are not effective and irreversible fouling is achieved, recovery cleaning is applied. The membranes then are removed from the tanks and extensive chemical cleaning is carried out by the application of chlorine or citric acid solutions. The need for recovery cleaning is usually associated with the adsorption of soluble compounds into the membrane, either organic or inorganic.

MBR fundamental parameters

Mixed liquor suspended solids (MLSS): The concentration of suspended solids in the mixed liquor contained in the aeration tanks. It is usually expressed as milligrams per litre (mg/L).

Hydraulic Retention Time (HRT): The amount of time wastewater spends in the aeration tank (eq. 2).

$$HRT = \frac{volume\ of\ the\ aeration\ tank\ (m^3)}{Flow\ \ (m^3/d)} \qquad \text{eq. 2}$$

Solids retention time (SRT): It is the time the solid fraction of the wastewater spends in system. In this thesis, this fraction is the concentration of MLSS, correlated to the sludge produced in the aeration tank (eq. 3). The equation is a modification from Metcalf and Eddy (2014), considering a side-stream configuration where,

$$SRT = \frac{X_N \cdot V_N + X_M \cdot V_M}{Q_W \cdot X_W} \qquad \text{eq. 3}$$

X_N = MLSS concentration in the aeration tank (kg/m^3); V_N = volume of aeration tank (m^3); X_M = MLSS concentration in the membrane separation tank (kg/m^3): V_M = volume of membrane separation tank (m^3); Q_W = waste sludge flowrate (m^3/d) and X_W = total suspended solids (TSS) concentration in the waste sludge (kg/m^3).

Food to microorganism ratio (F/M): Measurement of the food entering the system with respect to the microorganism concentration in the aeration tank (eq. 4),

$$\frac{F}{M} = \frac{Q_{in}\ \cdot BOD_{in}}{MLSS \cdot V_N} \qquad \text{eq. 4}$$

where Q_{in} (m^3/d) and BOD_{in} (kg/m^3) refer to the flow rate and BOD_5 concentration in the influent. BOD_5 is an indirect measure of the concentration of biodegradable organic compounds. It indicates the concentration of dissolved oxygen (mg/L) that is needed in a given time (i.e., 5 days) for the biological degradation of the organic wastewater constituents.

MBR design parameters

Membrane flux: Flowrate per unit area of the membrane, usually expressed as L/(m^2·d) (eq. 5). It's a crucial parameter to determine the required membrane surface area, air scour supply and membrane tank volume. It depends on the MLSS, temperature, transmembrane pressure and degree of membrane fouling.

$$Membrane\ flux = \frac{flow\ (L/d)}{membrane\ surface\ area\ (m^2)} \quad \text{eq. 5}$$

Transmembrane pressure (TMP): Pressure drop across the membrane, usually in bars. A certain range of TMP needs to be achieved in order to get the desired flux. Membranes with small pore sizes usually have higher TMPs.

Permeability: Ratio between the membrane flux and the TMP, thus the flux per unit of pressure (eq. 6).

$$Permeability = \frac{membrane\ flux\ (L/m^2 d)}{TMP\ (bar)} \quad \text{eq. 6}$$

MBR technology implementation

Compared to CAS systems, MBR technology possesses many advantages (Sipma et al., 2010). It is associated with a lower footprint, since less area is required due to the absence of a secondary clarifier and the reactor enables higher organic loads and MLSS. Even if it is operated at higher SRTs, less sludge is produced compared to CAS. Due to the presence of the membranes, issues related to the poor sedimentation of the sludge in the second clarifier are negligible (Metcalf & Eddy, 2014). The quality of the effluent is higher, with almost the absence of suspended solids, low turbidity and partially disinfected, which makes this technology suitable for water reuse (Judd, 2011). In addition to that, investigations on full-scale MBRs show that they not only provide a stable treatment for conventional pollutants, but a promising potential for removal of emerging contaminants (especially in combination with other treatments) (Radjenovic et al., 2008; Verlicchi et al., 2012).

The implementation of the first MBRs dates from the late 1960s, with side-stream MBRs developed commercially by Dorr-Oliver for ship-board sewage treatment and other industrial applications (Judd, 2011). From the late 1980s to the early 1990s, relevant commercial improvements led to the application of MBRs for the treatment of domestic wastewater and industrial effluent in Japan and, by the late 1990s, the development several MBR products around the globe caused an explosion in the market (Judd, 2011). MBR scientific literature and patent publications have experienced an exponential increase since the 1990s and 2000s, respectively. As to MBR implementation, large-scale (≥ 10,000 m^3/d) and super large-scale (≥ 100,000 m^3/d) MBRs have been increasingly put into operation in most developed countries (Xiao et al., 2019). The annual global growth rate of MBR technology from 2011 to 2018 has been approximately 15%. The greatest expansion of this technology has occurred in China due to the water scarcity associated issues this country is experiencing and subsequent the need for water reuse for agricultural purposes (Krzeminski et al., 2017; Xiao et al., 2019). Nowadays, MBR technology is a convenient option for medium size WWTPs (up to 100,000 population equivalent, PE or less than 50,000 m^3/d) (Krzeminski et al., 2017; Vaccari et al., 2022). In Italy, more than 70%

of the MBR plants treating municipal wastewater have a capacity of up to 10,000 PE (Vaccari et al., 2022).

Nowadays, MBR technology is adapted for treating both municipal and industrial wastewater. The main driving forces for MBR implementation have been (i) the stricter discharge standards and quality requirements for water reuse, (ii) the acceptance of the technology, mainly related to the reduced footprint and the reliable operation that MBRs provide, (iii) the decrease of the investment costs, and (iv) the high quality of the final effluent, often comparable or superior to a CAS tertiary treatment (Judd, 2011). Indeed, MBRs have been proposed as a promising technology for water reuse in a water scarcity context. For instance, many Southern European countries have discharge limits for reclaimed water that conventional CAS coupled with disinfection does not ensure to meet (e.g., 10 mg/L of TSS) (Krzeminski et al., 2017). Additionally, MBR has proved to be suitable for an on-site upgrade of existing WWTPs. Finally, their modular design often allows further expansion of the existing treatment trains.

However, the full-scale application of MBR faces several challenges. There is still room for further improvement in the mitigation of membrane fouling and energy consumption, especially with regard to reducing aeration for membrane scouring. Today, MBR systems still have higher capital and operating costs compared to CAS without the tertiary treatment, but comparable to it when tertiary treatment is added (Sipma et al., 2010). For instance, the average footprint for full-scale MBRs treating municipal wastewater in China is around 0.8 $m^2/(m^3/d)$, while CAS with tertiary treatment ranges between 1.2 – 1.6 $m^2/(m^3/d)$ (Xiang et al., 2018). Regarding energy consumption, MBR has approached CAS consumption over the years. Design and process optimization has helped to reduce the capital and operating costs of MBR plants, as well as to increase membrane lifespan over time. Indeed, MBR technology provides a reliable operation due to process automation, which allows for remote monitoring of the system and minimal operator attention (Krzeminski et al., 2017). On the other hand, MBRs require skilled operators, particularly with membrane handling and maintenance (Vaccari et al., 2022).

As mentioned before, there is still room for the improvement of MBR technology. Krzeminski et al. (2017) summarize the energy savings solutions and potential improvements of MBR systems found in the scientific literature. Namely, they are related to the improvement of the hydraulic loads and flow conditions, the modification of the membrane's surface and the aeration control systems and the improvement of hydrodynamics on the membrane surface. Integration of novel systems coupled to MBR has been extensively studied in the literature (Echevarría et al., 2019; Qin et al., 2018; Rizzo et al., 2019). Enhanced removal of OMPs energy recovery and improved operation are the main drivers for improvement in the scientific community.

1.4 Hybrid MBRs

According to Neoh et al., (2016), the integration of MBR with other innovative technologies can be considered a multiple-barrier approach for wastewater treatment. Hybrid reactors are defined as the integration of two or more technologies with diverse removal mechanisms to treat contaminants (Figure 1.4) (Goswami et al., 2018). In the case of hybrid MBRs, the biological degradation is coupled with physicochemical methods or additional biological trains. In this section, a summary of the main types of hybrid MBRs is done, with special attention to the adsorption onto activated carbon.

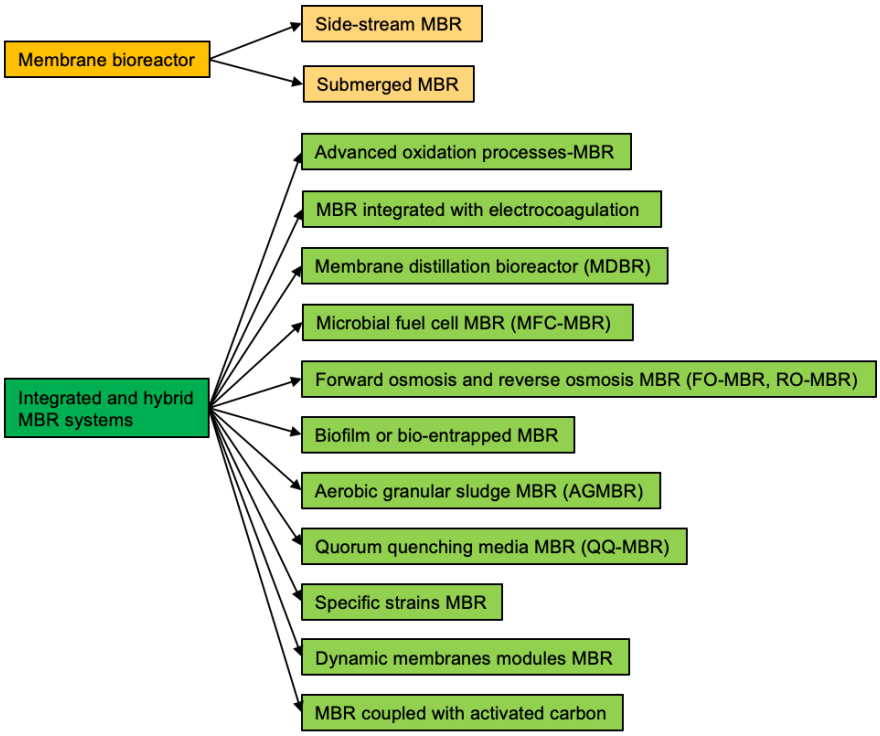

Figure 1.4. Overview of integrated and hybrid MBRs. Adapted from Goswami et al., (2018).

1.4.1. MBRs coupled with advanced oxidation processes

Integration of MBR with advanced oxidation processes (AOPs) has been found to be effective for the removal of OMPs by chemical oxidation. AOPs are a set of chemical treatment procedures designed to degrade contaminants by oxidation through the generation of reactive oxygen species. The most relevant reactive oxygen species is the hydroxyl radical (·OH), which is a non-specific oxidant, efficient in the oxidation of almost all compounds. AOPs are based on the combination of a strong oxidizing agent (O3, H2O2) with a catalyst and/or radiation (UV, ultrasound). They are classified into three main groups: ozone-based processes, photocatalytic processes and Fenton reaction based-processes (Rekhate and Srivastava, 2020). AOPs can be

used as an advanced post-treatment for MBR effluent or as a pre-treatment before the MBR. The efficiency of the system depends on the proportion between biodegradable and recalcitrant substances present in the wastewater. If biodegradable organics are present in higher concentrations, it is convenient to treat the wastewater in the biological reactor before the use of AOPs. If recalcitrant pollutants are predominant over biodegradable compounds, AOPs are used prior to the MBR to increase the successive biodegradation step (Goswami et al., 2018).

AOPs have been drawing scientific attention for the past years, although they are not widely applied in wastewater treatment (except for O_3 and UV/H_2O_2) but rather in niche applications. Although most of the OMPs can be treated with AOPs, efficiency, safety and cost-related issues question their large-scale implementation. Another important limiting factor common in all AOPs is the presence of scavengers in the wastewater, which may diminish the AOPs efficiency by reacting with the ·OH species (Neoh et al., 2016). For this reason, the water matrix and the treatment objective will define the fit-for-purpose application. It is noted that oxidation processes transform OMPs but do not mineralize them (Verlicchi et al., 2015). Even if they are able to mineralize, doing so would be economically unfeasible in most cases. The formation of transformation by-products can be an issue due to their potential toxicity and non-specific effects (e.g., mutagenicity and oxidative stress).

Ozone-based processes

Ozone-based AOPs are the best AOPs for the removal of trace organic chemicals. Ozone (O_3) is a powerful oxidant that acts either by direct electrophilic attack or indirectly by the formation of ·OH radicals produced through the ozone decomposition process (Rekhate and Srivastava, 2020). Degradation through ozonation depends on many factors such as the nature of the contaminant, the dose of ozone or the pH of the medium (Cuerda-Correa et al., 2020). The formation of ·OH radicals depends greatly on the presence of natural organic matter (NOM), and it is considered the main influencing parameter (Rizzo et al., 2019). Indeed, ozone dose is usually expressed with respect to the dissolved organic carbon (DOC) content in the wastewater (i.e., specific ozone dose). Ozonation has been widely implemented in combination with other treatments (i.e., O_3/UV, O_3, O_3/H_2O_2, O_3/metal oxide catalyst, O_3/ultrasound…) that can enhance the production of ·OH radicals and thus the treatment efficiency (Bui et al., 2016).

However, there are some drawbacks associated with the use of ozonation-based AOPs. The effects of ozonation after biological treatment have been widely studied (Cruz-Alcalde et al., 2017; Yin et al., 2017). Apart from the formation of transformation products derived from OMPs, the oxidation by-products derived from the wastewater matrix and the presence of bromate and NDMA are important issues during ozonation. Ozonation treatment usually requires continuous control, regular inspections and maintenance with skilled operators. Additionally, O_3 generation consumes great energy due to its low efficiency of conversion (Bui et al., 2016).

Photocatalytic processes

Photocatalytic processes imply the use of a photoactive catalyst to accelerate the photochemical reactions that degrade pollutants in wastewater. Light is absorbed by the catalyst, which creates electron-hole pairs (h^+/e^-) on its surface that start redox reactions which will promote the degradation of the contaminant. The most common photocatalyst is TiO_2, but other semiconductors materials may be used (e.g., ZnO). Considering the source of light, UV-based processes have become feasible alternatives for OMPs removal. However, direct UV radiation is effective only for certain kinds of pollutants (Yang et al., 2014), and it is usually needed to combine it with oxidants and/or photocatalysts. The removal efficiency of OMPs by UV radiation is dependent on some factors as the source of the UV light (solar light, lamps); wastewater composition and pH (Yang et al., 2014). The optimization of the system configuration, electricity consumption and the cost of chemical reagents are the main drawbacks to the implementation of these technologies (Loeb et al., 2019).

Fenton reaction-based processes

Fenton reaction-based processes combine ferrous ions, used as a catalyst, with an oxidizing agent and/or radiation to form ·OH radicals (e.g., Fe^{2+}/H_2O_2, Fe^{2+}/H_2O_2/UV). In Fenton process, Fe^{2+} ions react with H_2O_2 in a preferably acidic environment that creates both ·OH radicals and Fe^{3+} ions, which are then reduced to Fe^{2+} by reacting with H_2O_2 again (Clarizia et al., 2017). In photo-Fenton processes, the presence of UV enhances the reduction of Fe^{3+} to Fe^{2+}, producing even more radicals. This treatment is considered very efficient for the abatement of OMPs (Clarizia et al., 2017). However, as stated previously for the abovementioned AOPs, associated costs related to energy consumption and the use of chemical agents (Fe, H_2O_2, acids) and separation of soluble Fe species from the treated wastewater/sludge make it difficult to implement at full-scale (Rizzo et al., 2019).

1.4.2. Other hybrid MBRs

Advancements in MBR technology look to reduce one of the main drawbacks to the wide MBR implementation: energy consumption. To deal with it, two main strategies have been addressed by hybrid MBRs. The first one intends to produce energy while treating wastewater in order to reduce the need for an external energy supply, as in the case of microbial fuel cells coupled to MBR (MFC-MBR). In this hybrid process, the membrane of the MBR acts as a cathode for electricity generation and as a filter (Malaeb et al., 2013; Qin et al., 2018). MFC-MBRs avoid the need of air supply and offer good-quality effluent for conventional parameters (COD, N-NH_3). However, they are still not optimized regarding their operation and energy consumption (Malaeb et al., 2013). The second strategy to reduce the energy demand is based on diminishing the hydraulic pressure in the system and thus mitigating the membrane fouling. In this way, forward osmosis and reverse osmosis membranes integrated into MBRs (FO-MBR and RO-MBR, respectively) have attracted interest for their low energy

consumption and high quality of the effluent. The hydraulic pressure difference is the only driving force for these membranes. Contaminants, either hydrophobic or hydrophilic, which are larger than the molecular cut-off weight of the membranes are retained, increasing the probability of their biodegradation. The high-quality effluent with low dissolved organics and salts make these hybrid systems suitable for potable water reuse treatment trains (Rizzo et al., 2019). A second strategy for the reduction of the hydraulic pressure in the system is the membrane distillation bioreactors (MDBRs). MDBRs refer to the combination of thermophilic biodegradation with membrane distillation. The vapour generated through a thermal gradient passes across a hydrophobic membrane to the permeate tank. The lack of hydraulic pressure makes this system less susceptible to membrane fouling, with a high potential for the removal of OMPs (Wijekoon et al., 2014).

As a matter of fact, the heterogeneous nature of the mixed liquor and wastewater makes membrane fouling inevitable in MBRs, and common strategies for fouling control constitute a significant proportion of the energy consumption (Iorhemen et al., 2017). To reduce energy-related costs, many of the MBR modifications studied over the years have been focused on dealing with them. They include quorum quenching (QQ) bacteria/enzymes, aerobic granular sludge MBR (AGMBR), granular media with air scouring, and the use of adsorbents, among others (Iorhemen et al., 2017). The use of granular media provides extra mechanical abrasion during the air scouring and thus reduces the cake layer formation, extends the filtration period between membrane cleanings and increases the membrane flux. Quorum quenching strategy is based on the isolation and immobilization of specific strains/enzymes that are able to block the intercellular communication in the mixed liquor, impeding the secretion molecules that cause membrane fouling. In AGMBR, the microorganisms agglomerate in absence of biocarriers. The extracellular polymeric substances (EPS) produced by the microorganisms will act as an adhesive, increasing the size and settleability of the biomass. In this way, the organic fouling rate is reduced, allowing long-term operation with stable organics and nutrient removal.

Other strategies include the development of membranes with anti-fouling materials or dynamic modules. Surface modification techniques include chemical grafting with plasma or polymerization treatment, nanoparticle blending with either inorganic or carbon-based materials or surface coating. The resulting modified composite membranes have antimicrobial properties, increased hydrophilicity, and photocatalytic properties (Qin et al., 2018). Lastly, mechanical solutions have been tested to increase the shear stress besides conventional air scouring on the membrane surface. Shear stress is obtained by dynamic modules consisting of hollow fiber or flat sheet membranes which are supported in movable modules that can rotate, vibrate or oscillate (Qin et al., 2018).

1.4.3. MBR coupled with activated carbon

The use of carbon-based materials in water applications dates from ancient times. Sushruta Samhita, an ancient Sanskrit text from the 6th century before common era (BCE), recommends the use of coal to filtrate the water previously stored in copper vessels and exposed to sunlight, to remove harmful substances and disinfect the water (Bhishagratna, 1907). Although the use of carbonaceous adsorbents has been described since ancient times, the wide use of activated carbon dates from the second half of the 20th century, as a consequence of the increasing awareness of the environment-related issues (Çeçen and Aktaş, 2011a). Nowadays, the use of activated carbon (AC) is related to many industrial areas for liquid and gas phase adsorption. Still, it is predominantly used for environmental pollution control in the removal of organic and inorganic species in groundwater, surface water and wastewater.

Activated carbons are amorphous carbonaceous adsorbents which present a high specific surface area and porosity. They are considered the most used adsorbent material in water and wastewater treatment. When they were first introduced into wastewater treatment, they were mainly intended for tertiary treatment. However, it was found that the adsorption of organic matter on the surface of activated carbon could have synergistic effects on adsorption and biodegradation processes, fostering its implementation inside the biological tank(s).

Adsorbents as activated carbon applied to MBRs were primarily intended to reduce the membrane fouling propensity by providing media for bacteria attachment and adsorbing dissolved organic polymers secreted by the microorganisms (Iorhemen et al., 2017). MBRs are designed to remove organic matter and, potentially, nutrients. Additionally, the inclusion of membrane separation is known to enhance the performance of the biological process. Still, MBR has not been designed to remove OMPs. Thus, any of the advantages that MBR shows compared to CAS in micropollutant removal cannot justify its implementation solely for that purpose.

Some OMPs are amenable to either adsorption or biological biodegradation, or even both processes. A combination of activated carbon adsorption and biological processes in the same unit often offers a synergism, i.e., higher removal efficiency is achieved compared to individual processes. For many pollutants that are considered slowly biodegradable, integration of adsorption with biological removal may provide an opportunity for biological degradation. This integrated approach may enable the elimination of OMPs at trace levels.

The most common forms of activated carbon are in the form of powder or granules, being named as powdered activated carbon (PAC) and granular activated carbon (GAC), although other less common forms are also manufactured. The main difference between PAC and GAC is their average particle size, which is PAC ranges from 15 – 25 μm and in GAC between 0.2 and 0.5 mm.

When GAC is used, the granules are often packed in a column which is fed and crossed by the secondary effluent of the MBR. The OMPs and remaining organic matter in the secondary effluent are adsorbed by the GAC, which may promote the attachment and growth of microorganisms over time. Adsorption of contaminants and subsequent

biodegradation by the microorganisms attached to the GAC surface transforms the GAC filter in a biofilm reactor, referred to as a biologically activated carbon (BAC). However, the GAC/BAC filters can still get saturated over time due to the organic load and the adsorption or formation of non-biodegradable substances. In this way, to clean the GAC filter and remove the retentate, periodical backwashes are planned and carried out (Baresel et al., 2019). In this context, some parameters must be taken into account for GAC operation:

- Empty bed contact time (EBCT), that is, the HRT of the wastewater within the GAC column. EBCT has to be set to guarantee the time for the OMPs transfer from the bulk phase to the GAC surface and also inside its grain. In this way, the minimum EBCT according to Metcalf & Eddy, (2014) should be between 5 – 30 min.
- Filtration velocity (v_f) is the ratio between the influent flow rate and the surface area of the GAC filter. According to Metcalf & Eddy (2014), it should be between 5 – 15 m/h.
- The working age. This parameter depends on the empty bed volumes of the column (EBV).
- Effective contact time, defined as the product of the EBCT and the bed porosity.

Regarding PAC, it may be used inside the bioreactor or as a post-treatment (PT) after the biological tank. When used as a PT, PAC is added to a contact reactor receiving secondary effluent to then be separated from the final effluent by either membranes or sand filtration (Löwenberg et al., 2014; Margot et al., 2013). The retained PAC can be withdrawn (Kovalova et al., 2013b) or recycled back to the biological reactor (Lipp et al., 2012). In this case, PAC separation is the main challenge of this configuration, which requires additional energy demand. Sufficient mixing is required to guarantee homogenous conditions, as well as a proper HRT in the contact reactor to not limit the adsorption of the pollutants, leading to inefficient use of PAC capacity.

PAC added inside the reactor of an MBR is an update of the well-known powdered activated carbon treatment (PACT), developed in the 1970s by DuPont to remove organic matter and protect the biological system from shock loads (Çeçen and Aktaş, 2011b). In PACT, the activated carbon is added inside the biological tank of a CAS instead of an MBR, which is then separated from the final effluent by the secondary clarifier and an (optional) additional filter and/or coagulation. In hybrid MBRs, PAC is also added inside the biological reactor, but no further filtration is needed thanks to the MF or UF membranes of the reactor. In this treatment configuration, PAC leaves the system with the waste sludge for its final disposal or incineration. In comparison with PAC added as a PT, PAC is within the system for much longer times (similar to SRT), creating a dynamic equilibrium with the dissolved and suspended material of the mixed liquor. Although the specific removal mechanisms and effect of the PAC addition inside the reactor are going to be further explained in the successive sections and chapters, specific parameters must be taken into account when operating MBR with PAC added inside the biological tank, as summarized below.

- HRT of the wastewater in the bioreactor. It must be long enough to guarantee the OMP transfer from the wastewater to the activated carbon surface,
- SRT, which may be long enough to promote the biodegradation of specific OMPs,
- Activated carbon retention time in the bioreactor, which is the time AC spends in the tank before its disposal (≥ SRT),
- Activated carbon working age, which measures the time since it was added to the system (an indirect measure of its level of saturation).

In the last years, other patented technologies combining MBR with activated carbon have been developed. Among them, SUEZ's MAC MBR, which adds activated carbon to the biological tank of the MBR (SUEZ, 2017) and Siemens' PACT ® MBR (Siemens AG, 2018), which combines Siemens' PACT® technology with the ceramic flat-sheet membranes of Meidensha Corporation, to treat very high strength wastewater from large petrochemical industries. In addition to that, PAC used as a post-treatment to treat the secondary effluent has been applied to technologies as Pulsagreen™. Proposed by SUEZ, the system uses a pulsed settling tank with PAC, which optimizes the contact of micropollutants with PAC during the lamellar setting and prevents the release of the PAC with the final effluent (SUEZ, 2018). Other example is CarboPlus® by Saur, a micro-gain activated carbon fluidized bed that has shown to remove to a high extent several OMPs at full-scale (Guillossou et al., 2019).

1.5 Characteristics of the activated carbon

Activated carbon (AC)structure consists of hexagonal rings of carbon distributed in flat aromatic sheets combined with amorphous sections that define the orientation of the pores (Figure 1.5). It possesses functional groups on the surface that arise from the raw materials or during the activation process. They can be located on the surface, attached on the edges, or intercalated between the aromatic sheets. They play an important role in the adsorption of organic molecules. Adsorption of OMPs that occur on the flat surface is based mainly on van der Waals forces, while chemical adsorption occurs on the edges. A certain percentage of ash (1 – 12%) is also contained in the activated carbon from the manufacturing process. It generally increases the hydrophilicity of the activated carbon, which results in an advantage in case PAC is to a wastewater treatment line.

AC can be originated from many high-carbonaceous materials (e.g., wood, coal, lignite, coconut shells, petroleum coke). The manufacturing process consists of two phases: carbonization and activation. Carbonization removes undesirable substances and prepares the material for the activation process. It consists of pyrolysis within a temperature range between 400 – 600 °C under oxygen-deficient conditions. On the other side, the term activation refers to the development of the adsorption capacity of the activated carbon, as it allows the formation of micropores (explained below). Activated carbon can go through two types of activation procedures: physical and chemical activation. Physical activation is carried out by oxidizing or steaming the carbon at >800 °C, whereas chemical activation consists of the impregnation of the adsorbent with chemicals such as phosphoric acid, potassium hydroxide or zinc chloride.

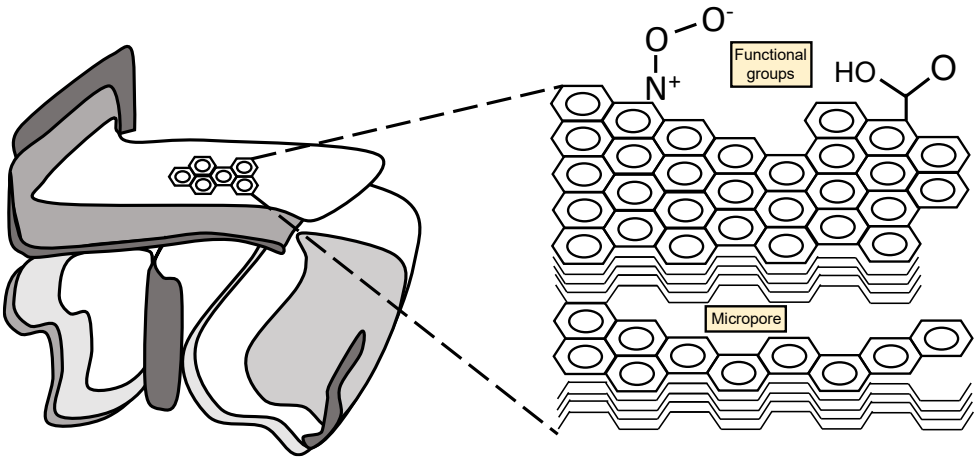

Figure 1.5. Structure of the activated carbon. Adapted from Bansal et al., (1988).

Adsorption in activated carbon is a multi-factorial process which depends to a certain extent on its intrinsic characteristics, summarized below. The influence of these characteristics on OMP removal will be thoroughly discussed in Chapter 3.

Particle size

Particle size defines mostly the mode of operation of activated carbon (depending if it is in the form of powder or granules). PAC is defined as a sieve of 0.297 mm (American Water Works Association Standard) or 0.177 mm according to ASTM D5158 (Çeçen and Aktaş, 2011b) and their average particle size is 15 – 25 μm. GAC particles instead range from 0.2 to 0.5 mm.

Specific surface area

The main intrinsic characteristic of ACs is their very high specific surface area, which is the portion of the total area that is available for adsorption. It is usually measured as Braeuer–Emmett–Teller (BET) specific surface area (m^2/g) and it can range from 500 to 1400 m^2/g (Yapsakli and Çeçen, 2010).

Porosity

According to IUPAC recommendations (Rouquerol et al., 1994), the total porosity of an adsorbent is classified by defining three types of pores, macropores (>50 nm), mesopores (2 – 50 nm) and micropores (< 2 nm). In AC, macropores and mesopores are responsible for the transportation of the OMPs through the micropores, while micropores are directly responsible for OMPs adsorption. Indeed, most of the specific surface area is due to the presence of micropores, while the surface ascribed to the macropores is usually negligible.

Pore volume

Pore volume is defined as the space that occupies the different pores. Pore volume is one of the main controlling parameters regarding adsorption in micropores. An interesting parameter to measure the porosity of activated carbon is the *iodine number*. This technique is defined as the amount of iodine (mg) adsorbed by 1 g of activated carbon. It is a quick and cheap technique to determine the adsorption capacity of the activated carbon (ASTM D4607-94).

Bulk density

Bulk density is defined as the mass of activated carbon per unit of volume (including particle, inter-particle void and internal pore volume). It is also denominated *apparent* density in some studies. It results in a useful parameter in the case that specific analyses of the AC surface are not available.

Point of zero charge (pH_{PZC})

The point of zero charge (pH_{PZC}) defines the pH at which there are as many positively charged functional groups as negatively charged functional groups on the AC surface. If the wastewater pH is below pH_{PZC}, the carbon surface is mostly positively charged and, if it is greater, the AC is mostly negatively charged (Alves et al., 2018). The surface charge of the activated carbon may influence the adsorption of ionized OMPs.

Carbon surface chemistry

The functional groups created on the surface of the AC during the activation process may influence the adsorption of OMPs to a certain extent. Generally, chemically activated carbon is less hydrophobic and more negatively charged, which reduces the overall adsorption of organic compounds. On the other side, thermally activated carbons have been found to present higher absorbability (Alves et al., 2018).

1.6 Characteristics of the OMPs

Molecular weight

The molecular weight (MW) is defined as the sum of the atomic weights of the individual atoms composing a compound. It is used to determine the stoichiometry in chemical reactions, and it can be expressed as the atomic mass or unitless. For OMPs, the tendency of adsorption of a compound in activated carbon increases at higher molecular weights (Alves et al., 2018).

Solubility

The solubility is defined as the ability of a compound to dissolve in a solvent at a specific temperature (normally 25 °C). In this thesis, solubility refers to the amount of compound that can be dissolved in water. High solubility means that the bonds between the solute and the water are stronger than between the solute and one adsorbent (i.e., AC). A hydrophilic compound will tend to remain in the water, whereas a hydrophobic compound will tend to be adsorbed in the AC surface.

Octanol-water partition coefficient (K_{ow})

The octanol-water partition coefficient is a measure of the tendency of a non-ionised compound to be in hydrophobic conditions (i.e., octanol used as a solvent) compared to aqueous solutions (i.e., water solubility). It is expressed as follows (eq. 7),

$$K_{ow} = \frac{C_{octanol}}{C_{water}} \quad \text{eq. 7}$$

on which $C_{octanol}$ is the concentration of the compound in octanol and C_{water} its concentration in water. However, it is common to find the values of K_{ow} expressed in a base-10 logarithmic scale ($\log K_{ow}$). According to Rogers (1996), the sorption potential of an organic compound may be classified as follows: low ($\log K_{ow} < 2.5$), medium ($2.5 < \log K_{ow} < 4$) and high ($\log K_{ow} > 4$).

The sorption potential of an OMP to be adsorbed on activated carbon may be predicted by K_{ow} since high values of this coefficient indicate a higher tendency to be adsorbed in the surface of this material. However, K_{ow} is a useful predictor only for apolar compounds. In case a compound is ionizable, the octanol-water distribution coefficient (D_{ow}) is a more accurate parameter for assessing the partition behaviour.

Defining an acid as an ionisable compound able to release hydrogen ions (i.e., protons) and a base as a compound that can accept hydrogen ions, the D_{ow} of a certain compound may be calculated based on the $\log K_{ow}$ as follows,

$$logD_{ow} = logK_{ow} + log\frac{1}{1 + 10^{pH-pKa}} \quad \text{eq. 8}$$

$$logD_{ow} = logK_{ow} + \frac{1}{1 + 10^{pKa-pH}} \quad \text{eq. 9}$$

in which the pK_a is the dissociation constant (defined below) and the pH is evaluated at the solution equilibrium. Eq. 8 is suitable for acidic compounds, while eq. 9 for basic compounds. For neutral compounds, it is assumed that $\log D_{ow} = \log K_{ow}$. As a rule of thumb, compounds with a $\log D_{ow} < 3.2$ are considered hydrophilic and in the case of $\log D_{ow} > 3.2$, hydrophobic (Tadkaew et al., 2011).

Dissociation constant (pK_a)

The dissociation constant (pK_a) is defined as an equilibrium constant that measures the strength of an acid, that is, its tendency to dissociate in an aqueous solution. By definition, the acid (HA) can dissociate in an aqueous solution into a conjugate base (A^-) and a hydrogen ion (H^+) as follows (eq. 10),

$$K_a = \frac{[A^-][H^+]}{[HA]} \qquad \text{eq. 10}$$

or alternatively,

$$pK_a = -logK_a = log\frac{[HA]}{[A^-][H^+]} \qquad \text{eq. 11}$$

where $[HA]$, $[A^-]$ and $[H^+]$ are the concentration of HA, A^- and H^+ in the solution.

1.7 Removal mechanisms in the biological reactor

Removal of OMPs from wastewater refers to the difference in the concentration of an OMP in the liquid phase between the inlet and the outlet. The removal may be associated with transformation or degradation processes. The transformation is defined as the modification of the compound's structure due to biological or chemical reactions, while the degradation refers to the transformation of the compound into mineralized forms (CO_2, CH_4, H_2O…). In biological systems, the main removal mechanisms are biological transformation/degradation, sorption onto the sludge and abiotic transformation/degradation, which include both chemical transformation and volatilization.

1.7.1. Sorption

The sorption process in the biological reactor is associated with the activated sludge and thus the microorganisms living in it. It is usually ascribed to two different interactions: adsorption and absorption (Figure 1.6). Adsorption is based on the electrostatic interactions between a substance and the solid phase surface to which it is sorbed. Absorption instead refers to a substance that enters the bulk volume of another substance. In a biological reactor, absorption refers to the hydrophobic interactions of the pollutants with the lipophilic cell membrane of the microorganisms or lipid fractions of the sludge (Ternes et al., 2004).

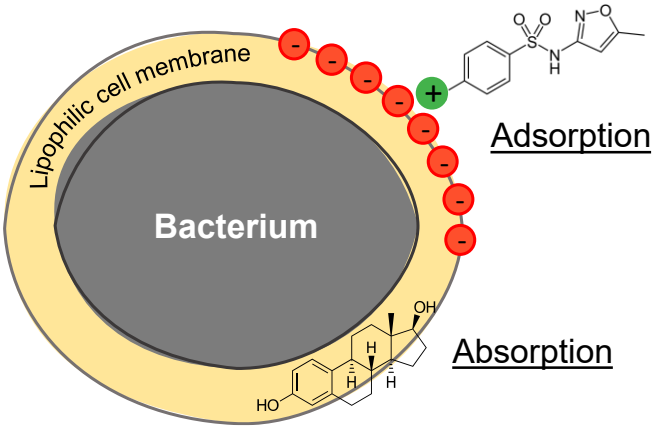

Figure 1.6. Sorption processes (adsorption and absorption) of an OMP in a microorganism from a biological reactor.

Sorption is usually quantified by the solid water distribution coefficient (K_d). K_d (L/kg) is defined as the concentration in the solid phase (C_s, µg/kg) with respect to the concentration in the liquid phase (C_w, µg/L) at the equilibrium. It can be expressed by the eq. 12.

$$K_d = \frac{C_s}{C_w} \quad \text{eq. 12}$$

Sorption may be predicted by the octanol-water partition coefficient value (K_{ow}) and the octanol-water distribution coefficient (D_{ow}) which are, as explained previously, a measure of the compound's tendency for the hydrophobic conditions in neutral and ionizable compounds, respectively.

1.7.2. Biological transformation

Biological transformation is related to the metabolic reactions carried out by the microorganisms present in the biological reactor. Microorganisms may use a compound as a primary substrate for growth or energy source (metabolism) or it may be transformed by enzymes for which the pollutant is not the main substrate for growth (cometabolism). Due to their low concentrations in wastewater, OMPs are more prone to be removed by cometabolism (Margot et al., 2015). In any case, biological transformation is the main mechanism of OMP removal in MBR systems. By definition, a compound that is fully biotransformed until its mineralization is considered biodegraded.

OMP biodegradation is a highly complex phenomenon that depends, among other factors, on the physicochemical properties of the contaminant (chemical structure, solubility), but also the mixed liquor properties (redox conditions, inhibitors presence, availability of nutrients) and the type of biomass present in the reactor (Çeçen and Aktaş, 2011b). For instance, the absence of microorganisms able to degrade certain OMPs, the limitation in nutrients, the recalcitrant nature of the compound or its low bioavailability in the mixed liquor (i.e., low concentration) are just a few factors that may limit biodegradation. In addition, the reactor's operating conditions play an important role in driving microbial growth in the reactor. For instance, it has been observed that the increasing HRT and SRT may entail an enhancement in the co-metabolic reactions in the aeration tank (Clara et al., 2005). In the same way, it has been proved that increasing temperature enhances the metabolism of microorganisms and thus the biodegradation rate of OMPs (Alvarino et al., 2018). Indeed, since the biodegradation process is difficult to describe in full, only empirical formulas may be derived. So far, the pseudo-first-order kinetic model (eq. 13), is commonly used to calculate the biodegradation rate,

$$\frac{dC}{dt} = K_{biol} X_{ss} S_{soluble} \quad \text{eq. 13}$$

where C is the concentration of the OMP (µg/L); $S_{soluble}$ the concentration of the soluble part of the contaminant (µg/L); K_{biol} is pseudo-first-order reaction rate constant ($L/g_{ss}/day$) and X_{ss} is the concentration of suspended solids (g_{ss}/L).
The rate constant of eq. 13 (K_{biol}) has been proposed and widely used as a method to classify a compound's tendency for biodegradation. In this sense, Joss et al. (2006) proposed the following classification: hardly biodegradable OMPs ($k_{biol} < 0.1$ $L/g_{ss}/d$), moderately biodegradable OMPs ($0.1 < K_{biol} < 10$ $L/g_{ss}/d$) and highly biodegradable OMPs ($K_{biol} > 10$ $L/g_{ss}/d$).

1.7.3. Abiotic transformation

The abiotic transformation includes both chemical transformation and volatilization of the compounds in the biological reactor.
Chemical transformation refers to a combination of processes that take place during wastewater treatment without the intervention of the present microorganisms, such as photodegradation, oxidation and deconjugation. However, not all of them have relevance to biological reactors. For instance, due to the high turbidity of the mixed liquor, the degradation of OMPs due to photodegradation is uncommon. On the other side, some advanced wastewater treatments are focused on the chemical transformation of pollutants to enhance the biodegradability of the compound in the subsequent biological reactor (e.g., AOP-MBR system). And, in addition, many advanced tertiary treatments focus on the chemical transformation of recalcitrant pollutants that are poorly removed in the previous treatment stages. However, these processes are beyond the limit of this section.
Regarding volatilization in WWTPs, organic contaminants transfer from the water phase to the air mainly due to stripping during aeration. In this way, reactor operating conditions (such as agitation, aeration rate and temperature), as well as OMP's physicochemical characteristics, determine the volatilization of OMPs. The volatilization potential of organic compounds is predicted by the Henry constant (H_c) (Alvarino et al., 2018). Most of the OMPs have low values of H_c and therefore volatilization is commonly considered negligible in comparison to other removal mechanisms (Alvarino et al., 2017).

1.8 Sorption onto the activated carbon

Adsorption is the deposition of substances to a surface or interface. The adsorbing phase is known as adsorbent, and the substance being adsorbed is the absorbate. Adsorption takes place between two phases, namely liquid-solid. In the case of wastewater and activated carbon, this process results from the transport and concentration of the solute from the liquid phase (i.e., wastewater) to the boundary layer of the solid phase (i.e., activated carbon) (Weber and Morris, J.C., 1963). The reason for this is that the attractive forces between the solute and the liquid phase are smaller than the ones between the liquid molecules (i.e., surface tension), which causes the transportation of the soluble material to the interface layer.

To better understand the adsorption process of OMPs in activated carbon, we need to consider two main driving forces: the solubility of the OMP and its affinity for the solid phase due to electrochemical attraction. Regarding solubility, hydrophilic substances will tend to stay in the wastewater and not adsorb to the solid phase, while hydrophobic substances will adsorb to the activated carbon rather than remain in the liquid phase. This driving force may be easily measured by K_{ow} and D_{ow} constants. The affinity of the solute towards the activated carbon may be categorized as physical adsorption (physisorption) and chemical adsorption (chemisorption) (Çeçen and Aktaş, 2011b). Physisorption is driven by Van de Waals forces, which are usually weaker than chemical bonds. In this case, molecules are adsorbed to the surface of the activated carbon in favourable energy sites and the exchange of electrons does not occur. For this reason, it is independent of the electronic properties of the adsorbate and the adsorbent (Mutavdžić Pavlović et al., 2018). Chemisorption instead is based on the chemical bond formed between the solute and the surface of the adsorbent by the exchange of electrons. Chemical bonding possesses a higher specificity between the adsorbate and the adsorbent, and it requires greater energies to break the bonds. Adsorption mechanisms rely on the properties of both adsorbates and adsorbents. The rate of adsorption (kinetics) is defined as the rate to reach an equilibrium state, and it is usually limited by the mass transport towards the active sites of the activated carbon. As originally stated by Walter and Weber (1984), the adsorption process in porous adsorbents like AC is differentiated into four stages (Figure 1.7). Briefly, adsorbate is transported to the boundary layer of the liquid phase that surrounds the activated carbon particle (bulk transport). Secondly, the adsorbate is diffused into the surface of the activated carbon due to the concentration difference across the boundary layer (film diffusion). The adsorbate is then subjected to intraparticle diffusion where the compounds are diffused through the surface of the activated carbon and towards the pores to reach the active sites.

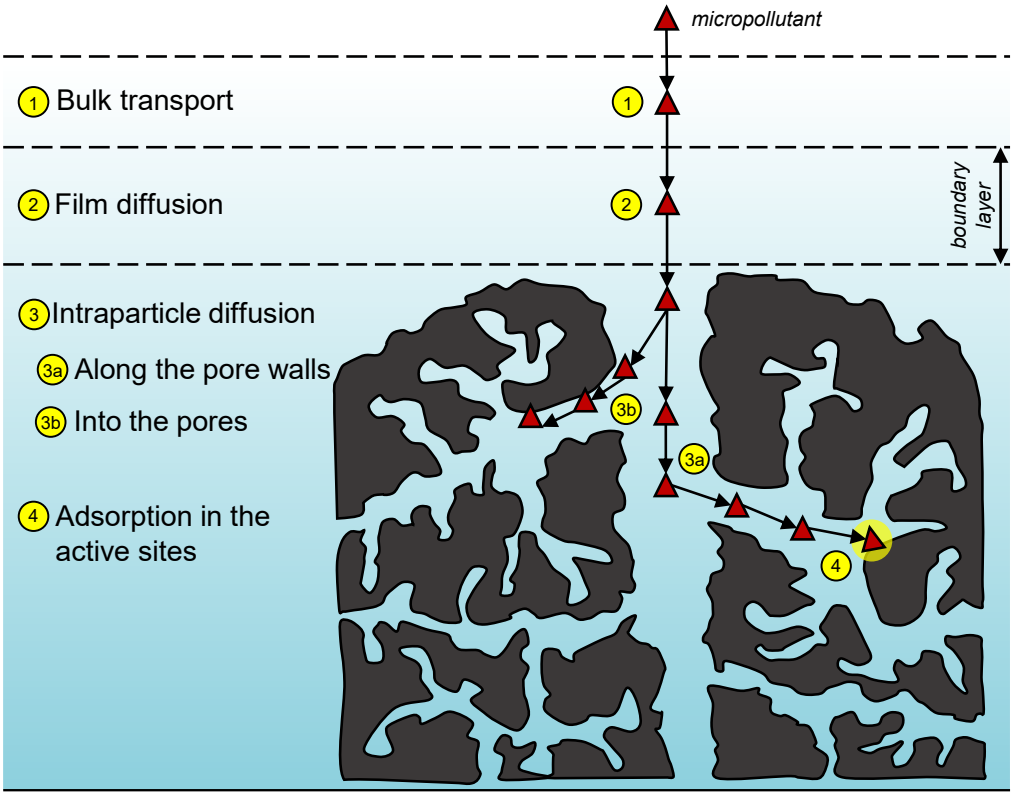

Figure 1.7. The four stages of the adsorption process. Image adapted from Walter and Weber, (1984).

The structure of complex organic substances (e.g. humic acids, fulvic acids, polymers…), such as the OMPs commonly found in wastewater, contain both hydrophilic and hydrophobic radicals. In this case, the adsorption process may become complex, as the hydrophobic groups will tend to adsorb easily to the AC while the hydrophilic parts will remain in solution.

In order to quantify the adsorption of pharmaceuticals, mathematical models are often useful tools for assessment. First, to quantify the AC adsorption capacity, that is, the amount of adsorbed OMPs per mass of AC, eq. 14 is used,

$$q_t = \frac{(C_0 - C_e)V}{W} \qquad \text{eq. 14}$$

where q_t (mg/g) is the amount of OMP adsorbed at time t, C_0 and C_t are the initial OMP concentration and at time t (mg/L), V is the volume of the liquid phase (L) and W is the mass of the adsorbent (g).

1.8.1. Kinetics

Kinetics of adsorption, which defines the rate of the OMP to reach the active sites of AC is usually described by three kinetics models, Lagergren pseudo-first order, pseudo-second-order and intraparticle diffusion model, which are going to be explained in detail in Chapter 6.

Lagergren pseudo-first order

$$\frac{dq_t}{dt} = k_1(q_e - q_t) \quad \text{eq. 15}$$

which can also be expressed as eq. 16 , eq. 17 or in the linear form of eq. 18.

$$q_t = q_e\left(1 - e^{-k_1 t}\right) \quad \text{eq. 16}$$

$$\ln\left(\frac{q_e - q_t}{q_e}\right) = -k_1 t \quad \text{eq. 17}$$

$$\log(q_e - q_t) = -\frac{k_1}{2.303}t + logq_e \quad \text{eq. 18}$$

In these equations, k_1 is the constant of the rate of adsorption (1/h) and q_e is the equilibrium concentration (mg/g).

Pseudo-second-order model

$$\frac{t}{q_t} = \frac{1}{k_2 q_e^2} + \frac{t}{q_e} \quad \text{eq. 19}$$

In this equation (eq. 19), k_2 is defined as the constant rate for the pseudo-second-order (µg/g min).

Intraparticle diffusion model

$$q_t = k_{id} t^{1/2} + C \quad \text{eq. 20}$$

where k_{id} is the intraparticle diffusion rate constant (µg/g·min$^{1/2}$), intercept C provides information about the thickness of the boundary layer.

1.8.2. Isotherms

In the adsorption process, a mass transfer of the adsorbate is produced from the liquid to the solid phase (adsorbent). When the adsorbent is exhausted and no more molecules of adsorbate can be adsorbed, the system achieves the equilibrium state. Isotherms represent the distribution of an adsorbate between the solid phase and the liquid phase at the equilibrium state. They depend on the adsorbate concentration and the temperature and serve as a primary source to understand the adsorption process of OMPs into the AC. Considering the heterogeneity and complexity of the surface of the activated carbon, isotherm modelling requires elaborated equations. Adsorption isotherms may exhibit different shapes as shown in Figure 1.8. Fig. 1.8a shows a linear isotherm where the affinity of the adsorbate towards the adsorbent is maintained constant. It is usually found at low concentrations of the solute where the adsorbent active sites are still predominantly free. Adsorption isotherms of Figs.1.8b and 1.8c reflect the case that at higher adsorbate concentrations, the adsorption decreases. In Fig. 1.8c, at a certain adsorbate concentration (C_e) the active sites become saturated, and no additional adsorption is possible. Mixed isotherms (Fig 1.8b and 1.8d) are usually found in complex matrixes where more than one adsorbent is found (e.g., sludge and activated carbon). In this case, the overall adsorption isotherm results from the superimposition of multiple individual adsorption isotherms. Under certain circumstances, the solute already adsorbed at low concentrations contributes to further adsorption (Fig.1.8e), or the adsorption is promoted only for a range of adsorbent concentrations, resulting in a sigmoidal isotherm (Fig. 1.8f).

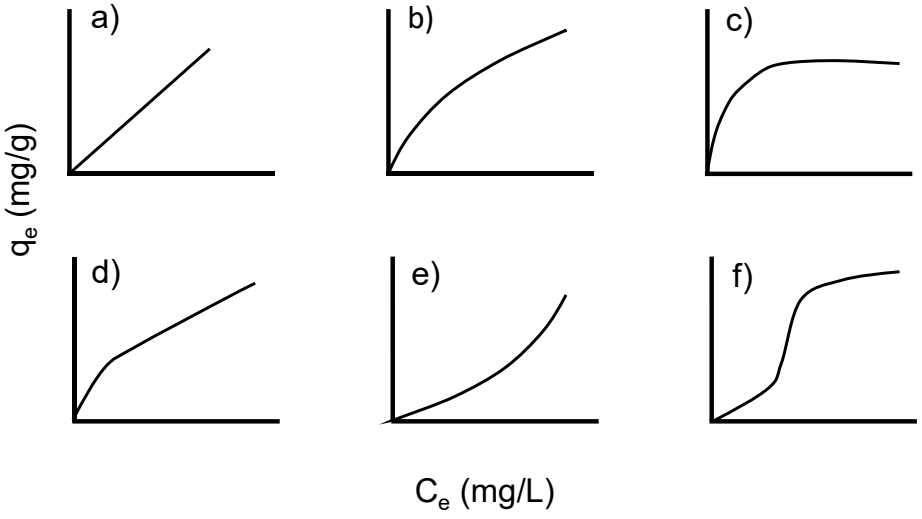

Figure 1.8. Representation of different isotherm types. C_e is the equilibrium concentration of the adsorbate in the liquid phase and q_e is the amount of adsorbate per mass unit of adsorbent. Adapted from Schwarzenbach et al., (2002).

Adsorption isotherms can be described in many mathematical expressions, the most common of which are described below.

BET theory

In the BET theory, a number of layers of the adsorbate forms at the surface of the adsorbent in a multilayer adsorption. In this model, only the first adsorbed layer is strongly attracted to the surface, while the subsequent layers are adsorbed to the previous adsorbed ones. In this model, it is assumed that the layers beyond the first one have equal energies of adsorption and that the layers do not need to be fully formed prior to the creation of the subsequent ones (Çeçen and Aktaş, 2011b). In this context, the equation of the model is described below,

$$q_e = \frac{B C_e q_m}{(C_{sat} - C_e)[1 + (B+1) \cdot (C_e/C_s)]} \quad \text{eq. 21}$$

where C_{sat} is the saturation coefficient of the solute (mg/mL), C_e is the equilibrium concentration of the solute (mg/mL), B is a unitless constant expressing the energy of interaction with the surface and q_m the maximum sorption capacity (mg/g).
This theory was the first attempt to create a universal explanation of the physical adsorption despite its many restrictions. It allows the correct calculation of the specific surface area of AC (described earlier) and other macroporous adsorbents. However, when it is applied under experimental conditions, it usually overestimates the adsorption capacity due to the enhanced adsorption in micropores. For this reason, other isotherms models should be used for its estimation (Rouquerol et al., 2007).

Linear isotherm

$$q_e = K_d C_e \quad \text{eq. 22}$$

where K_d is the distribution coefficient (mL/g).

Langmuir isotherm

In this isotherm, monolayer adsorption is assumed with a finite number of energetically equivalent sites,

$$q_e = \frac{q_m K_L C_e}{1 + K_L C_e} \quad \text{eq. 23}$$

linearized as,

$$\frac{C_e}{q_e} = \frac{1}{q_m K_L} + \frac{C_e}{q_m} \quad \text{eq. 24}$$

where K_L is the adsorption constant, related to the sorption bonding energy (L/mg).
Langmuir model assumes the surface is homogeneous, and thereby all adsorbent sites have the same energy and therefore adsorption capacity.

Freundlich isotherm

This type of isotherm assumes that the surface of the sorbent is heterogeneous, and the sorption occurs in active sites with different energy levels (Çeçen and Aktaş, 2011b). Its empirical expression defines a logarithmic dependence for the multilayer adsorption (eq. 25),

$$q_e = K_F C_e^{1/n} \quad \text{eq. 25}$$

linearized as (eq. 26),

$$\ln q_e = \ln K_F + \frac{1}{n} \ln C_e \quad \text{eq. 26}$$

where KF is the adsorption constant ((mg/g) (mL/mg) 1/n); 1/n is the heterogeneity constant, and it represents the intensity of adsorption. When 1/n<1, the process is considered favourable, while if 1/n>1 is unfavoured.

1.9 Analytical methods for micropollutant identification and quantification

Due to the increasing awareness of ubiquitousness of the OMPs, the analytical methodologies for their determination and quantitation in complex environmental matrices has evolved along the years, with increasing literature in this regard. In this context, the analytical methods that have experienced the greatest progress in their development and application are liquid chromatography-mass spectrometry (LC-MS) and LC-tandem MS (MS/MS) (Petrović et al., 2005). The research on environmental analysis of these contaminants is very active, with the publication of many papers every year, especially regarding the obtention of fast, sensitive, and reliable methods that enable the determination of a wide range of organic contaminants at trace level (Gros et al., 2012; Szymańska et al., 2019). The development of the instrumentation includes the application of ultra-high-performance liquid chromatography (UHPLC); high-mass accuracy MS, like the time-of-flight (TOF), and the use of tandem MS such as the triple quadrupole (QqQ), the quadrupole time of flight (QqTOF), and the quadrupole linear ion trap (QqLIT), that provides improved sensitivity and specificity of the analysis (Petrovic and Barceló, 2006).

1.9.1. Liquid chromatography-mass spectrometry

Liquid chromatography (LC) separates the components of a sample based on the differences in their affinity to the stationary phase and mobile phase. LC techniques have evolved through the years with the application of different principles of separation and retention (e.g., reserved-phase LC, ion exchange chromatography, size exclusion chromatography, etc.), to subsequently evolve to the use of smaller particle sizes and higher pressures to obtain a higher efficiency, speed, sensitivity and resolution in the so-called high-performance liquid chromatography (HPLC), and ultra-high-performance liquid chromatography (UHPLC). The use of short, narrow bore columns packed with particle sizes of <2 μm, high mobile phase flow rates and ultrahigh pressures allows the obtention of a much faster chromatographic separation in UHPLC, which is essential when conducting monitoring studies (Gros et al., 2012).

Compounds separated in the column are detected by optical detectors. The resulting chromatograms identify substances based on their retention time and quantify analytes based on the intensity and area of the peak. LC provides great quantitative accuracy when the detected peak comprises a single analyte. However, to obtain the same resolution becomes challenging when multiple components elute at the same time because of complex mixtures. Compared to optical detectors, mass spectrometry (MS) allows a highly specific and sensitive multi-component analysis that offers a unique identification of molecules. The analytes are ionized and separated according to their mass-to-charge ratio (m/z). The resulting mass spectra measure the

intensities of the relative ion abundances generated at each time point, and therefore the concentration level of each ion given a specific mass. LC-MS provides information based on their elution time in the chromatogram, together with molecular and structural information of the eluted analytes in the mass spectra.

The basic principle of the MS is to generate ions from organic or inorganic compounds, to then separate them by their mass-to-charge ratio (m/z), to detect them qualitatively and quantitatively according to their m/z and abundance (Gross, 2017). A mass spectrometer always contains the following elements (de Hoffmann and Stroobant, 2007): (i) A sample inlet, where the compounds to analyse are going to be introduced; (ii) a ionization source that will produce the ions from the sample; (iii) at least one mass analyser that will separate the ions; (iv) a detector that will measure the signal from the last analyser and (v) a data processing system that will be able to produce a mass spectrum.

MS requires ions to be in gaseous state to be detected under high vacuum conditions. The vaporization of the sample was one of the main drawbacks of the widespread application of LC-MS, which was overcome with the introduction of atmospheric pressure ionization (API). APIs can vaporize as well as ionize the LC eluent prior to their introduction into the MS. Compared to other forms of ionization (i.e., electron ionization (EI), chemical ionization (CI)), APIs are a soft form of ionization that include electrospray ionization (ESI), atmospheric-pressure chemical ionization (APCI) and atmospheric pressure photoionization (APPI). These ionization techniques can be operated in either positive or negative mode (Baronti et al., 2000). Once the ions in gas-phase have been produced, they are separated according to their mass-to-charge ratio (m/z) by using magnetic or electric fields. As for ionization sources, several types of mass analysers have been developed over time. The most common mass analyser is the quadrupole.

The quadrupole MS is a device which uses the stability of the trajectories in oscillating electric fields to separate ions (de Hoffmann, 2005). Since the resolution of the system is set electronically rather than mechanically, the quadruple instrumentation is ideal for remote or unattended operation. Unlike other mass analysers, it offers mechanical simplicity, high scanning speed, and allows the successive coupling with successive mass analysers. The principle of the quadrupole was described by Paul and Steinwedel, at Bonn University, in 1953 (de Hoffmann, 2005). Physically, quadrupole analysers are made up of four parallel rods of circular or, ideally, hyperbolic cross-section (de Hoffmann, 2005). The filtering action of the quadrupole comes from the application of a time-independent (direct current, DC) and a time-dependent (alternating current, AC) potential using radio frequency (RF). By selecting a suitable ratio of RF to DC the two directions together give a mass filter which is capable of resolving individual atomic masses. By simply adjusting the RF/DC-ratio we can create a convenient filter for a particular mass. Simultaneously, by varying the amplitude of DC and RF voltages, the entire spectrum can be scanned.

Another commonly used analyser is the time-of-flight (TOF). It separates the ions according to their m/z as they travel down in a field-free flight tube. Ions generated

in the ionization unit are accumulated (pulsed MS) and introduced in the flight tube. Ions are then accelerated by a high acceleration voltage between the electrodes (same electric potential) and the detector measures the time they take to reach it. TOF is a simple mass spectrometer that uses fixed voltages and does not require a magnetic field. It provides high transmission efficiency, very low detection limits, fast scan rates and an unlimited mass range to measure.

1.9.2. Liquid chromatography–tandem mass spectrometry

Single MS allows the quantitative and qualitative analysis of analytes based on their m/z and can provide information about their structure and elemental composition. However, single MS resolution may be insufficient in cases where the target analytes are at trace concentration or there are co-eluting components of the matrix that may interfere. In tandem and hybrid MS (also denoted as MS/MS), two mass analysers are connected in series with a collision cell in between. After passing the first mass analyser (MS1), ions (precursor ions) undergo fragmentation in the collision cell, resulting in the generation of product ions, which are subsequently separated in the second mass analyser (MS2) and detected (Shimadzu Corporation, 2019). The single mass analysers described earlier can be integrated into MS/MS systems.

The most common method of fragmentation in a collision cell is the collision-induced dissociation (CID). In this method, precursor ions are accelerated by an electric potential applied that increases their kinetic energy to subsequently collide with chemically inert gas (commonly He, Ar or N_2) the collision cell is filled with. The kinetic energy is then converted into molecular excitation (i.e., internal energy) that causes bond breakage and fragmentation of the precursor ions into product ions (Sleno and Volmer, 2004). The degree of fragmentation of the precursor ion depends on the energy supplied in the collision cell.

As for the single quadrupole, the MS1 and MS2 can act either in scan mode or fixed mode (single ion monitoring, SIM). Depending on the mass analyser used and the configuration of the system, the MS/MS system can operate at various scan and monitoring modes, as described below,

- For a **product ion scan**, the MS1 selects a specific precursor ion while MS2 scans through a certain m/z range. The scan acquires all the product ions from the fragmentation of the precursor ion.
- A **precursor ion scan** involves MS1 in scan mode while MS2 detects only one specific product ion of a particular m/z. This mode is particularly useful to determine the precursor ions that produce certain m/z product ions.
- In a **neutral loss scan,** both MS1 and MS2 operate at scan mode while keeping a specific m/z shift difference. This scan mode determines precursor ions that lose a specific part of the molecule during fragmentation (e.g., phosphate group, hydroxyl, etc.).
- A **selected reaction monitoring** (SRM) scan specifies both the precursor and product ion of a certain m/z in MS1 and MS2.

Note that the SRM acquisition mode allows to obtain a higher sensitivity and selectivity with respect to SIM, due to the detection of selected decomposition reactions of ions that are characteristic to certain compounds (de Hoffmann and Stroobant, 2007).

By combining two or more mass spectrometers, several tandem MS/MS combinations can be obtained. The triple quadrupole MS (QqQ) is the most common MS/MS instrument. The operational principle of this MS can be described in a similar fashion of the single quadrupole. First (Q1) and third (Q3) quadrupoles act as MS1 and MS2 respectively. The second quadrupole (Q2) acts as a collision cell in RF-only mode by the addition of a collision gas at a pressure of around 0.1 – 1 Pa. Note that the triple quadrupole MS can be also used as single MS by setting two of the three quadrupoles in RF-only mode. Either Q1 or Q3 can be used as a mass filter to obtain the full m/z spectra (full scan) or in SIM mode for fixed m/z. When both Q1 and Q3 are used as mass analysers, the four MS/MS scan and monitoring modes can be applied. Triple quadrupole is commonly used for target analysis because of the high selectivity, specificity and sensitivity when used as precursor ion scan, neutral loss scan and MRM mode. However, it does not result useful for untargeted analyses, since the mass accuracy and resolution are lower compared to other MS/MS.

Quadrupole TOF (QTOF) is obtained by switching the last quadrupole mass analyser of a triple quadrupole MS in a TOF MS. The inclusion of TOF provides an excellent mass range, a high mass resolution and accuracy, which makes it able to perform good quantitative analysis. Additionally, it is commonly used for high resolution accurate mass analysis, which allows the identification of unknown molecules and untargeted analysis (Shimadzu Corporation, 2019).

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Chapter 2

OBJECTIVES AND

FRAMEWORK OF THE THESIS

2.1 Objectives

In the last years, the awareness of the human impact on the environment and climate change has increased worldwide. Environmental challenges, such as increasing pollution, water scarcity or unpredictability of rain patterns have triggered the demand for water treatment technologies that address the improvement of water quality from a multi-barrier approach. In this way, research and market development have been promoted towards the use of new materials and the upgrade of existing technologies to further regulate pollution emissions, especially with regard to contaminants of emerging concern. Among them, OMPs have gained attention due to their vast diversity of origins and continuous release into the environment.

In the general introduction of this thesis, WWTPs were described as one of the main sources of OMPs in nature. OMPs, even if they are commonly found at very low concentrations in wastewater, have been the subject of research to limit their discharge to water bodies. In this context, my PhD is part of a Marie Skłodowska-Curie Actions – Innovative training networks (MSCA-ITN) research project "Nowelties", that aims at the development of inventive wastewater treatment technologies to improve the removal of OMPs across a diversity of approaches: advanced biological treatments, innovative oxidation processes and hybrid systems. Nowelties project comprises 14 individual projects with the same purpose, the removal of OMPs from wastewater. Among them, individual research project 11 is based on the use of advanced biological treatments (MBRs) coupled to PAC added to the biological reactor.

In this regard, the objectives of my research are:

1. To understand and evaluate the removal of OMPs from wastewater by a hybrid system consisting of an advanced biological system (MBR) coupled with PAC.
2. To test the potential enhancement of the removal of OMPs in an MBR coupled to PAC, fed with real wastewater.
3. To contribute to the understanding of the sorption process onto PAC for a selection of OMPs, especially with regard to the water matrix.

The hypotheses of my research, according to the insights given in the general introduction are:

- The addition of activated carbon may improve the removal of OMPs from wastewater due to the enhancement of adsorption and biodegradation processes.
- Adsorption is a complex process that depends on many influencing factors, such as the properties of the micropollutants, operating conditions or the water matrix.

2.2 Framework of the PhD

1. *Understanding the hybrid system of MBR coupled to activated carbon*

The first phase of the PhD was intended as the theoretical basis for the subsequent experimental activities. To this end, a systematic review was written (Figure 2.1, aim 1) where we summarized the state-of-the-art research dealing with the removal of OMPs in hybrid systems consisting of MBR coupled to activated carbon. We performed a qualitative and quantitative analysis of a collection of 66 papers selected under eligibility criteria. The resulting review addresses the increase in removal efficiencies of OMPs under different treatment configurations and operational conditions, especially with regard to the PAC dosage (Chapter 3). Additionally, we studied the influence of the use of activated carbon in the operation of the MBR. Since the removal of OMPs is a multi-factorial process that depends on the properties of the contaminant, the adsorbent, the operating conditions, and the nature of the wastewater under treatment, we extendedly discussed and summarized the main findings in the literature regarding the influence of these factors. Among them, the dissolved organic matter stood out as one of the main challenging factors to predict and enhance the removal of OMPs.

During this phase, one of the main demanding tasks was to manage the collected literature data on concentrations and removal efficiencies and to draw general conclusions to individual research investigations performed under different conditions. One of the suggestions for further research was the use of meta-analysis that may zoom out the particularities of the published papers and reduce the variables that determine the extent of the removal to just a few. For that purpose, we performed statistical analyses of the collected data in collaboration with the Department of Economics and Management of UNIFE. The results of the work contributed to the understanding of the factors that influence the most the removal of OMPs in MBR with PAC added in the reactor. The results, which are summarized in Chapter 4, were published during the third year of the PhD in Stoten (June 2022).

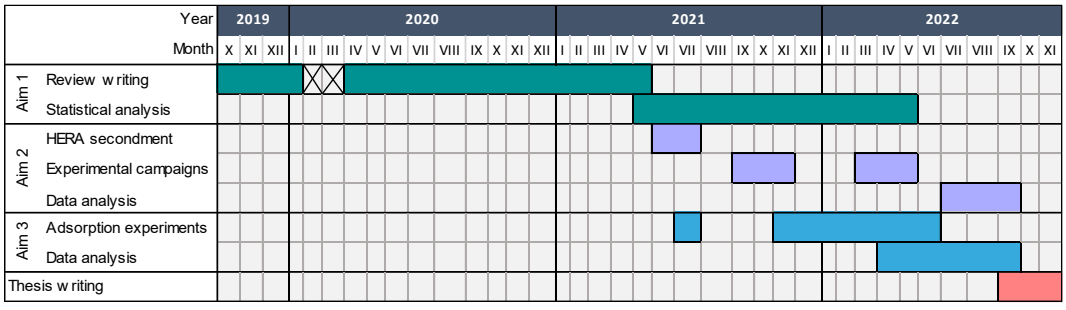


Figure 2.1. Gantt chart of the PhD evolution and development (total duration of 36 months). Cells with a cross indicate a temporary contract suspension.

2. *Enhancement of the removal of OMPs in a full-scale MBR with the addition of PAC inside the bioreactor*

The main aim of this PhD is to investigate the removal of a selection of OMPs from real wastewater by a hybrid system consisting of MBR coupled to PAC (Figure 2.1., aim 2). To that end, extensive monitoring and experimentation were carried out in a full-scale MBR treating mainly hospital wastewater in northeastern Italy. The experiments were conducted over a year (2021 – 2022), in one of the installations of HERA company, where I participated in a PhD secondment since it collaborates as a partner organization in the Nowelties project.

However, the use of the full-scale WWTP was not the original plan for the PhD. According to the project, a pilot plant fed with real wastewater should have been installed for the conduction of the experiments. To that end, several meetings and technical visits were organized with HERA managers and technicians (HERA secondment), after which we concluded that the experiments could be conducted directly in the full-scale MBR. HERA managers showed interest to test the activated carbon in their installations to potentially use it in future scenarios. Since PAC is easy to operate compared to other advanced technologies, there were no major issues with the addition of the adsorbent to the biological reactor. Indeed, due to the limitations of the pandemic, the conduction of the experiments in the full-scale MBR allowed us to make up for the time lost due to the lockdown period during which UNIFE installations were closed.

The results of these experiments allowed the characterization of the hospital effluent and influent wastewater of the WWTP during a year for OMPs and conventional parameters. We were able to test two PAC doses in order to collate the results at different operating conditions and we analyzed the impact on the receiving water body through an environmental risk assessment. Thanks to the collaboration with Croatian Waters, a public institution for water management in the Republic of Croatia, we were able to quantify a vast set of OMPs (232), instead of the initially planned 25 OMPs, that allowed us a full characterization of the wastewater and the treatment efficiency. In addition, 83 non-targeted OMPs were found through screening using the same analytical method. In this regard, the results were above expectations and Q1 publications are expected after the conclusion of the PhD (Chapter 5).

3. *Understanding the adsorption process of OMPs*

As part of the Nowelties project, a secondment of 12 months of duration was initially planned for the Faculty of Chemical Engineering and Technology (FKIT) of the University of Zagreb. The aim of the secondment was the analysis for the quantification of OMPs in the collected wastewater samples in Ferrara. Additionally, adsorption batch experiments were programmed to further contribute to the understanding of the adsorption process of OMPs onto the surface of activated carbon (Figure 2.1, aim 3). Since the collaboration with Croatian Waters was achieved, more room to conduct adsorption batch experiments was available. To this end, additional

samples of wastewater and mixed liquor were collected from different sampling points of the WWTP. The originally planned activities were modified to further study the PAC adsorption process under different conditions, especially regarding a better understanding of the effect of the water matrix (and dissolved organic carbon) in the adsorption of OMPs. The experiments aimed to study the adsorption capacity of PAC for three pharmaceuticals (i.e., diclofenac, sulfamethoxazole and trimethoprim), in water matrices of increasing complexity and different operating conditions. Results are deeply discussed in Chapter 6 and subsequently published in Molecules (Q2 journal) in February 2023.

Chapter 3

ACTIVATED CARBON COUPLED WITH ADVANCED BIOLOGICAL WASTEWATER TREATMENT: A REVIEW OF THE ENHANCEMENT IN MICROPOLLUTANT REMOVAL

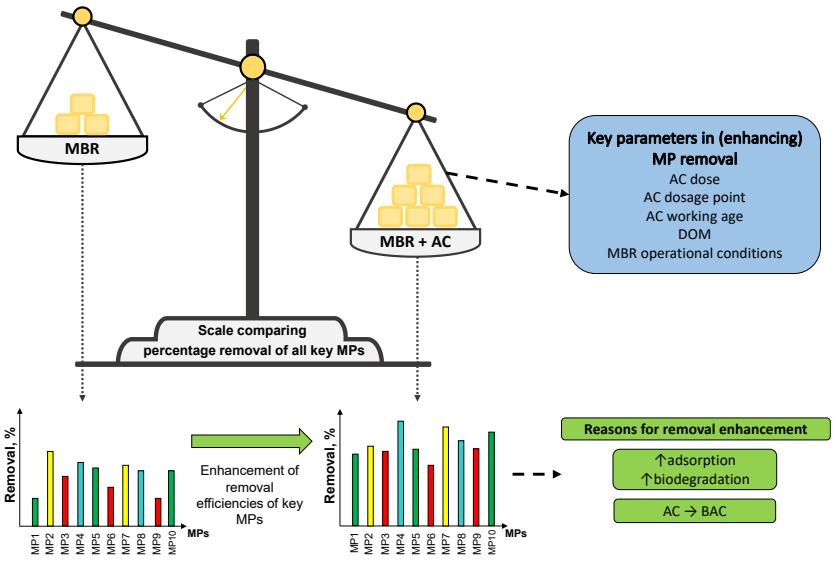
TABLE OF CONTENTS

Summary of the chapter, in a nutshell

- This chapter consists of a systematic review in hybrid membrane bioreactors (MBR) coupled to activated carbon (powder or granules) to treat urban and domestic wastewater for the removal of organic micropollutants (OMPs).
- The removal efficiencies and effluent concentrations for a wide spectrum of OMPs are presented and compared considering the treatment configuration. The influence of micropollutants properties, characteristics of the activated carbon, operational conditions and the presence of organic matter is discussed.
- Results show that the activated carbon enhances the removal of most of the OMPs due to the adsorption in the adsorbent surface, which then enhances their degradation. Dissolved organic matter is a strong competitor in the adsorption of OMPs, but it may promote the transformation of the activated carbon in biologically activated carbon, thus enhancing the biodegradation of OMPs.

This chapter is part of a manuscript published in October 2021 with the title: *Activated carbon coupled with advanced biological wastewater treatment: A review on the enhancement in micropollutant removal* by Marina Gutiérrez, Vittoria Grillini, Dragana Mutavdžić Pavlović and Paola Verlicchi, which can be found in Appendix 2.

Graphical abstract



3.1 Introduction

In the last two decades, there have been extraordinary developments in membrane technologies applied to wastewater treatment. MBRs have become a widely used technology in treating urban (Xiao et al., 2019) and industrial wastewater (Cattaneo et al., 2008). The combination of biological treatment with a membrane separation provides a better-quality effluent over CAS regarding many regulated contaminants, in particular suspended solids and microorganisms. One of the main drawbacks of MBRs is membrane fouling which leads to an increment in the operational and maintenance costs and a reduction in the membrane's effective lifespan (Xiao et al., 2019).

Depending on the nature of the influent and the required effluent quality, promising insights have been obtained in recent years using advanced biological systems (MBRs) in combination with innovative treatment technologies: these systems are often called hybrid MBRs (Alvarino et al., 2017) or integrated MBRs (Neoh et al., 2016; Woo et al., 2016). Hybrid MBRs are designed not only to guarantee a specific effluent quality but also to improve the MBR operation. In this way, the use of adsorbents, such as AC, to mitigate membrane fouling has been the subject of research efforts in recent years (Iorhemen et al., 2017).

WWTP influent is characterised by a high content of organic matter. Of all the substances commonly found, there has been a focus on OMPs in recent years (Verlicchi et al., 2012). OMPs consist of organic substances from natural and anthropogenic sources and, although their origin can be very diverse, they are strictly correlated to mass-produced materials for anthropogenic activities. While most OMPs in WWTP influents range from ng/L to µg/L, some can exhibit higher concentrations (Verlicchi et al., 2012). In this context, biological treatments (mainly CAS and MBR) have not been designed to remove OMPs from wastewater, but conventional macro pollutants (namely suspended solids, organic substances, nitrogen and phosphorus compounds, microorganisms), and thus some of the most commonly consumed or recalcitrant OMPs can be found in WWTP effluents at > 1 µg/L (Verlicchi et al., 2012). The high adsorption capacity of AC has been proposed as one of the most promising mechanisms to remove OMPs from wastewater. Adsorption processes do not generate toxic by-products in comparison with other advanced technologies used in hybrid MBRs (e.g., ozonation, photocatalysis) and may also remove biological treatment inhibitors at the same time. One drawback to consider is the potential reduction in AC adsorption capacity due to the presence of dissolved organic matter (DOM) which is present in the stream under treatment (Guillossou et al., 2020; Margot et al., 2013). However, adsorbed DOM may contribute to the development of microorganisms on the AC surface, enhancing biodegradation processes by the attached biomass (Fundneider et al., 2021b). In this way, design parameters and operational conditions that could contribute to increasing the efficiency of the hybrid systems are crucial (Grandclément et al., 2017).

This review, published in October 2021, aimed to give a snapshot of hybrid MBRs where PAC is added within the biological reactor or as a post-treatment to it for the removal of OMPs from wastewater.

The review attempted to respond to the following questions: Is it possible to increase the removal efficiency of selected OMPs from wastewater by combining an advanced biological system (i.e., MBR) with an adsorbent as AC? What is the best AC configuration to achieve the highest OMP removal efficiencies? How does AC influence the MBR operation?

To provide the tools needed to answer these questions, an in-depth focus was first carried out on the main OMP removal pathways occurring once AC is present in the wastewater under treatment. After that, we presented and discussed literature data regarding the removal efficiencies achieved for a vast set of OMPs as well as the final wastewater quality (measured as the occurrence of OMPs), considering the treatment configuration and operational conditions. The influence of the main OMP characteristics, AC properties, and DOM presence was discussed as well as how AC may influence the MBR operation, based on lessons learned from collected studies.

3.2 Methodology

The present review has been developed following the PRISMA guidelines (Moher et al., 2009), a protocol established in 2009 that defines the steps to obtain a systematic review. Systematic reviews intend to answer specific questions on a particular topic and the selection of the studies is based on a defined search strategy and eligibility criteria. Literature data are assessed to ensure quality assurance of the selected studies, and the data collected is compared and discussed to obtain overall conclusions (Figure 3.1).

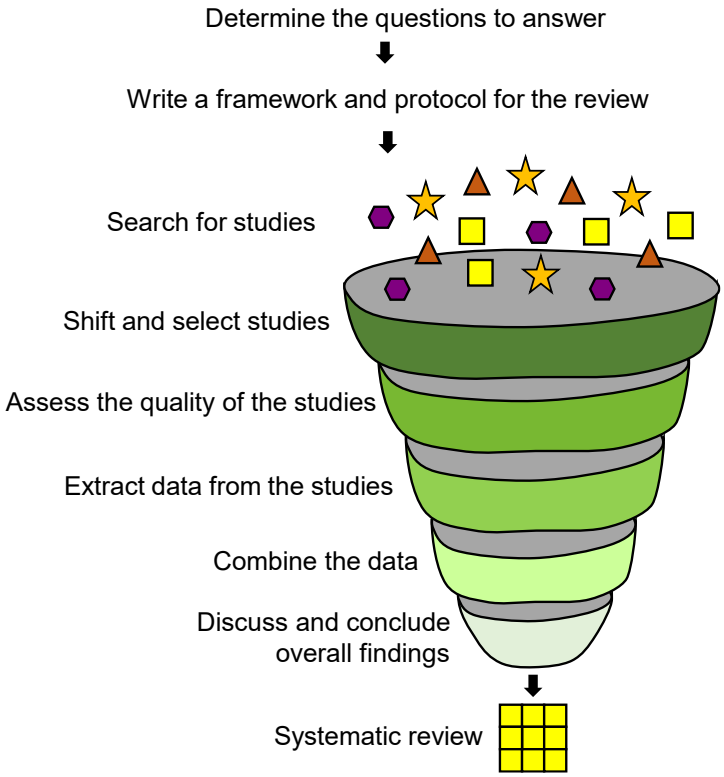


Figure 3.1. General scheme of systematic reviews.

3.2.1. Identification of the studies for the analysis

Following PRISMA guidelines, a research engine was chosen and key terms were identified in order to initially gather a wide collection of peer-reviewed papers (records). In the present paper, a collection of 379 records was obtained through Scopus. Further to this, 30 records were identified among the references of the collected papers, for a total of 409 records. The first screening resulted in 252 papers rejected based on the title and abstract of each record. The eligibility criteria included only peer-reviewed papers written in English and concerning municipal or urban, domestic and hospital wastewater.

After the first screening, selection criteria were applied to only include membrane bioreactors enhanced/coupled with AC. As a result of this process, a collection of 64

peer-reviewed papers, published between 2009 and 2020, was defined. This selection was the basis for this study and allowed the authors to conduct a *qualitative* synthesis. Then, a further refinement lead to the identification of 26 records within the selection of 64, on which a *quantitative* synthesis was carried out referring to removal of OMPs in MBR-coupled AC (PAC or GAC). A few studies (4) referring to CAS where AC was present were included as they provided useful insights into the analysis of OMP removal. A summary of the process followed to define the collection of papers to be included in the review can be found in Figure 3.2.

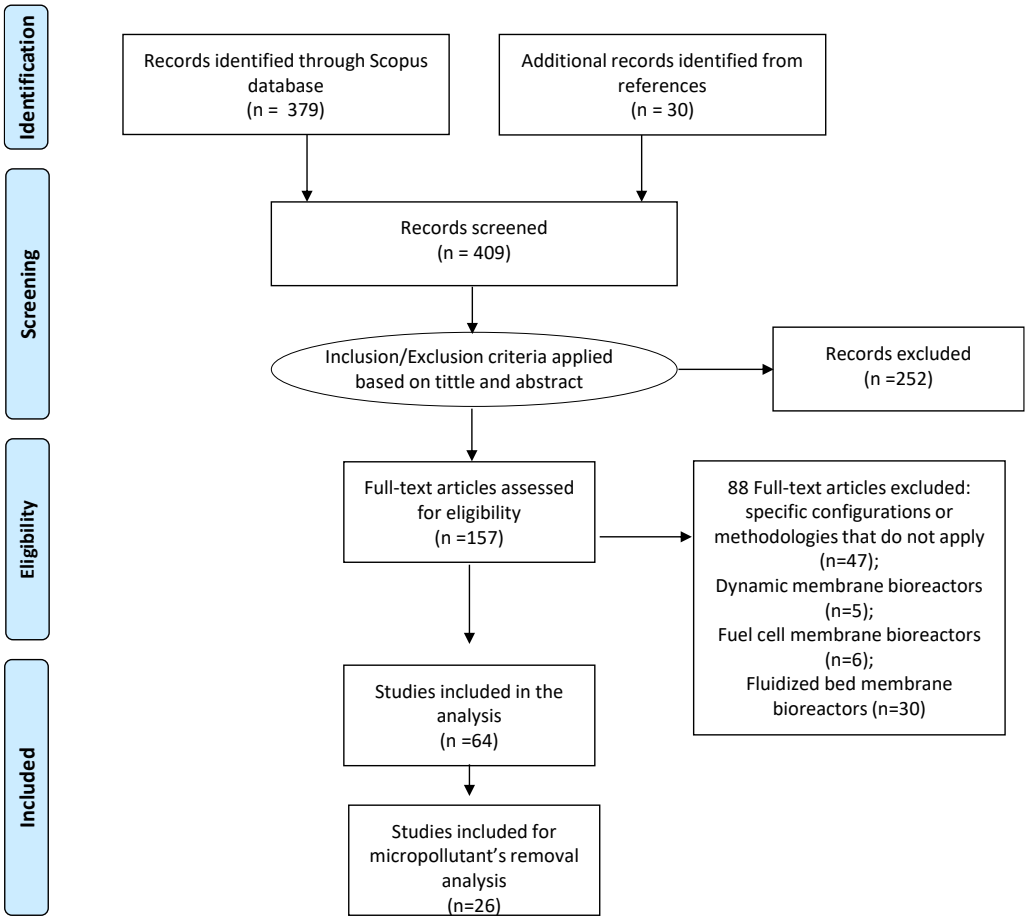


Figure 3.2. Summary of the steps followed during the selection of studies included in the review paper.

3.2.2. Main characteristics of the reviewed studies

The studies included in this review had to provide a clear description of the plant configuration and report information on sampling (mode and frequency) and the adopted analytical methods for OMP determination. There had to be also sufficient collected data to support the study discussion, for instance: (i) number of *investigations* and their duration; (ii) plant scale (lab, pilot or full); (iii) design parameters and operational conditions of the biological reactor; (iv) type of wastewater in the feed (real, synthetic or real wastewater with spiked OMPs); (v) mode of operation of the feeding (continuous or in batch); (vi) AC type and characteristics and, in case the AC is used as a post-treatment, (vii) data about the GAC column or the contact reactor for PAC.

Note that *investigation* is defined as the experimental campaign referring to a specific treatment configuration, under defined conditions (e.g., MBR with addition of 0.5 g/L of PAC in the biological reactor). According to this definition, there was a total of 46 investigations in the 26 papers,

The plant configurations selected, together with a brief description and the corresponding references are schematically reported in Table 3.1. The studies included lab (46%), pilot (42%) and full-scale plants (12%). In 50% of the studies, the feeding was synthetic wastewater, resulting from the addition of specific compounds miming the matrix effect (the composition is provided), and in 50% it was real wastewater. Out of these, only one study spiked OMPs into the real wastewater (Remy et al., 2012). Regarding the real wastewater, 69% was urban and 31% hospital effluent. The feeding was continuous in all the studies with the exception of Alvarino et al., (2017) and Serrano et al., (2011). Further details about the studies under review may be found in the published review.

3.2.3. The selected compounds

The analysed micropollutants included 179 compounds belonging to 30 classes (Table 3.2). The compounds in italics and with an asterisk were investigated, but they were never detected. As a result, 163 compounds are included in the graphs and belong to 28 classes.

Table 3.1 Configurations of biological treatment coupled with AC considered in the review together with the corresponding references.

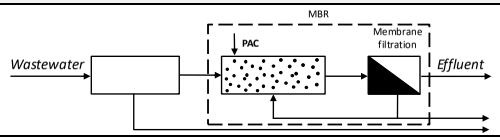
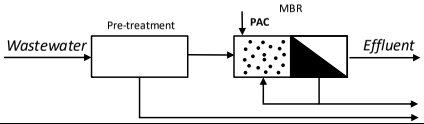
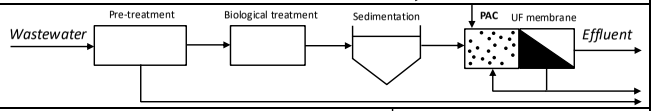
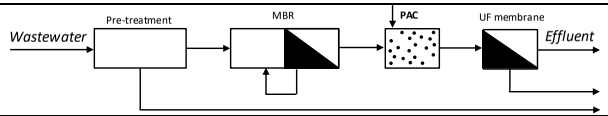
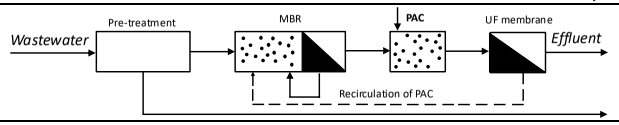
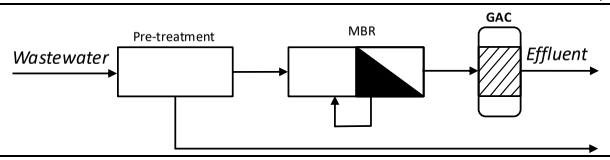
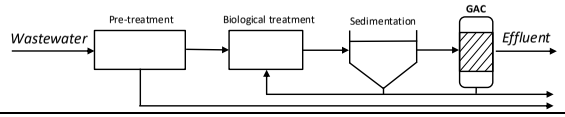
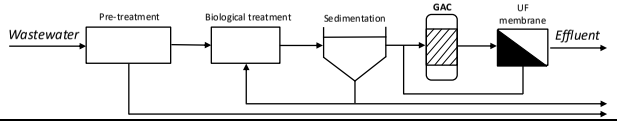
Configuration		Description	References
I Side stream **(MBR+PAC)**		PAC is added directly in the bioreactor. The membrane unit is in a separate tank. The sludge recycled into the bioreactor contains an amount of (embedded) PAC. A fraction is lost with the excess sludge.	Alvarino et al., 2016; Asif et al., 2020; Echevarría et al., 2019; Remy et al., 2012; Serrano et al., 2011, Wei et al., 2016;
II Submerged **(MBR+PAC)**		PAC is added directly in the bioreactor. The membrane unit is in the same reactor. The sludge recycled into the bioreactor contains an amount of (embedded) PAC. A fraction is lost with the excess sludge.	Alvarino et al., 2017; Li et al., 2011; Nguyen 2013a; Nguyen et al., 2014; Yang et al., 2010; Yang et al., 2012; Yu et al., 2014
III (PT) **CAS→(PAC+UF)**		PAC is used in the post treatment. The CAS effluent is sent to the PAC and a UF membrane unit retains the powder. A small amount is recycled. In Margot et al., 2013, 5% of the influent is treated in an MBBR and then mixed with the CAS effluent	Löwenberg et al., 2014, Margot et al., 2013
IV (PT) **MBR→PAC→UF**		PAC is used in the post treatment. The permeate is sent to the PAC and a UF membrane unit retains the powder. In the MBR there is no PAC.	Kovalova et al., 2013b
V (PT) **MBR→PAC→UF** & recirculation		PAC is used in the post treatment. The permeate is sent to the PAC and a UF membrane unit retains the AC powder and is completely recycled in the bioreactor.	Lipp et al., 2012
VI (PT) **MBR→GAC**		GAC is used as a post treatment. The permeate is sent into the GAC column and then directly discharged. In two studies (those with the asterisk in the adjacent column) there is an ozonation step between MBR and GAC.	Baresel et al., 2019; Itzel et al., 2018*; Langenhoff et al., 2013; Nguyen et al., 2012; Nguyen 2013a; Nguyen et al., 2013b; Paredes et al., 2018; Paulus et al., 2019*
VII (PT) **CAS→GAC**		GAC is used as a post treatment. The CAS effluent is sent into the GAC column and then directly discharged.	Grover et al., 2011
VIII **CAS→GAC→UF**		GAC is used as a post treatment. The CAS effluent is sent into the GAC column, then filtered (by UF membrane) and then discharged.	Sbardella et al., 2018

Table 3.2. Compounds included in the review grouped according to their class. In brackets, the number of compounds for each class considered in this study.

Class	Symbol	Compound
Analgesics/Anti-inflammatories (**18**)	**A**	4-acetamidoantipyrine; 4-aminoantipyrine; 4-formylaminoantipyrine; 4-methylaminoantipyrine; antipyrine/phenazone; diclofenac; formyl-4-aminoantipyrine; ibuprofen; indometacin; ketoprofen; mefenamic acid; morphine; n-acetyl-4-aminoantipyrine; naproxen; paracetamol/acetaminophen; salicylic acid; tramadol; *meclofenamic acid**
Anaesthetics (**2**)	**B**	Lidocaine; thiopental
Antibacterials (**29**)	**C**	Amoxicillin; ampicillin; azithromycin; cefalexin; ciprofloxacin; clarithromycin; clindamycin; erythromycin; flumequine; lincomycin; metronidazole; N4-acetylsulfamethoxazole; norfloxacin; ofloxacin; oxolinic acid; oxytetracycline; rifaximin; roxithromycin; sulfadiazine; sulfamerazine; sulfamethoxazole; sulfamethoxypyridazine; sulfamoxole; sulfapyridine; sulfathiazole; sulfisoxazole; trimethoprim; *doxycycline**; *tetracycline**
Anticoagulants (**1**)	**D**	Warfarin
Antidiabetics (**1**)	**E**	Metformin
Anti-hypertensives (**3**)	**F**	D617; verapamil; *enalapril**
Antimycotics (**4**)	**G**	Carbendazim; fluconazole; propiconazole; *ketoconazole**
Antineoplastics (**5**)	**H**	Cyclophosphamide; flutamide; hydroxytamoxifen; ifosfamide; tamoxifen
Antiseptics (**1**)	**I**	Triclosan
Antiviral (**3**)	**J**	Oseltamivir; oseltamivir carboxylate; ritonavir
Beta-agonists (**1**)	**K**	Terbutaline
Beta-blockers (**6**)	**L**	Atenolol; atenolol acid; bisoprolol; metoprolol; propranolol; sotalol
Calcium channel blockers (**1**)	**M**	Amlodipine
Contrast media (**7**)	**N**	Amidotrizoic acid (diatrizoate); diatrizoate and iothalamic acid; iohexol; iomeprol; iopamidol; iopromide; ioxitalamic acid
Diuretics (**2**)	**O**	Furosemide; hydrochlorothiazide
Gastrointestinal disorder drugs (**1**)	**P**	Mebeverine
Hormones (**14**)	**Q**	17α-ethinylestradiol (EE2); 17β-estradiol (Estradiol/E2ß); 17β-estradiol-acetate; boldenone; boldione; cyproterone acetate; dihydrotestosterone; estriol (E3); estrone (E1); etiocholanolone; nandrolone; testosterone; *norethindrone**; *progesterone**
Lipid regulators (**5**)	**R**	Bezafibrate; fenofibric acid; gemfibrozil; simvastatin; *clofibric acid**
Non-ionic surfactants (**2**)	**S**	4-tert-octylphenol; nonylphenol
Others (**15**)	**T**	4(5)-methylbenzotriazole; 4-n-nonylphenol; 4-tert-butylphenol; 5-methylbenzotriazole; benzalkonium chloride; benzothiazole; benzotriazole; bisphenol A; bisphenol A diglycidyl ether; bisphenol F diglycidyl ether; irgarol (cybutryne); methylbenzotriazole; octylphenol; perfluorooctanoic acid (PFOA); perfluorooctanesulfonic acid (PFOS); *tris(2-carboxyethyl)phosphine (TCEP)*; tris(1,3-dichloroisopropyl)phosphate (TDCPP)**
Pesticides (**8**)	**U**	Atrazine; diuron; fenoprop; isoproturon; mecoprop; N,N-diethyl-meta-toluamide (DEET); pentachlorophenol; terbutryn
Psychiatric drugs (**16**)	**V**	10,11-Dihydro-10,11-dihydroxycarbamazepine; carbamazepine; citalopram; diazepam; fluoxetine; gabapentin; levetiracetam; N,N-didesvenlafaxine; oxazepam; primidone; risperidone; sertraline; venlafaxine; *amitriptyline**; *dilantin**; *thioridazine**
Receptor antagonists (**7**)	**W**	Eprosartan; irbesartan; losartan; ramipril; ranitidine; valsartan; valsartan acid
Stimulants (**3**)	**X**	Caffeine; ritalinic acid; theophylline
Sweeteners (**1**)	**Y**	Aspartame
Synthetic musks (**3**)	**Z**	Celestolide; galaxolide; tonalide
UV filters (**4**)	**AA**	2-phenyl-5-benzimidazolesulfonic acid; benzophenone-3; butyl methoxydibenzoylmethane; oxybenzone
Veterinary drugs (**12**)	**BB**	Enrofloxacin; marbofloxacin; sarafloxacin; sulfachloropyridazine; sulfaclozine; sulfadimethoxine; sulfadimidine; sulfadoxine; sulfamonomethoxine; trenbolone; tylosin; *monensin**
*Anti-histamines (**1**)***		*Diphenhydramine**
*Urological drug (**1**)***		*Finasteride**

* Compounds investigated and never detected

** For these classes a symbol is not set as they are not included in the graphs

3.3 The role of activated carbon in the removal of OMPs

Activated carbon may be added in the bioreactor or it can be used as a post-treatment (PT) fed by the secondary effluent or the permeate, as reported in Table 3.1. Its presence favours similar removal mechanisms for the OMPs in the case of granules (i.e., GAC) or powder (i.e., PAC). PAC and GAC are characterised by a high specific surface (m^2/g) due to the presence of micro-, meso- and macropores. The internal structure of a grain, without taking into consideration its specific size, is reproduced in Figure 3.3.A. On its whole surface there is a high number of *active* sites where compounds (micro- and macro-pollutants) occurring in the wastewater can bind, depending on their affinity with the AC surface, and thus they are removed from the liquid phase via sorption mechanisms (Figure 3.3.B). Pores in the granule or in the powder are of different sizes resulting in different thresholds for the size of the molecules which can penetrate and then adsorb on the internal surface of the AC grain.

OMP affinity towards an AC is strictly correlated to the physical and chemical characteristics of the AC, namely pore size and texture, surface functional groups (Fig 3.4.C) and charge, and mineral matter content (Alves et al., 2018; Choi et al., 2005; Fuente et al., 2003; Kovalova et al., 2013b). Micropores are directly responsible for OMP adsorption (El Gamal et al., 2018).

Adsorption is expected to decrease over time due to a gradual saturation of the active sites during operation (Choi et al., 2005). Dissolved organic matter (DOM), and in particular the fraction of low molecular weight organics, if present in the liquid phase in contact with AC, tends to adsorb on the AC surface (Filloux et al., 2012). Organic particles may enter the macropores, thus they may represent a barrier for the OMPs in their movement to reach the active sites of meso- and micropores. DOM and OMPs are numerically present at different levels. In this context, Rattier et al., (2012) found that DOM acts as a strong competitor when it occurs 10^3 – 10^6 times higher than OMPs. In the presence of DOM in the liquid phase (wastewater under treatment), microorganisms may develop on the AC surface area and macropores (Alves et al., 2018), promoting the growth of a biofilm, thus favouring biodegradation processes due to microorganism metabolic reactions. The AC thus becomes *biologically activated carbon* (BAC) (Figure 3.3.C). The OMP biodegradation processes are enhanced here due to the development of a more specialised biomass, and the coexistence of aerobic and anoxic zones in this biofilm (Alvarino et al., 2016).

OMPs occurring in the wastewater may be sorbed by two mechanisms: *adsorption* due to electrostatic interactions between OMP charged groups and the oppositely charged biofilm or AC surface, and *absorption* into the biofilm stratum due to OMP hydrophobic interactions of the aliphatic and aromatic groups with the lipophilic cell membrane of the microorganisms or the lipid fractions of the suspended solids. Then some may biodegrade by means of microorganisms in the biofilm, transform and even mineralise; others may remain as they are (Baresel et al., 2019).

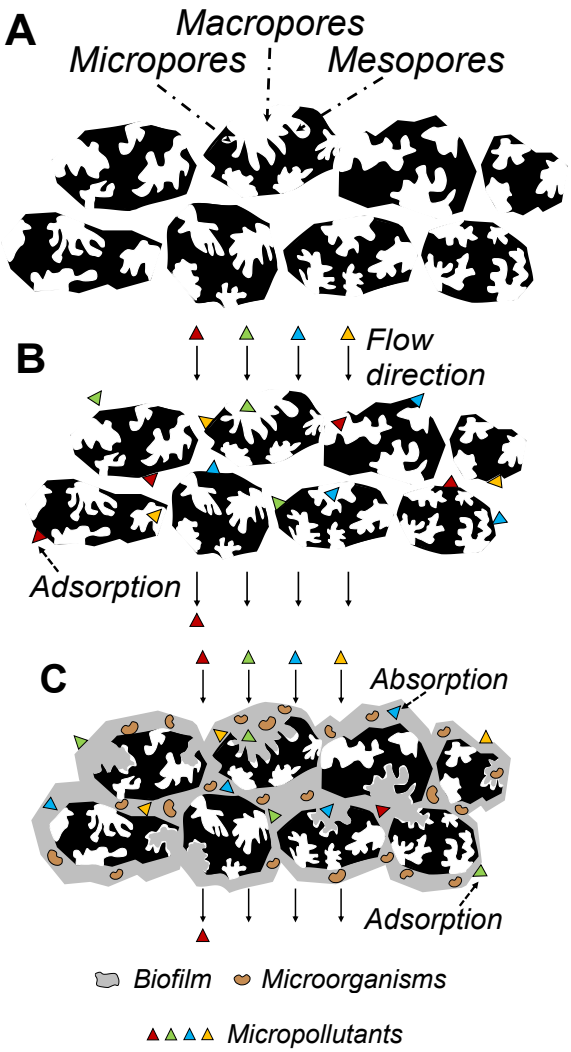


Figure 3.3. Schematic representation of (A) the structure of activated carbon; (B) adsorption of micropollutants on the surface of the AC; (C) BAC, with micropollutants absorbed and adsorbed on its surface.

When AC is added in the bioreactor, it comes into contact with the flocs (activated sludge): some AC particles are incorporated within them, others are suspended within the liquid phase, depending on the AC added quantity (Ng et al., 2013; Remy et al., 2010) (Figure 3.4.A).

Sludge flocs are dynamic systems where incorporated AC particles may be covered by the biofilm becoming BAC or they may have their surface partially free (Figure 3.4.B). In this last case, OMPs may directly adsorb on the AC surface. If the AC is covered by the biofilm, OMPs may be absorbed in the biofilm, desorbed from it and adsorbed on the smallest AC pores. Bacteria can only colonise macropores due to size exclusion. Extracellular polymeric substances (EPS) instead can also enter into meso- and micropores and thus act as a catalyst for the biodegradation processes of OMPs which manage to reach the surface of these pores and attach to it (Alves et al., 2018).

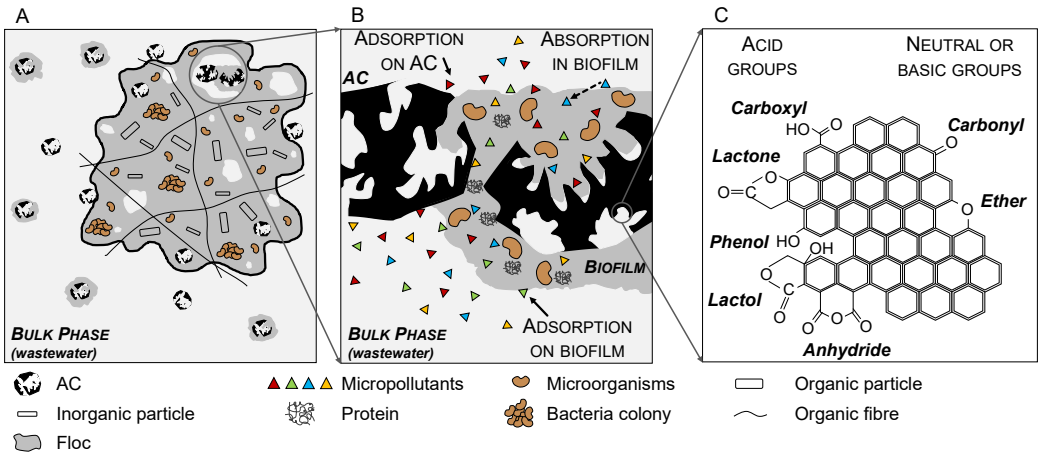


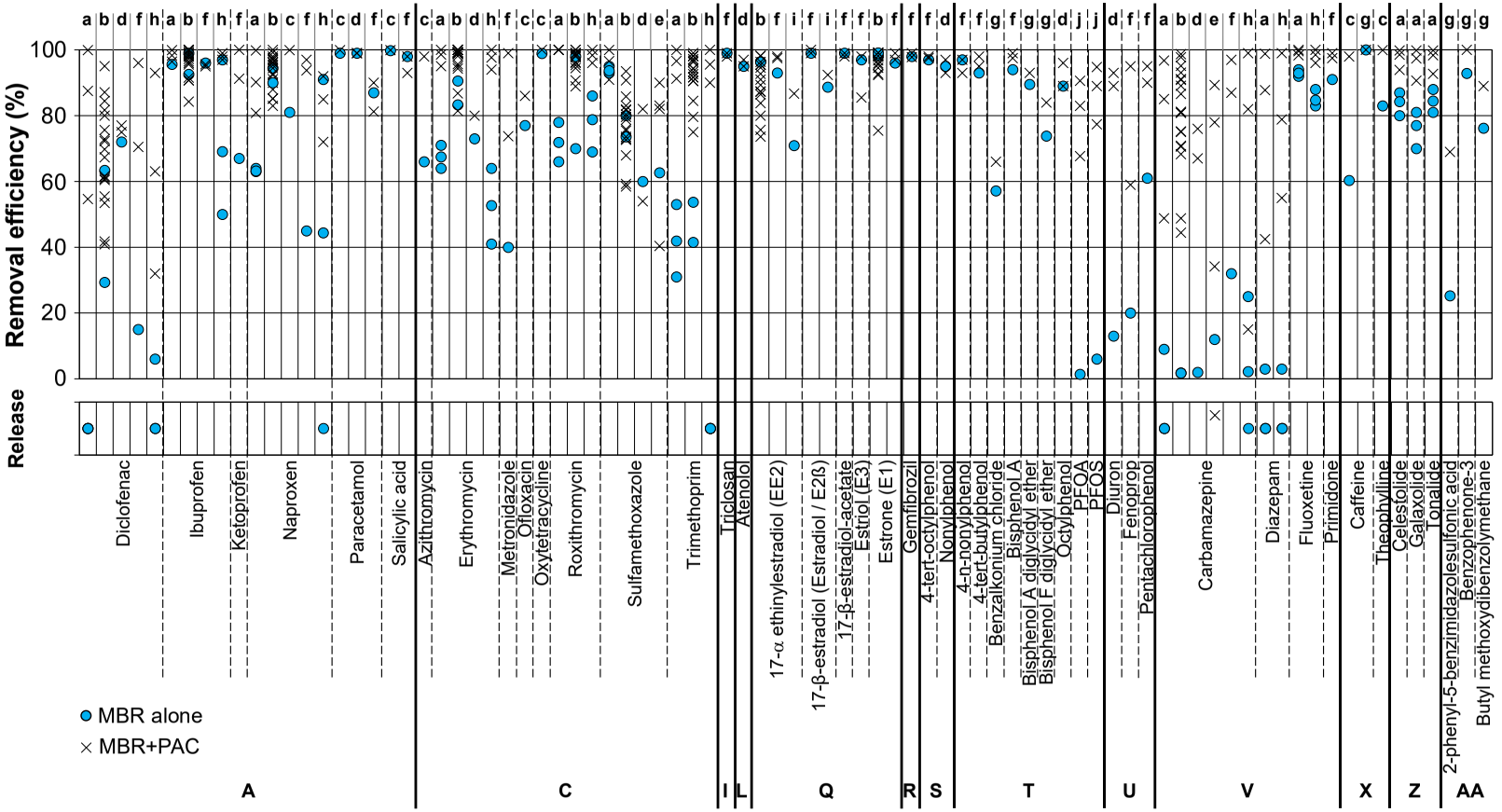
Figure 3.4. Schematic representation of a sludge floc in the bioreactor in the presence of AC (A); OMP removal mechanisms in an AC particle incorporated in the sludge floc (B); main functional groups on the surface of AC (C).

If AC acts as a PT, by PAC (as reported in Pills, 2012) or GAC (Sbardella et al., 2018), the development of the biofilm on its surface is still possible: DOM may be retained by the granules (Seo et al., 1996; Sun et al., 2020) and, over time, it may promote the growth of an autochthonous biomass (Sbardella et al., 2018). Sorption and biodegradation are complementary mechanisms that extend the AC life. During backwashing operations of the GAC filter, some OMPs could be detached from the filter and found in the backwash water (Baresel et al., 2019). At long operating times, mature or aged biofilm developed on the AC surface may detach giving rise to the biological regeneration process. This cleans the AC surface, and the AC active sites are now free for OMP adsorption even at long operating times. The regeneration is not able to create the original conditions and AC replenishment may become necessary to guarantee optimal operating conditions.

To sum up, OMP removal mechanisms are the results of continuous interactions among OMPs and AC particles, biofilm and organic matter. For this reason, BAC has to be considered a dynamic system where OMP sorption and biodegradation occur simultaneously (El Gamal et al., 2018).

3.4 Results

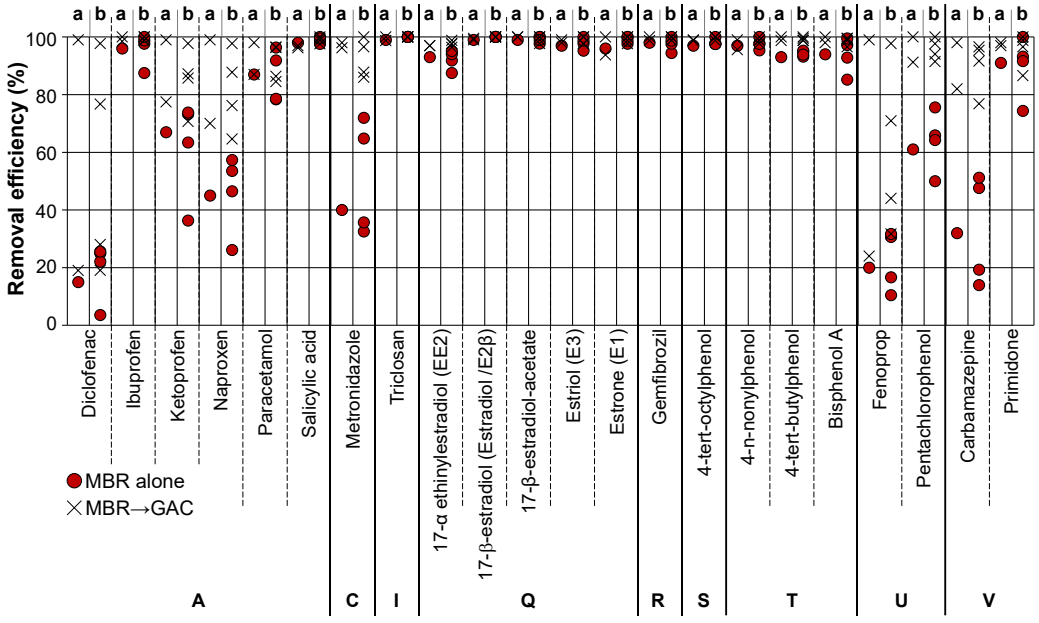
Collected data provided by the investigations included in this review were processed in order to compare the OMP removal achieved by the selected configurations in Table 3.1, at different AC dosages and under different operational conditions. The first analysis carried out refers to the contribution of AC in removing OMPs in the case of PAC added in the bioreactor (Figure 3.5) or GAC used as a PT (Figure 3.6) in comparison with the removal achieved by a biological treatment alone. Note that both Fig. 3.5 and Fig. 3.6 do not correlate removal efficiencies with specific operational conditions and configurations: the hybrid MBR is considered a *black box* and the details regarding quantity of added PAC or operational conditions referring to PAC or GAC are not reported, or when the PAC is added (in the anoxic or in the aerobic compartment), since they will be discussed in the following sections.
In more detail, Figure 3.5 refers to the removal achieved for 48 compounds belonging to 13 classes in MBR and MBR coupled to PAC (MBR+PAC). It emerges that the presence of AC added in the biological tank improves the removal of most of the compounds: it occurred in 79 out of the 108 reported cases. In 13 of the remaining 29 cases, OMP removal did not improve and, according to the authors, this was due to the fact that the compound was almost completely removed in MBR and, due to the presence of AC, the contribution was not relevant (Nguyen et al., 2013a). In the last 16 cases, the MBR presents a higher removal efficiency than the corresponding case of MBR+PAC. Among the reasons explained by the authors we can find: influence of the AC working age (fresh PAC *versus* saturated PAC) (Alvarino et al., 2017; Nguyen et al., 2013a); differences in the sludge properties and thus filtration in the membrane (Alvarino et al., 2017) and accidental temperature drop (Li et al., 2011). As to Figure 3.6, it includes 22 compounds belonging to 9 classes and 44 columns. The removal in MBR with a post-treatment of GAC (MBR→GAC) was higher in 27 cases than in MBR alone. In 16 cases, MBR reached almost complete removal efficiencies and the removal efficiency did not increase after the GAC stage. In only one case referring to paracetamol, the trend is not clear.



a Alvarino et al. 2016; **b** Alvarino et al. 2017; **c** Asif et al. 2020; **d** Echevarría et al. 2019; **e** Li et al. 2011; **f** Nguyen et al. 2013a; **g** Remy et al. 2012; **h** Serrano et al. 2011; **i** Yang et al. 2012; **j** Yu et al. 2014

Figure 3.5. Comparison among removal efficiencies achieved in MBR alone and MBR coupled with PAC. While lower case letters refer to the referenced studies, capital letters group the compounds by class according to Table 3.1. The separate grid at the bottom of the graphic indicates the release of the OMP, that is, negative removals obtained in the referenced studies.

Figure 3.5 shows that OMP release occurred occasionally with the only exception of trimethoprim, which was always released in the investigations by Serrano et al., (2011). The authors explained this finding by the fact that nitrifier bacteria were absent in the biomass within the MBR and trimethoprim was not degraded by the different species developed in the microbial community. In the other cases, OMP release was ascribed to the following causes: changes in operational conditions (for instance a sharp increment of the OMP concentration in the influent) (Li et al., 2011), environmental conditions such as a decrement in temperature which strongly affects biological reaction rates (Li et al., 2011); AC saturation (Alvarino et al., 2016), re-generation of parent compounds starting from the corresponding metabolites or transformation products (for diclofenac and carbamazepine) (Alvarino et al., 2016). Another possible reason, not reported in the reviewed studies, but often remarked in the literature (Verlicchi et al., 2012), is an inappropriate sampling protocol. These first rough comparisons lead to the consideration that the presence of AC has the potential to improve removal for most compounds.



a Nguyen et al. 2013a; **b** Nguyen et al. 2013b

Figure 3.6. Comparison among removal efficiencies achieved in MBR alone and MBR coupled with GAC. While lower case letters refer to the referenced studies, capital letters group the compounds by class according to Table 3.2.

3.4.1. Removal in MBR+PAC

In order to better investigate the influence of the amount of PAC added in the bioreactor, literature data were reported in Figure 3.7 considering the different PAC dosages, between < 0.05 g/L and 20 g/L of PAC. PAC dosages were classified as: < 0.05 g/L, 0.05 – 0.1 g/L; 0.25 g/L, 0.5 g/L, 0.75 g/L, 1 – 2 g/L and 20 g/L.

Based on the collected data, 48 compounds belonging to 13 different classes were analysed, and the most studied were: carbamazepine (31 values), diclofenac (28), naproxen and sulfamethoxazole (27), ibuprofen (26), trimethoprim (24), erythromycin (23), roxithromycin (22), EE2 (21) and E1 (20). The remaining compounds have only 1–6 values of removal efficiency. It emerges that all the compounds can be removed by MBR+PAC, even the most recalcitrant diclofenac and carbamazepine. The variability ranges are 32% to 99% for diclofenac, with the highest values found in Alvarino et al. (Alvarino et al., 2016), and 15% to 99% for carbamazepine, with the top removal reported in T. Alvarino et al. (2017). At the lowest doses of PAC (< 0.05 g/L), the removal efficiency is at least 60% with the only exception of sulfamethoxazole (it needs at least 0.25 g/L to achieve 60% removal). The high dosage of 20 g/L in Asif et al. (2020) was selected in order to guarantee a homogeneous integration of PAC and sludge and to achieve the best rheological properties of the sludge.

An analysis of the collected data highlights that the addition of PAC as low as 0.1 g/L is sufficient to achieve a removal of 80% for 34 out of the 37 compounds which were investigated in this range of PAC addition.

PAC addition in the MBR leads to a relevant increment in PFOS and PFOA removal (Figure 3.7): from < 7% in the MBR to the range 68% to 94% in the MBR+PAC, depending on the concentration of AC and the compound (Yu et al., 2014). Their removal is only due to adsorption on PAC and 0.08 g/L seems to be enough to reach 80% of removal. The Authors underline that the expected removal with the addition of PAC should be much higher, especially at the highest PAC dosages, but probably because of fouling due to sludge and DOM, the available PAC surface for PFOA and PFOS adsorption was greatly reduced. For the most investigated compounds (diclofenac, sulfamethoxazole and carbamazepine), the addition of PAC leads to an increment in removal efficiency, despite its value varying in a range greater than 50%. This leads to the conclusion that PAC added in the MBR does not guarantee a minimum removal for the compounds due to many factors that influence their behaviour.

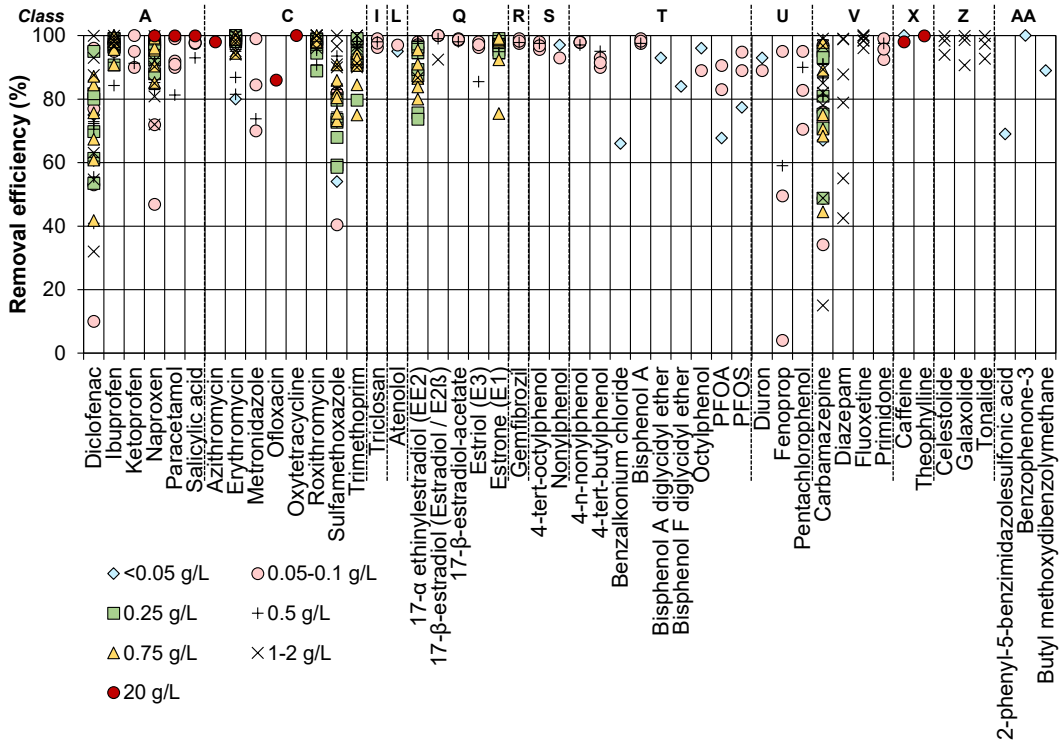


Figure 3.7. Removal efficiencies for the compounds investigated in MBR+PAC with a submerged or side stream membrane unit. Data from: Alvarino et al., (2016), T. Alvarino et al., (2017), Asif et al., (2020), Echevarría et al., (2019), Li et al., (2011), Nguyen et al., (2013a), Remy et al., (2012), Serrano et al., (2011), Yang et al., (2012) and Yu et al., (2014). Capital letters group the compounds by class according to Table 3.1.

3.4.2. Removal when AC is used as a post-treatment

An analysis of the removal efficiencies achieved when PAC is used as a PT is reported in Figure 3.8: PAC treatment follows the biological step consisting of a CAS (Löwenberg et al., 2014; Margot et al., 2013) or an MBR (Kovalova et al., 2013b). The tested PAC doses were < 0.05 g/L for CAS and MBR and 1 – 2 g/L for CAS.

Removal values of compounds in MBR→PAC < 20% were found at the lowest doses of PAC (0.008 g/L). This was the case for all the contrast media (class N) with the only exception of iopromide which exhibited a removal of 47% already at these dosage conditions. Diatrizoate and ioxitalamic acid were always poorly removed: between 1% and 18% at the different tested doses. Moreover, it was found that poor removal (21% to 35%) is achieved for all contrast media in MBR alone (Margot et al., 2013) (data not shown) and PAC addition may remove them, depending on the added dose. Fluctuations in the removal efficiencies of such recalcitrant compounds may be ascribed to variations in their influent concentrations (Lipp et al., 2012) and to a sampling mode that implies the analysis of the grab or composite samples taken not considering the HRT of the monitored treatment stage (Verlicchi et al., 2012). It emerges that a higher dose does not imply a higher removal achieved for diclofenac, sulfamethoxazole, mecoprop and carbamazepine. At the same dose of PAC as a PT

after a CAS or an MBR, the removal achieved after an MBR is higher with respect to the removal achieved after a CAS for diclofenac (95% to 99% compared 82% to 85%) and carbamazepine (99% compared 90% to 99%), lower for sulfamethoxazole (2% to 60% compared 58% to 64%) and partially overlapped in the case of benzotriazole (68% to 92% compared 90% to 92%). This can be ascribed to the interactions between the organic matter and the AC surface, which are more relevant in the case of CAS effluent due to its higher concentration with respect to MBR permeate. In these configurations, there was a higher number of compounds with a variability of more than 50% in their removal efficiency compared to PAC added in the biological tank (Figure 3.7) where only three compounds presented such a variability range.

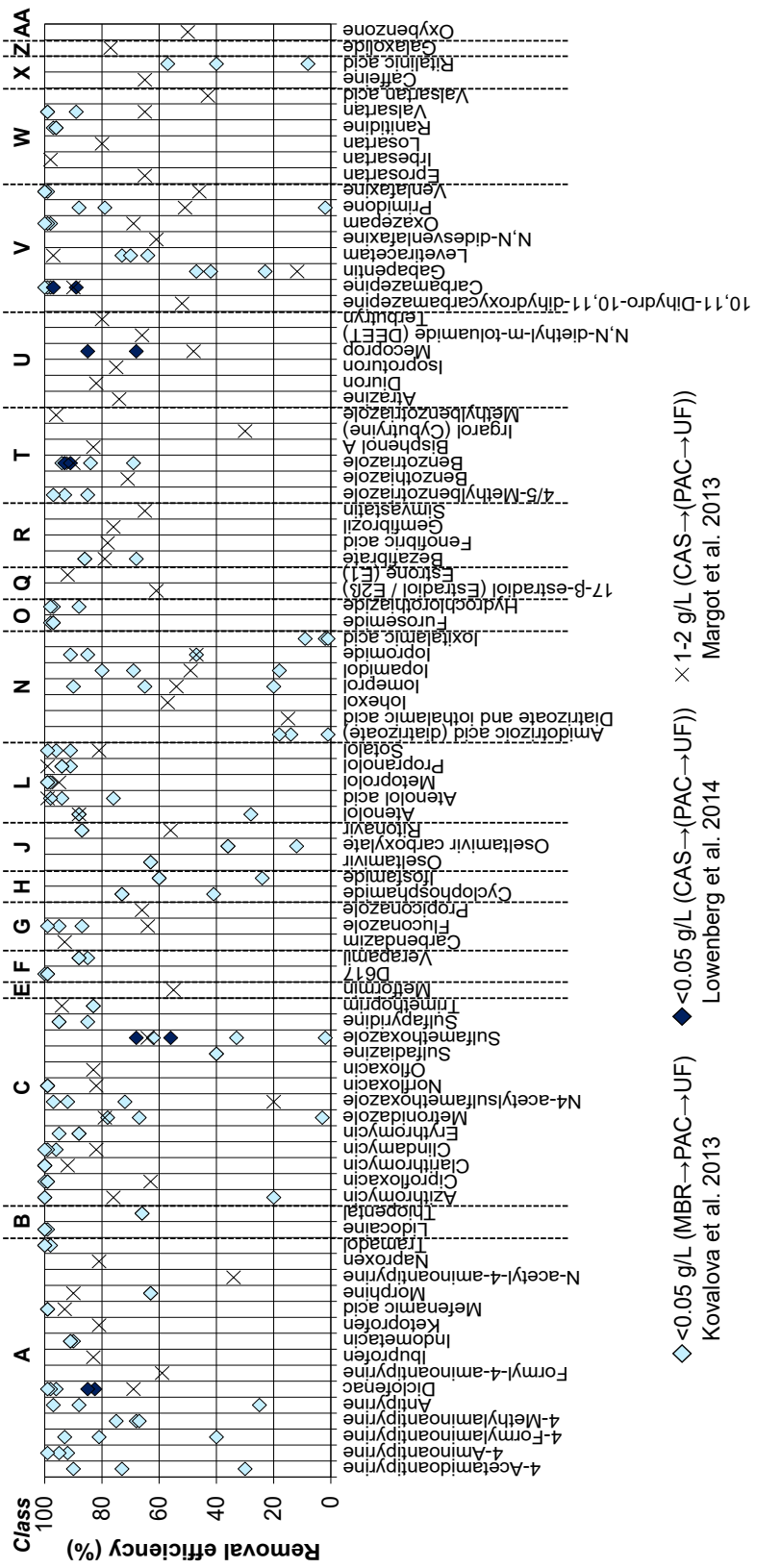


Figure 3.8. Removal efficiencies of the compounds included in the reviewed studies referring only to the PAC post-treatment, following a CAS or an MBR. Capital letters group the compounds by class according to Table 3.1 Data from: Kovalova et al., (2013b), Löwenberg (2014), Margot et al., (2013).

Figure 3.9 refers to OMP removal efficiencies in a GAC column acting as a PT at different empty bed volumes (EBV), that is, the GAC working period. They varied between < 1000 EBV (Nguyen et al., 2013b, 2012) and 60,000 EBV (Baresel et al., 2019). It emerges that for most investigated compounds the removal efficiencies vary greatly. The smallest variability intervals were found for bisphenol A (6%, between 77% and 83%), ciprofloxacin (23%, between 63% and 86%), and 4-n-nonylphenol and 4-tert-butylphenol (25%, 50% to 75% and 74% to 99%, respectively). The widest interval was found for diclofenac (3% to 99%), with the lowest value found in Nguyen et al., (2013b) and the highest values collected in Paredes et al., (2018) and Baresel et al., (2019). The extremely low removal was ascribed to the saturation of the GAC column, whereas the highest removal values may be ascribed to the biological regeneration within the BAC which thus allowed a high and continuous OMP removal from the real wastewater, even at high EBVs. As diclofenac is poorly removed in biological processes, the contribution of the GAC column in its removal is fundamental. The removal achieved with the GAC filtration is related to OMP nature, its biodegradability and sorption potential, the degree of saturation level of the AC filter, the EBCT, as well as OMP concentration in the GAC influent. If a compound is highly removed in the bioreactor, the resulting concentration in the treated effluent is low. In this case, OMP removal efficiencies are around 40% to 50% in the GAC column and are still to be considered very good as they lead to a very high overall removal. This is the case for ibuprofen, paracetamol, E3, 4-tert-octylphenol, 4-tert-butylphenol and 4-n-nonylphenol. When OMP removal in the bioreactor is moderate and also variable in a wide range (20% to 70%), it emerges that the GAC can have two different behaviours, which mainly depend on the nature of the compound. GAC can exhibit a fairly constant removal efficiency up to its saturation (ketoprofen); on the other hand, it seems that GAC performance may adapt to the variations in the permeate concentration. This was the case for metronidazole for which GAC was able to guarantee a very high removal efficiency leading to an overall removal between 86% and 99% (Nguyen et al., 2013b). This issue will be discussed later and compared with recent literature findings. In the case of compounds with very low removal efficiencies in the bioreactor, GAC may greatly contribute to their removal and its presence is essential for assuring a good removal of such recalcitrant compounds. If a decrement occurs, it may be correlated to GAC saturation conditions (fenoprop, carbamazepine and diclofenac). If biological regeneration occurs, OMPs may still be removed by adsorption. This explains the behaviour of atenolol, metoprolol and propranolol, the antibiotic trimethoprim and the diuretic hydrochlorothiazide, and also diclofenac, which maintain a medium-high removal efficiency for a long working time (Baresel et al., 2019; Sbardella et al., 2018). In the case of GAC saturation, biodegradable compounds absorbed in BAC or adsorbed in GAC may still undergo biodegradation processes which maintain a good removal efficiency at long operation times (azithromycin, ciprofloxacin, ofloxacin, and sulfamethoxazole) (Sbardella et al., 2018).

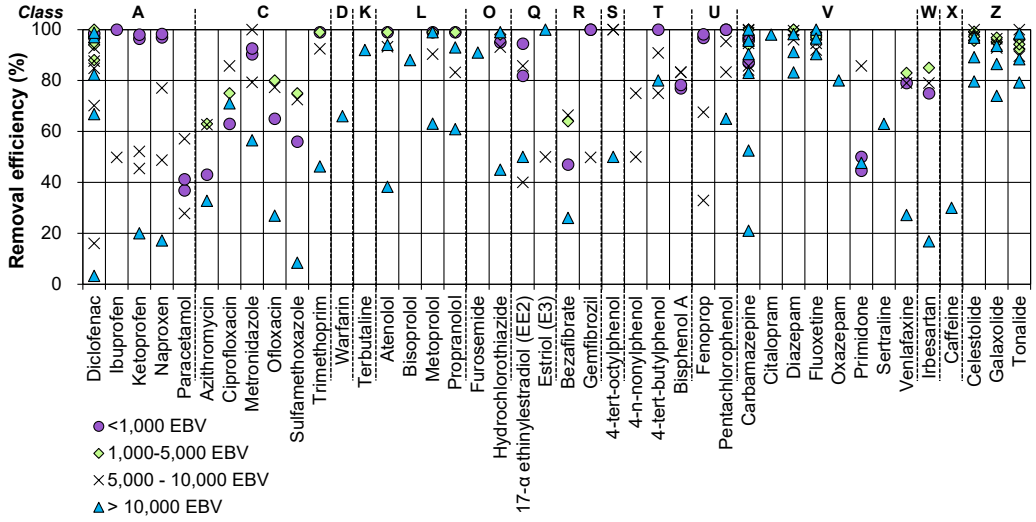


Figure 3.9. Removal efficiencies obtained in the GAC unit acting as a PT for the compounds under review at different empty bed volumes (EBV). Capital letters group the compounds by class according to Table 3.1. Data from: Baresel et al., (2019), Nguyen et al., (2013b), Nguyen et al., (2012), Paredes et al., (2018) and Sbardella et al., (2018).

3.4.3. OMP concentrations in MBR+PAC effluent

Figure 3.10 refer to OMP concentrations in the effluent from (MBR+PAC) systems included in the review. The different symbols used for these effluent quality data depend on the value of the corresponding biological stage influent. The data reported in these figures refer to different types of MBR and operating conditions (e.g., different microbial community species, AC doses and age, influent characteristics). For this, the analysis of the reported trends requires great caution.

OMP concentrations lower than 0.01 μg/L correspond to a very good quality of the effluent. They refer to compounds which have a high sorption potential ($\log D_{ow} > 3$, as for E2β), or are highly degradable (caffeine), or have a low influent concentration (naproxen). Additionally, they refer to high PAC dosages (naproxen, paracetamol, salicylic acid and oxytetracycline, azithromycin, caffeine) (Alvarino et al., 2017; Asif et al., 2020) or to fresh PAC (erythromycin, roxithromycin, sulfamethoxazole, fluoxetine) (Alvarino et al., 2016, 2017).

The highest effluent concentrations correspond to the highest influent values or ranges of concentrations: this was the case for sulfamethoxazole (Li et al., 2011) (in Fig. 3.10A), PFOA and PFAS (Yu et al., 2014) and carbamazepine (Li et al., 2011) (in Fig. 3.10B). There is an exception: carbamazepine in Fig. 3.10B has an effluent concentration similar to the influent one (around 22 μg/L). According to the authors (Serrano et al., 2011), this might be ascribed to the saturation of the AC after three months of continuous operations. The release of carbamazepine reported in Li et al., (2011) was related to an accidental low temperature which may have reduced the kinetics of the biological processes and the transfer of the OMP from the solid (sludge or AC) to the liquid phase. The effluent concentration increased to 190 μg/L from 100

µg/L in the influent. Paracetamol (Fig. 3.10A), an easily degradable compound, was found at a very low concentration also with an influent concentration equal to 118 µg/L (Echevarría et al., 2019) and with a PAC dosage in the range 0.025–0.050 g/L. On the other hand, diazepam (Fig. 3.10B), a poorly degradable compound, was found in the effluent at 0.1–11 µg/L with the corresponding influent in the range 10–25 µg/L (Serrano et al., 2011). The highest effluent concentrations are due to PAC saturation (Alvarino et al., 2016).

If a threshold is set equal to 1 µg/L for the effluent concentration of an AC treatment, out of the 48 reported OMPs in Figure 3.10, 32 compounds are always below such threshold, and 16 compounds are at least one value above.

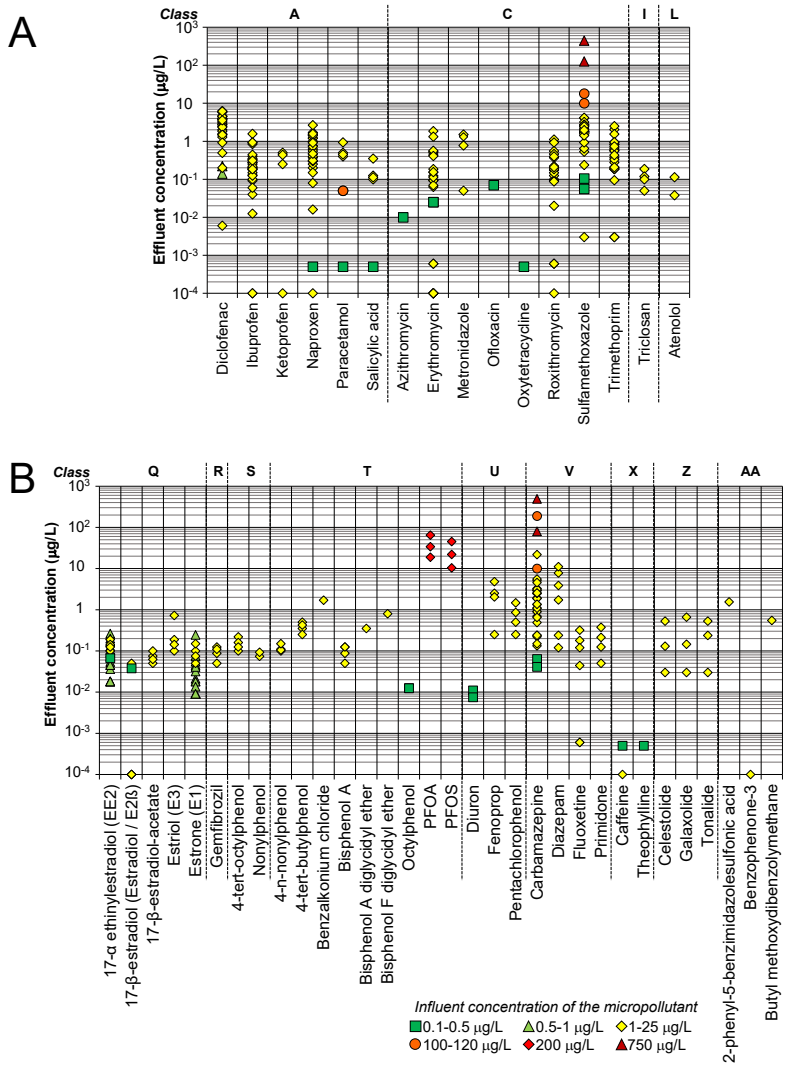


Figure 3.10. Concentration in the effluent of MBR+PAC for micropollutants belonging to the other classes included in the review. Capital letters group the compounds by class according to Table 3.1. A) OMPs from classes A – L. B) OMPs from classes Q – AA. Data from: Alvarino et al., (2016), Alvarino et al., (2017), Asif et al., (2020), Echevarría et al., (2019), Li et al., (2011), Nguyen et al., (2013a), Remy et al., (2012), Serrano et al., (2011) and Yu et al., (2014).

3.5 Discussion

The potential of AC in removing OMPs from wastewater prompted specific investigations on adsorption batch tests under controlled conditions (e.g. aqueous solutions and synthetic water with a simulated matrix effect) (de Ridder et al., 2010; Dickenson and Drewes, 2010). However, removal mechanisms of OMPs in hybrid MBRs are not limited to adsorption processes as described in Section 3.3.
AC and OMP structure and properties, wastewater composition, and operational conditions strongly influence the overall removal of OMPs in MBR coupled with AC. At the same time, AC presence can influence OMP fate during treatment, change sludge properties and also have an effect on membrane fouling. These issues will be discussed in the following sections.

3.5.1. Factors influencing the removal of OMPs by the presence of AC

The main factors influencing OMP removal are related to compound properties, AC characteristics and dosage frequency and mode, wastewater composition (namely DOM and its content of large molecules and low molecular weight organics), and treatment operational conditions. The interactions between OMP and AC depend on their properties. The extent at which these interactions may develop is related to the available quantity of AC and OMP and the conditions under which these interactions occur.

Micropollutant properties

The main properties affecting OMP removal mechanisms include molecule charge, $\log K_{ow}$ or better $\log D_{ow}$, pK_a, molecular size, and specific functional groups within the molecule.

Charge

OMP charge is a leading parameter if its removal is due to electrostatic interactions with AC in a hybrid MBR. It emerges that cationic compounds seem more prone to be removed by AC treatment due to electrostatic interactions between the positively charged surface of the pollutants and the negative surface of the carbon, confirming the findings by Kovalova et al., (2013b). Cationic compounds seem to be mostly well removed regardless of their other properties (Mailler et al., 2015; Margot et al., 2013). This fact justifies their small removal variability range compared to anionic or neutral ones. In the case of neutral compounds, removal is influenced by hydrophobicity and molecular structure (mainly functional groups that allow H-bonds and π - π bonds) (de Ridder et al., 2010). For anionic compounds, electrostatic repulsion is expected between the AC and OMP surface. Although there seems to be a relation between hydrophobicity and removal efficiency in the case of PAC as a PT, no clear evidence of this phenomenon was found in the literature (Mailler 2015, Margot 2013). However, high OMP hydrophilicity can result in low adsorption capacity for charged compounds

even when electrostatic interactions are expected between AC and OMPs (Kovalova et al., 2013a). Moreover, it seems that saturation is more prone to take place for anionic compounds in wastewater (Mailler, 2015).

logD_{ow}

Although a significant positive correlation has been found regarding OMP removal and logD_{ow} (Mailler et al., 2015), no clear correlation have been found between the removal of many OMPs and the logD_{ow} in other studies (Alves et al., 2018; Kovalova et al., 2013b; Rattier et al., 2014). Referring to neutral compounds, it was found that at higher logD_{ow} values the removal efficiencies are higher and have a lower variability range. According to de Ridder et al. (2010) at logD_{ow} greater than 3.7 hydrophobic interactions become the dominant removal mechanism.

Molecular weight

Alves et al. (2018) found that if AC is added to OMP spiked water, there is a clear correlation between molecular size and removal efficiency: they stated that the higher the molecular weight, the higher the amount of AC to guarantee the same removal efficiency, confirming that steric hindrance of the large molecules hinders their adsorption rate.

Characteristics of activated carbon

The influence of the characteristics of the AC on the removal of selected OMPs were investigated by Alves et al., (2018), Choi et al., (2005), Mailler et al., (2016) and Paredes et al., (2018). In particular, Alves et al., (2018) compared the removal efficiencies for a wide selection of compounds with different types of AC in terms of activation (with steam or chemical), textural properties, chemical properties (related to the functional groups in the outer layer of the grain and in particular to the presence of oxygen surface groups, such as carboxylic, ethers and lactones), pH-point of zero charge (pH_{pzc}), as well as surface charge at pH = 8. They found that in ultra-pure water, chemical ACs are more prone to attract and bind OMPs than steam ACs and they guarantee 80% removal at lower doses. Choi et al., (2005) linked AC characteristics (specific surface area, pore volume and material) to OMP adsorption in GAC columns. They found a negative correlation between pore volume and the BET specific surface area; they remarked that the BET specific surface area and pore volume reduce as the operation time increases, their reduction occurs mostly in micro-pores and that OMP and DOM adsorbed onto macropores can subsequently cause a micropore blockage. The extent of this reduction depends on the carbon type. According to the investigations by Fundneider et al., (2021a), a balanced proportion of macro-, meso- and micropores in the GAC improve the OMP removal in the presence of DOC, whereas GAC with a high proportion of micropores is more affected by pore blockage due to DOC adsorption leading to a lower OMP removal. OMP removal is strongly affected by the presence of DOM which may partially cover the AC surface. If an AC is positively charged, it attracts DOM (negatively charged) and thus

its surface will have positively and negatively charged zones, thus attracting anionic and cationic OMPs respectively. Finally, it was also found that pore volume is more important than specific area and a larger pore volume generally allows a higher removal of OMPs (Rossner et al., 2009).
Mailler et al. (2016) studied the influence of the physical characteristics of four PACs on the removal efficiencies of 15 OMPs. They found that the BET surface area is positively correlated to OMP removal. On the other hand, the BET surface area is negatively correlated to bulk density, that is, a high BET surface area corresponds to low bulk densities. As bulk density is an easy-to-measure parameter it could be used as an indicator to select AC.

PAC dosage and losses

PAC dosage seems to be one of the crucial operational parameters regarding the influence on OMP removal. Tested dosages were generally defined on the basis of preliminary batch tests aiming at investigating the sorption potential of the specific OMP on an AC in pure water. Unfortunately test data regarding adsorption of OMPs in the case of PAC added in an MBR did not fit well with the adsorption isotherms (Li et al., 2011; Nguyen et al., 2013b).
PAC was added at the beginning of the investigations (Alvarino et al., 2016) or periodically during the experimental period (Alvarino et al., 2017; Li et al., 2011). In this last scenario, fresh AC mixes with "older" AC which is partially saturated. It was found that the addition leads to an improvement in the removal of recalcitrant OMPs such as carbamazepine and diclofenac and, for this reason, the concentration of carbamazepine was suggested as an indicator of the AC saturation level (Alvarino et al., 2017). The loss of the *potential* adsorption capacity of the AC is reduced not only by its progressive saturation, but also by its losses from the system by withdrawal of excess sludge or retentate from membrane PT units. PAC addition (replenishment) is thus necessary to maintain its desired concentration in the tank.

Dosage point

In some investigations PAC was added in the anoxic tank (Remy et al., 2012), in others in the aerobic one (Asif et al., 2020; Echevarría et al., 2019). In Asif et al., (2020), PAC was added in the aerobic compartment of the anoxic/aerobic side stream MBR and, due to sludge recirculation, a fraction of PAC embedded in the sludge flocs was fed to the anoxic compartment, promoting OMP removal in this environment. In addition to that, AC may also reach the biological reactor in a different way. This is the case in schematic representation V in Table 3.1: PAC is used as a PT followed by a UF unit for its separation. The recirculation of the retained PAC back to the MBR, promotes its mixing with activated sludge and thus improves OMP sorption and degradation (Lipp et al., 2012). Based on previous studies, it emerges that useful considerations can be found in Streicher et al., (2016) who suggested that the long contact time in the activated sludge processes might enhance the PAC removal efficiency of many OMPs compared to the short contact times in case of PT and that PAC addition in the anoxic

tank seems to be the best option. Finally, Boehler et al., (2012) reported that similar removal of OMPs can be achieved by adding 10−20 mg PAC/L in the case of a PT (DOM in the range 5−10 mg/L) and 30−40 mg/L of PAC if it is added in the biological tank.

Duration of the added PAC

The removal of an OMP is strictly related to the working age of the AC: once it is added in the bioreactor, the whole surface is available for sorption and all the active sites are free. After a period of operation, some sites are occupied by OMPs and DOM and the removal may be lower than in the case of fresh AC. Once sorbed, the OMP can be stable or subjected to biodegradation processes, leading to transformation products which could leave the carbon surface or remain sorbed on it (Baresel et al., 2019). As reported in section 3.2.3, doses of PAC added in the biological treatment varied between 0.004 g/L (Remy et al., 2012) and 20 g/L (Asif et al., 2020). Removal data provided in the studies are seldom correlated to the AC working age: only 8 studies provided removal as a function of time (Alvarino et al., 2016, 2017; Li et al., 2011; Löwenberg et al., 2014; Nguyen et al., 2013a, 2014; Serrano et al., 2011; Wei et al., 2016). In order to guarantee a good performance of the AC present in the treatment, T. Alvarino et al., (2017) validated a dosage of 250 mg/L added every 35 days.

Sludge retention time

Ng. et al. (2013) evaluated the influence of SRT in hybrid MBRs (configurations I and II in Table 3.1, SRT = 10 d, 30 d and > 100 d). At lower SRTs, a higher amount of fresh PAC is required to maintain a fairly constant AC concentration in the bioreactor. This would provide a higher adsorption of OMPs and DOM and at the same time this practice would reduce the risk of membrane fouling. On the other hand, higher SRTs promote the development of a diverse biomass species within the biological compartments and thus they would favour OMP biodegradation processes. Specific investigations on the influence of SRT on the removal of OMPs were not carried out in the reviewed studies: SRT ranged between 12 d (Echevarría et al., 2019) and 300 d (Nguyen et al., 2014) and no relevant removal differences were found.

Hydraulic retention time in PAC tank

According to kinetic studies, such as those by Kovalova et al., (2013a), Mailler et al., (2016) and Meinel et al., (2015) contact time influences the OMP removal rate. They found that short HRT (30 – 60 min) may be enough to guarantee an efficient adsorption of most OMPs (including atrazine, norfloxacin, ofloxacin and sulfamethoxazole). Larger molecules, such as erythromycin and roxithromycin require more than 1 h to achieve high removal. In the reviewed studies, the tested HRT for the PAC tank as a PT varied between 0.5 h and 24 h and it allowed the transfer of most of the OMPs from the liquid to the solid phase. According to Lee et al., (2009), in submerged MBR, high HRT, low flux and intense mixing in the bioreactor are the best operational conditions to maintain the PAC in the bulk phase and reduce its deposition against the membrane. In fact, they found that PAC against the membrane

reduces its sorption available surface thus its potential removal capacity. These findings refer to investigations carried out with deionised water, where biodegradation cannot occur for the investigated compound (E2). It is important to remark that the retention time of the PAC in the tank is another fundamental parameter, but unfortunately it is not possible to correlate OMP removal data to PAC retention time due to lack of data.

Dissolved organic matter

DOM is due to large organic molecules (biopolymers, humic substances and building blocks) and smaller molecules (low molecular weight organic acids and neutrals). Similar DOM concentrations (expressed as mg DOC/L) were found in the different compartments of the bioreactor as well as in a CAS effluent and in an MBR permeate, ranging between 5 mg/L and 18.4 mg/L (Altmann et al., 2014b; Fundneider et al., 2021a; Kovalova et al., 2013b; Meinel et al., 2015; Streicher et al., 2016). Based on Liquid Chromatography – Organic Carbon Detection (LC-OCD), it was found that different percentages of DOM constituents may occur (Altmann et al., 2014b; Filloux et al., 2012; Guillossou et al., 2020; Streicher et al., 2016; Zietzschmann et al., 2016, 2014) depending on the initial raw wastewater and the treatment. Interesting findings of DOC in the wastewater under treatment were obtained by Fundneider et al., (2021a) and Fundneider et al., (2021b) by size exclusion chromatography coupled with online DOC and UV_{254} detectors, where the fractionation of the DOC and sorption potential of each fraction were assessed. They found that the non-adsorbable DOC in wastewater was around 20 %, in agreement with the results achieved by Zietzschmann et al., (2014).

As mentioned above, DOM may affect OMP removal as it can compete for available surface/sorption sites and, to a lesser extent, pore blockage, depending on its characteristics (average molecular weight and hydrophobicity) and AC porosity (de Ridder et al., 2011). This fact is clearly evident in Dickenson and Drewes (2010), Guillossou et al., (2020) and Zietzschmann et al., (2016) who compared the removal curves of a selection of OMPs at the same dosage of PAC in ultrapure water, drinking water and wastewater. According to the investigations by Dickenson and Drewes (2010), the observed removal was almost complete for all the compounds in the first case and in the range 50% to 75% in the presence of DOM.

Background DOM decreases adsorption capacities to a greater extent than pH, ionic strength, and temperature. This occurs especially at low carbon doses where the competition for sorption sites is strong (Kovalova et al., 2013a). According to Zietzschmann et al., (2014) the different fractions of DOM present a different adsorption behaviour: small molecules adsorb quickly and overall better, instead large molecules show slow and lower adsorption. The effect of small DOM molecule competition seems to affect particularly medium and low adsorbable OMPs. In this context, Zietzschmann et al., (2016) found that low molecular weight organics are the main competitors for the active sites in AC, and the estimation of their concentration can be useful in evaluating the required AC dose to reach a desired OMP removal. On

the other hand, (Guillossou et al., 2020) found that in the case of wastewater characterised by a modest fraction of low molecular weight organics, the competition in adsorption is due to biopolymers and hydrophobic molecules. Moreover, OMPs may also interact with non-adsorbable DOM and thus remain in the liquid phase (Mailler et al., 2016).

Many authors suggest correlating OMP removal to the PAC dose normalised to the respective DOC (that is the specific PAC dose, expressed in terms of mg PAC/mg DOC) (among them: Kovalova et al., 2013b; Streicher et al., 2016; Zietzschmann et al., 2016). This parameter allows the estimation of the required dose of a given PAC to achieve the desired OMP removal from the wastewater. The interest toward DOM in the study of adsorption processes has increased in recent years being the adsorbed DOM (mg DOC/g GAC) the proposed assessment parameter of the performance of the GAC column instead of the commonly adopted EBV (Fundneider et al., 2021a).

DOM adsorbed onto the AC is generally negatively charged at the pH of the wastewater and thus can decrease the adsorption of negatively charged OMPs through repulsive electrostatic interactions (de Ridder et al., 2011) and increase the attraction of positively charged compounds (Mailler et al., 2015). At the same time, OMPs may interact with DOM through Van der Waals bonds, as well as covalent and hydrogen bonds, resulting in a higher removal in MBR systems. This was found for bisphenol A which can interact with microbial by product-like and humic acid-like DOM in wastewater, and carbamazepine and ibuprofen with fulvic acid-like compounds (Hernandez-Ruiz et al., 2012). These complex phenomena are also affected by a high ionic strength in the liquid phase which can reduce the effect of electrostatic repulsion and attraction (de Ridder et al., 2011). Moreover, the DOM attached to the surface may be a barrier for those compounds whose removal is mainly due to adsorption on the activated sites, such as carbamazepine, diclofenac, diazinon and naproxen (Rattier et al., 2012). Guillossou et al., (2020) showed that sufficiently long contact times allow a high removal of many OMPs, despite an increase in DOM sorption on AC. This fact was ascribed to a slow diffusion of OMPs through the adsorbed DOM on the PAC surface or to the formation of DOM-OMPs complexes which are progressively adsorbed on the PAC surface. As highlighted above, proper HRTs can guarantee the transfer of OMPs from the liquid to the solid phase.

Main factors affecting OMP removal by GAC

In a GAC column it is crucial to adopt proper EBCT and filtration velocity v_f. EBCT is a key factor for the design of the GAC column, influencing the breakthrough curves of OMPs. Generally, shorter EBCTs may lead to a lower adsorption of OMPs. In this context, v_f and column height can be adjusted in order to guarantee a proper EBCT for removing the different OMPs (Fundneider et al., 2021a). In the reviewed investigations, EBCT was between 7 and 50 min and the filtration velocity in the range 0.4 – 4.67 m/h (Baresel et al., 2019; Nguyen et al., 2013a, 2013b, 2012; Paredes et al., 2018; Sbardella et al., 2018). Investigations were carried out at a lab scale with the

only exception of Baresel et al., (2019) who had at a pilot scale plant. A comparison of the adopted values of EBCT and v_f and those provided by the literature Metcalf & Eddy (2014) (5 – 10 min; 5 – 15 m/h as well as filter bed height in the range 2–4 m) shows that:

- EBCT in these investigations is generally higher (with the exception of Nguyen et al., (2012) and (2013b) where EBCT is around 7 min);
- v_f is always less than the minimum literature recommended value;
- as to the height, in lab scale investigations it was between 0.12 m and 0.42 m, in the pilot plant it was 1 m.

The adopted operational conditions (very slow filtration velocity and high EBCT) promoted the transfer of OMPs from the liquid to the solid phase and counterbalanced the fact that the bed height was always less than the suggested one.

As to EBCT influence it is important to underline some main results. According to Fundneider et al., (2021a) the smaller the grain size, the larger the specific surface area of the GAC and the shorter the EBCT to reach the equilibrium conditions for the OMP mass transfer from the liquid phase to the solid phase. In their investigations, they correlated the OMP removal capacity of the GAC column with the DOC sorbed on the GAC mass. They found that operating with EBCT between 6 and 24 min, the measured sorbed DOC on the GAC was higher for GAC columns operating with higher EBCT. With EBCT in the range 24–33 min, no differences were found. Moreover, they found that EBCT ≤ 20 min has a stronger influence on the removal of well adsorbable OMPs (among them benzotriazole, carbamazepine and ibersartan) than on the removal of poorly/moderately adsorbable compounds (such as primidone, and gabapentin). This leads to suppose that there is a value for EBCT after which the utilisation capacity of the GAC cannot be further improved. Moreover, they found that longer EBCTs have a positive effect on biological processes which take place within the grains of the GAC column. They reported that the EBCT increment promotes the substrate uptake by the biofilm developed on the grain surface in agreement with Terry and Summers (2018). They concluded that there is a minimum value of EBCT allowing OMP removal by sorption and that an EBCT increment leads to an enhanced removal of OMP and a better utilisation of the sorption capacity of the GAC column.

As to OMP influent concentration, Zietzschmann et al., (2016) found that, below the threshold of 50 μg/L, it did not impact the breakthrough curve of the investigated compound (benzotriazole, carbamazepine and primidone) which was instead impacted by the low molecular weight organics occurring in the wastewater fed to the GAC filter.

Finally, some attempts to investigate OMP removal by Langmuir and Freundlich isotherm adsorption curves (Nguyen et al., 2013b; Paredes et al., 2018) pointed out that there is no clear evidence of direct correlations between isotherm parameters and any of the governing parameters such as $\log D_{ow}$, number of hydrogen bond donor/acceptor groups, dipole moment or aromaticity ratio of the compounds (Nguyen et al., 2013b).

Behaviour of the GAC filter over time

GAC filter removal capacity decreases over time due to the granules increasing saturation by OMPs and DOM. OMP and DOM loads (mass/time) are crucial parameters affecting the expected operation time. Many authors investigated the GAC filter saturation process through the so called breakthrough profiles which report the ratio between OMP effluent concentration c_{eff} and its influent concentration c_{inf} compared to the EBV (Baresel et al., 2019; Nguyen et al., 2013b, 2012; Paredes et al., 2018). Rapid small-scale column tests (RSSCTs) represent a suitable option to determine breakthrough curves faster than pilot GAC columns. RSSCTs are a scaled-down version (by simple design equations) of pilot GAC beds allowing sorption studies to minimise removal via biodegradation (Crittenden et al., 1991; Zhiteneva et al., 2020).

Once adsorbed on AC, as discussed in Baresel et al., (2019) and Fundneider et al., (2021b), some OMPs (among them oxazepam, carbamazepine and diclofenac) may undergo biodegradation, leading to transformation products which may leave the AC surface, thus contributing to AC filter bioregeneration. They noted that for oxazepam it was clearly evident that after 25,000 EBV there was a sharp increment in the ratio c_{eff}/c_{inf}, followed by a consistent decrement due to GAC bioregeneration which allows new molecules of oxazepam to be sorbed. This fact is discussed in Benstoem et al., (2017) who found a good removal of adsorbable OMPs when DOM equilibrium in the GAC column is reached. Moreover, it was also observedthat when the carbon is completely saturated (at long operating times), some OMPs (for instance azithromycin) exhibit a modest but constant removal which could be ascribed to the biodegradation process still occurring within the BAC (Sbardella et al., 2018).

Figure 3.9 reports the removal efficiencies for the reviewed compounds as a function of EBV. It emerges that for some compounds, good removal occurs after a long operation time (really high EBV) for the reasons just discussed, but also for a low influent OMP and DOM load (Paredes et al., 2018; Sbardella et al., 2018).

Investigations on the GAC filter lifespan are in any case necessary in order to plan periodical regeneration or replacement of the exhausted AC (Nguyen et al., 2013a, 2013b, 2012).

Very recent studies remarked that the parameter EBV does not take into consideration the fluctuations in influent in terms of OMP concentration and load which are fundamental for the GAC column lifetime and the breakthrough point. In addition, a variation in the influent flow rate results in an EBCT variation. For these reasons, Fundneider et al., (2021a) propose the adsorbed DOC (mg DOC/g GAC) as the assessment parameter of GAC column performance as it is independent of the influent fluctuations of concentrations and flow rate, whereas Zietzschmann et al., (2016) propose the low molecular weight organics per mass of GAC (mg C/g GAC) and the UV_{254} per mass of GAC. According to Fundneider et al., (2021a) recommendations and guidelines will be available in the near future for the efficient design and operation of GAC columns acting as a PT in WWTP by DWA, the German Association for Water, Wastewater and Waste.

Other parameters influencing OMP removal in MBR coupled with AC

Temperature.

It is well known that an increment in temperature leads to a decrease in sorption of an OMP (Nam et al., 2014), whereas it enhances its biodegradation (Alvarino et al., 2018).

Addition of the coagulant $FeCl_3$

An addition of the coagulant (4–15 mg/L) to the secondary effluent already mixed with PAC may lead to an improvement in membrane permeability and to control the TMP increase (Löwenberg et al., 2014). It may also favour the separation of the PAC (Margot et al., 2013). In the patented fluidised PAC bed (CarboPlus©), acting as a PT following an attached biomass system, $FeCl_3$ was added (2.5 mg/L) to stabilise the PAC bed and prevent PAC leakage (Mailler et al., 2015). They found a slight enhancement in the removal of carbamazepine, beta-blockers and diclofenac (5% to 15%), probably due to coagulation of the colloidal fraction, a lower removal for sulfamethoxazole (-30%) and no change for lorazepam and bezafibrate.

Redox conditions

Once PAC is added, a biofilm may develop on its surface, with aerobic and anoxic zones, thus creating a gradient in redox potential. Over time, the anoxic zone develops and the community structure changes, favouring the species diversity (Zhang and Zhao, 2014). In particular, it was found that PAC addition promotes the development of nitrifiers which favour the degradation of some OMPs, mainly hormones and ibuprofen (Alvarino et al., 2018). Alvarino et al., (2016) found that denitrification might occur to some extent also during the aerobic phase. This was due to the growth of a biofilm on the added PAC able to adsorb nitrate ions. This implies the coexistence of anoxic and aerobic zones and thus the development of OMP degradation processes occurring under different redox conditions.

Type of membranes

The size of the membranes (MF and UF), equipped in MBRs, slightly influences the removals of OMPs. It was found that for diclofenac the removal was higher in the case of UF (Alvarino et al., 2017). This fact can be ascribed not to OMP size exclusion, but to its sorption on smaller particles retained by the cake layer grown against the membrane.

3.5.2. Influence of the AC on the MBR operation

Most of the investigations on MBR coupled with AC in recent years have dealt with the removal of macropollutants, membrane fouling, analysis of the operational conditions and factors influencing and enhancing OMP removal. This section briefly discusses the main issues related to macropollutant removal, membrane fouling mitigation and sludge property changes.

Effluent quality

The presence of AC favours the development of the biomass leading to a slightly higher concentration of MLVSS. This could be ascribed to the sorption of organic matter onto the AC surface in the reactor which is then available to microorganisms for their anabolic activities (Cho et al., 2011; Guo et al., 2008; Johir et al., 2013). As to organic matter (COD, BOD_5, DOC) and suspended solids, it was found that the presence of AC may slightly improve their already high (> 95%) removal in MBR (Guo et al., 2008; Johir et al., 2013). A DOC removal of 81% was observed in the MBR investigated by Gao et al., (2016) and a very low removal of aromatic compounds with unsaturated bonds which led to a 34% reduction in UV_{254}. The addition of 1 g/L of PAC in the bioreactor not only incremented the DOC removal up to 91%, but strongly increased the removal of UV_{254} up to 83%. This was explained with the fact that organic compounds, both recalcitrant and easily degradable ones, are directly adsorbed on PAC, then they gather around the bacteria favouring the biodegradation of the recalcitrant compounds. Decrease in UV_{254} is therefore related to the adsorption of aromatic rings, both from OMPs and DOM constituents of wastewater (Altmann et al., 2014a; Streicher et al., 2016). As to nitrogen removal, studies remarked that PAC addition may lead to an increment of around 10% (Echevarría et al., 2019; Serrano et al., 2011)(Serrano et al., 2011) due to the formation and growth of a biofilm layer on the adsorbent surface that creates anoxic zones enabling denitrification, as well as an enhancement of nitrifiers (Alvarino et al., 2018). As to P, the observed removal efficiencies in MBR are low to moderate and do not significantly change with the presence of AC (Johir et al., 2013). It was found that the addition of 20 g/L of PAC may promote the development and growth of polyphosphate-accumulating-organisms (PAOs) which led to a 10% increment in the removal of total phosphorus from the wastewater (Asif et al., 2020). To sum up, the different removals achieved may be ascribed to a change in the composition of the mixed liquor (Pan et al., 2016).

Mitigation of the membrane fouling

Most of the studies have dealt with and are still dealing with the mitigation on the membrane fouling, one of the most critical problems to face and manage with membrane technologies (Iorhemen et al., 2017; Zhang et al., 2019). According to the nature of foulants, fouling can be divided into: *bio-fouling* related to the attached microorganisms on the membrane surface; *organic fouling* due to polysaccharides,

proteins, colloidal and humic substances, and bio-polymers and *inorganic fouling* caused by salts, scalants, metal oxides and other inorganic substances (Gkotsis et al., 2020). Deposition and attachment of foulants on the membrane surface lead to an increment in hydraulic resistance. As a result, the transmembrane pressure (TMP) increases and the flux through the membrane declines (Woo et al., 2016). Curves of transmembrane pressure (TMP) *versus* operation time shows a first stage in which the membrane does not require cleaning and TMP slightly increases, then in the second stage a sudden increase occurs. Jamal Khan et al., (2012) and Lin et al., (2011) found that the addition of 0.75 – 1 g/L of PAC approximately doubles the duration of the first stage, whereas Zhang et al., (2019) suggest 2 g/L as the optimum dosage of PAC as a mitigation strategy of membrane fouling control. In the field of urban wastewater treatment, the principal fouling which may occur is organic fouling. In order to avoid fouling, it is necessary to retain foulants with adequate pre-treatments that are able to reduce their content in the water under treatment.

As described previously, once AC is added in the biological tank, microorganisms and DOM are retained on its surface: their lower concentrations in the liquid phase reduce the membrane organic fouling and biofouling (Gao et al., 2016). Another positive effect of AC addition in the MBR is that it leads to an enhancement of the sludge floc strength (as will be discussed later on). As a consequence, the strong floc structure with incorporated AC will release fewer foulants (soluble COD, proteins and polysaccharides, Ca^{2+}, Mg^{2+}) and thus will reduce the formation of the gel-layer on the membrane (Johir et al., 2011; Remy et al., 2010). The velocity with which the membrane fouls depends on the TOC concentration in the wastewater; the *membrane flux*, and the added AC size (Ng et al., 2013). They found that membrane fouling prevention can be optimised by using: (i) fine rather than coarse PAC as it better reduces the TOC in the bulk phase; and (ii) relatively short SRTs (around 10 days), as they favour organic matter adsorption. At the same time, in order to reduce AC particle deposition, flux must be carefully set also on the basis of the aeration system used to detach foulants.

Changes in sludge properties after the PAC addition

PAC addition in the bioreactor leads to an enlargement of the floc size: the average sludge particle size was found around 90 μm in an MBR (70% in the range 10–100 μm) and 128 μm in an MBR + PAC (37% in the same range) (Pan et al., 2016). The sludge flocs enlarge because added PAC neutralises their negative surface charge, causing them to agglomerate (Zhang et al., 2017). The larger flocs increase their strength and are able to withstand greater impacts during aeration (Pan et al., 2016). They lead to a low content of SMP and/or EPS in the mixed liquor (Pan et al., 2016; Remy et al., 2010; Zhang and Zhao, 2014). PAC addition also leads to a change in the chemical composition of the sludge floc which results in a different sorption potential (Yang et al., 2012; Yu et al., 2014). It was also found that the PAC-embedded sludge floc exhibited a higher sorption capacity for recalcitrant aromatic compounds, resulting in a reduction in UV_{254} (Gao et al., 2016; Pan et al., 2016).

The sludge with incorporated PAC has better settling characteristics since less compressible flocs are formed. In this context, Johir et al., (2013) and Pan et al., (2016) found that the sludge volume index (SVI) for MBR sludge was around 90–110 mL/g and in the case of MBR+AC, it was reduced to 50–70 mL/g. The presence of PAC within a sludge floc leads to a more porous cake layer against the membrane compared to the absence of PAC: a higher volume percentage of particles was found in the range 300–700 μm in the case of MBR+PAC than in MBR operating with the same MLVSS (Jamal Khan et al., 2012; Li et al., 2011).

3.6 Conclusive considerations and need for further research

The current overview shows the effective contribution of AC in (advanced) biological wastewater treatment in enhancing the removal of many OMPs and at the same time the improvement of MBR. Collected results are strictly related to OMP nature, AC characteristics and the presence of DOM in wastewater and the complex interactions among these three actors define the OMP removal efficiencies. Although there is not a well-defined PAC dose to add in the MBR to reach a minimum removal for all the OMPs, 80% of removal was achieved for most of the tested compounds with a PAC concentration of 0.1 g/L. OMP removal efficiencies show a greater variability when PAC is in the PT in comparison to when it is added in the bioreactor. Moreover, it emerges that the effect of the presence of DOM is more evident in the case of PAC as a PT. OMP removal efficiency in the GAC unit working as a PT is highly dependent on MBR performance. For compounds with a moderate OMP removal efficiency in MBR, GAC can exhibit fairly constant removal until its saturation, otherwise it may adapt to the loading fluctuations in the column and guarantee fairly constant effluent quality. If GAC becomes BAC, biodegradable compounds retained on its surface may still maintain a good removal efficiency at long operation times due to biodegradation processes in biofilm. In the case of OMPs whose main removal mechanism is adsorption, GAC column bioregeneration is essential in order to allow a high and continuous OMP removal.

A loss in AC *potential* adsorption capacity occurs due to its progressive saturation and its removal from the system through excess sludge withdrawal or the retentate from the membrane PT unit. PAC addition (replenishment) is thus necessary to maintain its desired concentration in the tank.

AC influences the MBR operation mainly by changing the composition of the mixed liquor. The concentration of organic compounds in the liquid phase of the biological tank is reduced by the attachment of DOM onto the AC surface. The presence of AC in the floc increases its strength and improves its settling characteristics. The cake layer against the membrane becomes more porous than when AC is absent. AC added in the bioreactor prolongs MBR operation by mitigating membrane fouling.

Recent studies proposed to analyse OMP removal as a function of the DOC adsorbed on the AC (mg DOC/mg AC) as it better reflects the saturation level of the AC present in the studied system over time.

Further studies are necessary to better investigate the interactions between DOM and the different OMPs with regard to the characteristics of DOM (biopolymers, hydrophobic molecules) and the role played by inorganic ions. Moreover, the contributions due to adsorption and biodegradation to OMP removal may be identified under controlled conditions, by comparing the performance of AC biologically inactivated with a BAC. Values of biological constant rate k_{biol} when AC is added in MBR could be useful to predict the potential enhancement of the

biodegradation of selected OMPs as well as K_d values showing OMP sorption potential when PAC is added in MBR or AC unit acting as a PT. Their knowledge will make it possible to understand which removal pathway mostly contributes to the removal of a specific compound, despite the fact a multiparametric equation is not available to predict the behaviour of a compound in such a complex system.

Analysis of the performance of specific configurations should also include the monitoring of UV_{254} which quickly provides an indirect measure of the occurrence of many low molecular weight organics, becoming thus a reliable surrogate of this group of compounds belonging to the DOM.

Finally, investigations on real wastewater are necessary to better understand the removal mechanisms with regard to compounds of great concern or which could represent a group of compounds characterised by a similar behaviour in hybrid MBRs like those coupled with AC.

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Chapter 4

REMOVAL OF MICROPOLLUTANTS USING A MEMBRANE BIOREACTOR COUPLED WITH POWDERED ACTIVATED CARBON — A STATISTICAL ANALYSIS APPROACH

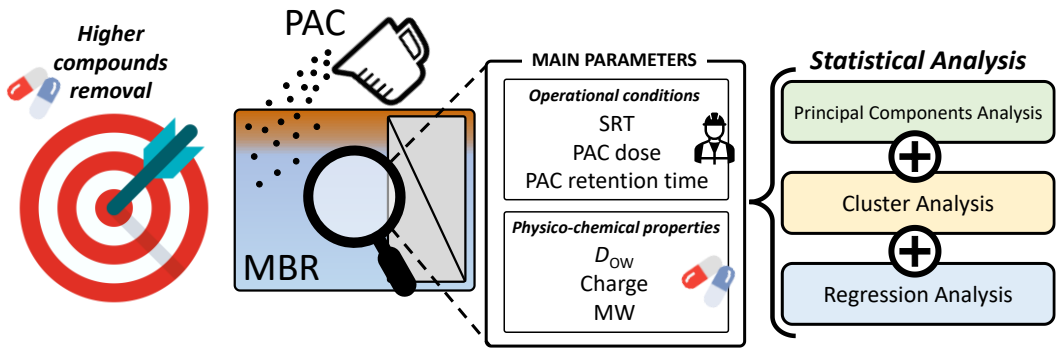
TABLE OF CONTENTS

Summary of the chapter, in a nutshell

- A meta-analysis based on statistic analysis was carried out to compare and discuss the results published in scientific literature regarding removal efficiencies of OMPs in wastewater treated in a MBR coupled to PAC.
- The statistical analyses, mainly based on exploratory methods and regression analysis were used in an attempt to determine which operational parameters and compound physicochemical properties influence the most the removal of OMPs from wastewater.
- The results show that the charge and logD_{ow} of the compound are the parameters that seem to play the most important role on OMP removal in MBR coupled to PAC.

The results of this chapter are part of a manuscript published with the title: *Removal of micropollutants using a membrane bioreactor coupled with powdered activated carbon – A statistical analysis approach* by Marina Gutiérrez, Andrea Ghirardini, Michela Borghesi, Stefano Bonnini, Dragana Mutavdžić Pavlović and Paola Verlicchi, which can be found in Appendix 2.

Graphical abstract



4.1 Introduction

In the previous chapter, the enhancement of the removal achieved for a multitude of OMPs by the addition of AC to the MBR or in the case of a specific post-treatment was presented and discussed. Limiting the attention to PAC added in the bioreactor, in the cited study, the removal efficiencies were related to different factors: OMP properties, AC characteristics, PAC addition point, duration, operational conditions (HRT and SRT), and characteristics of the wastewater under treatment (mainly DOM). It was remarked that for weakly charged substances, the lipophilicity of a compound plays a crucial role in its adsorption to the PAC surface, while in the case of charged ones also the electrostatic interactions between the PAC surface and the functional groups become relevant (Alvarino et al., 2017). Furthermore, the DOM present in the aeration tank may likely interfere with the PAC and the occurring OMPs leading to either direct competition with the OMPs for the adsorption sites of PAC or its pores constriction (Delgado et al., 2012). As a result, the parameters involved in the phenomenon are manifold.

Considering the compounds, it is worth mentioning (i) D_{ow}, which provides an indication of the lipophilicity of a substance, (ii) pK_a, (iii) the charge and the presence of specific functional groups for its electrostatics affinities, and (iv) the molecular weight (MW) and size, which give a view of the potential to be intercepted by the PAC pores (Kovalova et al., 2013).Otherwise, considering the adsorbent, the properties that mainly influence the fate of OMPs in MBR coupled with PAC regard (i) the characteristics of the adopted PAC (e.g., pore size and texture), (ii) the addition quantity and mode (PAC dosage, PAC retention time, and dosage point in the reactor), and (iii) the reactor operational parameters (e.g., redox conditions, pH, temperature, HRT, SRT, MLSS) (Alvarino et al., 2018a; Mailler et al., 2016).

The study, which includes 64 peer-reviewed papers published between 2009 and 2020, makes it evident the complexity of the *phenomena* under study. Furthermore, it emerged that the different operational conditions and wastewater characteristics adopted in the past investigations sometimes led to different, and in some cases difficult to coincide, findings. As a result, a more rigorous approach to elaborate and interpret the collected data is needed to identify the main parameters affecting the removal of OMPs in MBR coupled with PAC. This could be useful in designing such a hybrid system or in optimising its performances.

In this context, the main operational parameters (i.e., PAC dosage, PAC retention time, and SRT) and compounds physicochemical properties (i.e., logD_{ow}, charge, and MW) were selected on the basis of a dedicated screening step and then an attempt to clarify their influence on the removal of OMPs from wastewater during its treatment were carried out. To this end, a statistical analysis, mainly based on exploratory methods (cluster analysis and principal component analysis) and regression analysis, was carried out to compare and discuss the different results published in the scientific literature included in the cited review article.

4.2 Material and Methods

4.2.1. Characteristics of the adopted dataset

The dataset adopted in this work was retrieved by Gutiérrez et al., (2021) and refers only to the data (observations) provided by 10 studies investigating the fate of OMPs in an MBR coupled with PAC. Among these, only the observations in which all the parameters necessary for this study are available (i.e., SRT, PAC dosage, PAC retention time, D_{ow}, charge, MW) were maintained.

The resulting dataset includes 146 observations referring to 37 compounds (of which 6 non-steroidal anti-inflammatories drugs (NSAID), 7 antibacterial, 1 antiseptic, 5 hormones, 1 lipid regulator, 1 non-ionic surfactant, 2 pesticides, 4 psychiatric drugs, 2 stimulants, 3 synthetic musks, and 5 others uncategorised compounds) and collected from 7 studies namely, Alvarino et al., (2016); Alvarino et al., (2017), Asif et al., (2020), Li et al., (2011); Nguyen et al., (2013); Serrano et al., (2011) and Yu et al., (2014).

All the data included in the refined dataset refer to laboratory-scale plants, with the exception of the 9 observations reported by Serrano et al., (2011) which refer to a pilot-scale study. All the experimental reactors were fed with synthetic wastewater, made by the addition of specific compounds in water to simulate the matrix effects expected in real wastewater. Its compositions in the different studies were provided as reported in Gutiérrez et al., (2021).

The duration of the investigations ranges between 65 days (Asif et al., 2020) and 306 days (Nguyen et al., 2013). The configurations of the reactors adopted in the selected studies are schematically reported in Table 4.1. Here, in 4 out of 7 studies (providing a total of 117 observations) the membrane unit is placed in the biological reactor, while in the other 3 studies (29 observations) the membrane unit is in a separate tank (Table 4.1). The variability ranges of the operational conditions adopted in the studies are reported in Table 4.2.

On the basis of a dedicated screening of data availability and heterogeneity, six parameters were chosen. Their influence on the OMP removal mechanism during the treatment in MBR coupled with PAC is well known (Gutiérrez et al., 2021).

Table 4.1. The two configurations of MBR coupled with PAC together with the corresponding references included in this study.

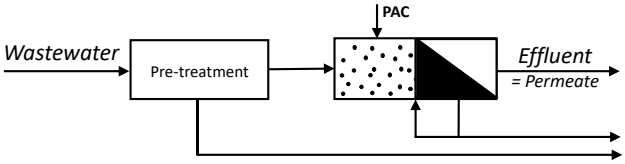
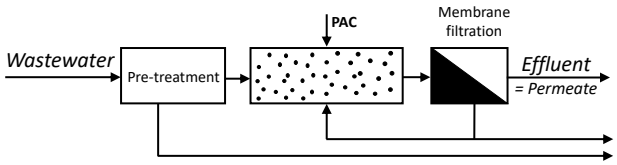
Configuration scheme	Description
	Submerged MBR: The membrane is placed in the biological reactor, where PAC is added.
Referring studies (num. of observations): *Alvarino et al., (2017) (60); Li et al., (2011) (7); Nguyen et al., (2013) (44); Yu et al., (2014) (6)*	
	Side-stream MBR: The membrane is placed in a separated tank. PAC is added in the biological reactor.
Referring studies (num. of observations): *Alvarino et al.,(2016) (13); Asif et al., (2020) (7); Serrano et al., (2011) (9)*	

Table 4.2. Selected operational conditions and corresponding values in the included investigations.

References (# observation)→ Operational conditions ↓	Alvarino et al. (2016) (13)	Alvarino et al. (2017) (60)	Asif et al., (2020) (7)	Li et al., (2011) (7)	Nguyen et al., (2013) (44)	Serrano et al., (2011) (9)	Yu et al., (2014) (6)
SRT (d)	118	200	30	92	100	288	30
PAC dosage (g/L)	1	0.25 – 0.75	20	0.1 – 1	0.1 – 0.5	1	0.03 – 0.1
PAC ret. time (d)	118	35 – 105	65	28 – 60	37 – 63	86	88 – 246

4.2.2. Statistic tools

Principal Component Analysis

A Principal Component Analysis (PCA) was applied in order to reduce the dimensionality of the dataset. The application of PCA aims to reduce the number of variables by eliminating a small proportion of data variability. PCA transforms the original correlated observed variables into new uncorrelated variables (Principal Components), with minimum loss of original information represented by the observed variability. The principal components are linear combinations of the original observed variables. The first component is the linear combination that explains most of the variance. It corresponds to the dimension along which the dispersion of data is maximum. The second component is the linear combination that explains the maximum variance among those corresponding to orthogonal directions with respect to the first component. The subsequent components are detected in a similar way, considering orthogonal directions and maximizing the variance. Hence,

the resulting PCs are uncorrelated themselves and represent a new set of variables, related to the original variables by a defined linear combination (Lever et al., 2017). The loadings are the correlations between principal components and original variables. They correspond to the weights of the linear combinations explaining the variables by the components. The scores of the principal components map the different samples in the new dimensional space of the principal components facilitating the investigation of the different relationships between the variables (Vasilaki et al., 2018).
In this study, PCA was performed using the R software (Beiras, 2018). Then, Varimax orthogonal rotation was applied for PCA axes and for reducing the contribution of the less relevant parameters within each PC (Jolliffe and Cadima, 2016).

Cluster analysis

Clustering techniques are widely applied in order to identify and group underlying patterns in high dimensional datasets. It is not easy to provide a crisp categorization of them, nevertheless they may be classified into four classes: partitioning, hierarchical, density-based, and grid methods. Cluster Analysis (CA) aims to group datapoints (or equivalently statistical units) into homogeneous groups (clusters). Therefore, in our study it was used to analyse the similarities among the different observations and gather potential relationships between them and their removal. The latter were then better investigated with the regression analysis.
In this study, CA was carried out adopting the K-means method which is one algorithm of the partitioning methods. *K*-means is a partitional clustering algorithm which creates a defined number (K) of groups (also called clusters, c_k) of datapoints x_i. The within-cluster sum of squares S between datapoints and the cluster empirical mean (i.e., the centroid, μ_k, which measures the within-cluster heterogeneity) between the datapoints-is minimised (Hennig et al., 2015).

$$S = \min \sum_{k=1}^{K} \sum_{x_i \in c_k} \|x_i - \mu_k\|^2 \qquad \text{eq. 1}$$

In particular, this algorithm begins by fixing the number of clusters K and their corresponding centroids. Then, each statistical unit is included into the cluster with the nearest centroid. Once all the units have been classified, every centroid is recalculated as the value providing the lowest distance to all the members of its class. As the centroids have changed, the distance between each datum and the centroids must be calculated again so that units are reassigned to the closest cluster. The process will be repeated until no improvement in the classification process is obtained (de la Vega and Jaramillo-Morán, 2018).
As this algorithm needs the number of clusters to be fixed prior to starting the clustering process, in some cases several possible K values must be tested and evaluated to find out which provides the best classification. The number of clusters

must not be too high in order to guarantee that the classification obtained is both useful and meaningful (de la Vega and Jaramillo-Morán, 2018).
The number of clusters (*K*) which better describes the similarities within the dataset is often tricky to evaluate and a predefined criterion for its evaluation does not exist (Jain, 2010). In this work, the well known Elbow and Silhouette methods were adopted to overcome this issue (Kassambara, 2017). The first was used to graphically identify a range of *K* which may be adopted for the analysis. In the former method, the sum of squares for each possible number of clusters is calculated and plotted, in order to detect an evident slope change point (a bend) that corresponds to the optimal number of clusters. The latter method provides a measure of the similarity of each unit with those inside its own cluster compared with those outside the cluster. Now, if the silhouette of each datum inside a cluster is represented in decreasing order, for all the clusters a graphic representation of the quality of the allocation of data inside them is provided. The mean value of the silhouettes for all the clusters will provide a measure of the quality of the clustering carried out, so that the higher the value, the better the classification. Therefore, the different clustering configurations were compared based on their average Silhouette value (Sil_{ave}) in order to assess the consistency of the solutions proposed by the graphical interpretation of the Elbow method results. Before the analysis, the dataset values were standardized to reduce outliers which may drive the grouping (Mohamad and Usman, 2013).

Regression analysis

Finally, the regression analysis was used to investigate the influence of the selected parameters on the removal of OMPs in a MBR coupled with PAC.
The regression analysis was conducted to find a possible relationship between average removal (response of the model) and some explanatory variables in order to predict the values of the response. The function *lm* in the R software environment was used to carry out the analysis, with a significance level $\alpha = 0.05$.
In the current study, the analysis was carried out considering two different sub-datasets. The first one included all the observations except the seven provided by the study of Asif et al., (2020), which were considered as outliers for the especially high PAC dosage adopted (20 g/L, compared to 0.1 to 1 g/L of the other studies). In this context, although the influence of PAC is not proportional to the added dosage, the especially high dosage may result in different *phenomena* in the reactor (e.g., changes in the rheological properties of the mixed liquor) which make the experiment hardly comparable to the others. Accordingly, the differences between these seven observations and the others were observed also in the exploratory data analysis.
Otherwise, the regression analysis was conducted considering only the observations related to negatively charged and neutral compounds, in order to investigate their expected particular behaviour in the reactor, as suggested by different studies (as Alves et al., (2018), Kovalova et al., (2013) and Mailler et al., (2016), to name just a few). A variable was considered significantly correlated to the removal when *p*-value resulted less than 0.05.

4.3 Results

4.3.1. Principal Component Analysis

The results of the PCA in terms of loadings of the considered variables are reported in Table 4.3, while biplots of the first 4 principal components are shown in Figure 4.1. These biplots of the PCs two by two were used in order to visualize the combined behaviour of significant variables that affect the system. The biplots enable the simultaneous visualization of the variables' loadings of the principal components and the scores of the principal components (Vasilaki et al., 2018).

The dimensionality of the dataset was reduced to 4 principal components (hereinafter PC1, PC2, PC3, and PC4) explaining the 87% of the total cumulative variance (27% up to PC1, 50% up to PC2, 70% up to PC3 and 87% up to PC4). For PC1, the highest loadings were exhibited by charge (0.901), followed by MW (0.804). As a result, high positive values of PC1 in Figure 4.1 represent high values of the two compounds' physicochemical properties charge and MW. SRT and the opposite of PAC dosage are mostly represented in PC2 (0.844 and -0.788, respectively) which mainly describes the variation of the operational conditions under study, as no considerable values of physicochemical properties-related loadings emerged (Table 4.3). High positive values of PC2 in Figure 4.1 correspond to high values of SRT, while negative values of PC2 represent high PAC dosage. PC3 and PC4 mainly represent the operational condition PAC retention time (0.962) and the physicochemical property D_{ow} (0.962), respectively. These two variables appear to be represented only by the respective principal components, with negligible loadings in the others (Table 4.3).

Table 4.3. Detail of the PCA loadings. Numbers in parenthesis represent the percentage of variance explained by each component.

Variable	PC1 (27%)	PC2 (23%)	PC3 (19%)	PC4 (18%)
SRT	0.253	0.844	-0.112	-0.147
PAC dosage	0.164	-0.788	-0.127	-0.375
PAC retention time	<0.10	<0.10	0.962	<0.10
logD_{ow}	<0.10	<0.10	<0.10	0.962
Charge	0.901	<0.10	-0.131	0.253
MW	0.852	0.126	0.239	-0.137

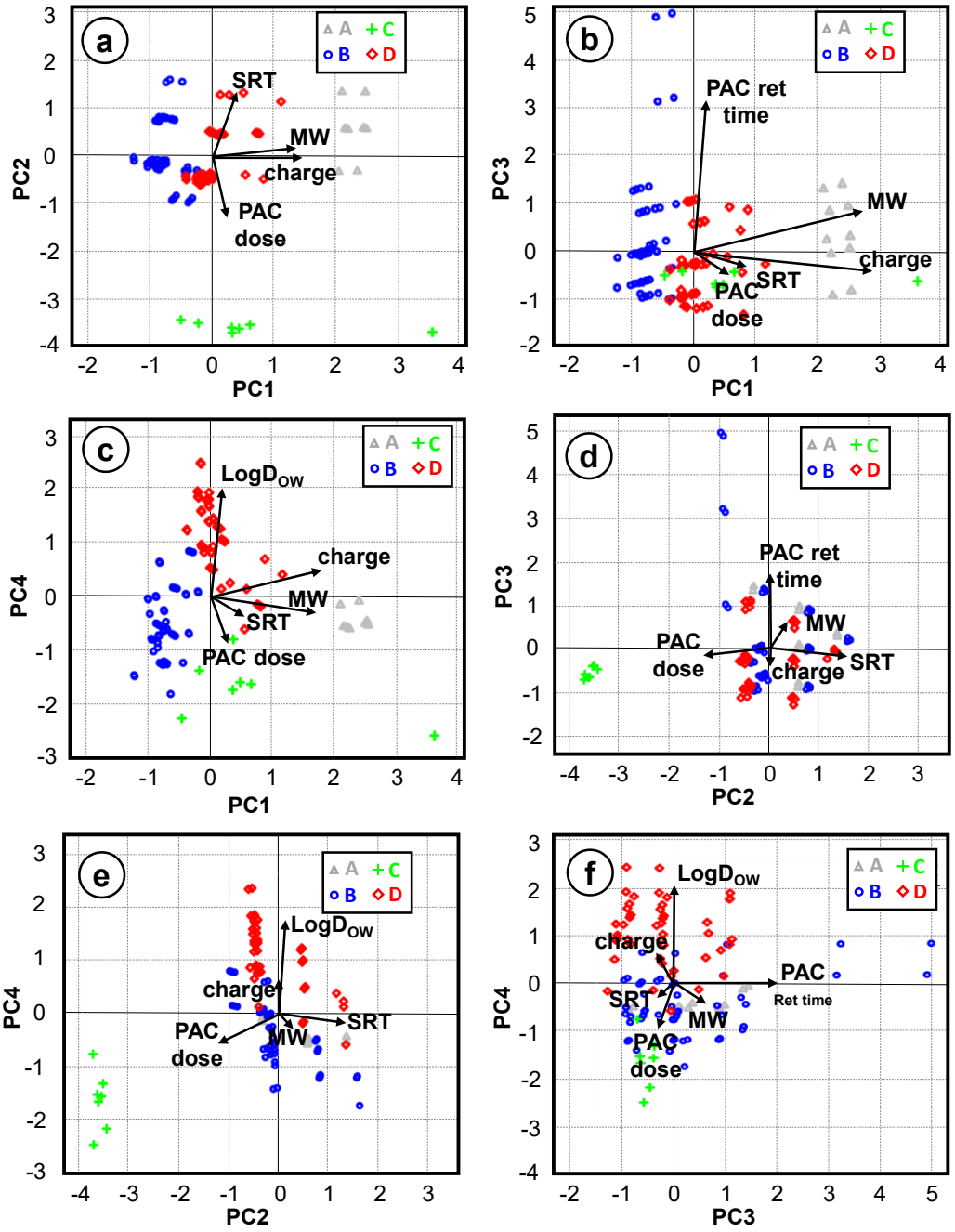


Figure 4.1. Biplots of the principal components, with representation of the datapoints included in each cluster.

4.3.2. Cluster analysis

The results of the elbow method indicate four as the optimal number of clusters. The centroids of the clusters obtained in terms of SRT, PAC dosage, PAC retention time, logD_{ow}, charge, and MW, together with the number of observations included in each cluster and their corresponding average removal efficiency after the treatment are reported in Table 4.4.

Table 4.4. Characteristics of the clusters, in terms of number of observations included in each cluster, average removal efficiency, and centroids of each of the six selected variables.

Cluster ID	Number of observations included	Average removal [%]	SRT [d]	PAC dosage [g/L]	PAC retention time [d]	logD_{ow}	Charge	MW
A	16	97.9	200.7	0.6	78.0	1.39	0.95	785.5
B	65	84.4	139.7	0.4	73.9	0.69	-0.90	261.5
C	7	97.4	30.0	20.0	65.0	-0.56	-0.07	286.3
D	58	91.0	156.1	0.5	67.8	3.35	0.12	261.8

As shown in Table 4.5, it emerges that while clusters A, B, and D include datapoints from various studies, cluster C grouped the observations of the only investigation conducted by Asif et al., (2020). This can be explained by the fact that cluster C grouped the observations characterized by an extremely high value of PAC dosage (Table 4.4), of which the centroid shows the highest value (20 g/L) compared to the other clusters in which the centroids are centred around a similar value of mean PAC dosage (0.4 to 0.6 g/L). This reflects the particular experimental features of the investigation conducted by Asif et al. (2020), in which the adopted PAC dosage (20 g/L) was considerably higher than those added in the other studies (0.03 to 1 g/L, as shown in Table 4.2). For this reason, the relevant distance between the observations included in cluster C and all the others points in Figure 4.1a, 4.1d, and 4.1e is not surprising, for the high relevance of PAC dosage in PC2. Furthermore, cluster C also exhibited the lowest average value of SRT (30 days). Indeed, with the exception of the 6 observations by Yu et al., (2014) referring to PFOA and PFOS (with SRT of 30 days), the experiment conducted by Asif et al., (2020) was the only one in which an SRT lower than 92 days was adopted (as better described below). The combination of different PAC dosage and SRT make it an outlier, in terms of operational conditions.

Table 4.5. Studies and compounds included in each cluster. Numbers of observations of each study included in the cluster are reported in brackets.

	Cluster A (16 observations)	**Cluster B (65 observations)**	**Cluster C (7 observations)**	**Cluster D (58 observations)**
Studies included → / **Compounds ↓**	- Alvarino et al. (2016) (2) - Alvarino et al. (2017) (12) - Serrano et al. (2011) (2)	- Alvarino et al. (2016) (4) - Alvarino et al. (2017) (24) - Li et al. (2011) (4) - Nguyen et al. (2013) (24) - Serrano et al. (2011) (3) - Yu et al. (2014) (6)	- Asif et al. (2020) (7)	- Alvarino et al. (2016) (7) - Alvarino et al. (2017) (24) - Li et al. (2011) (3) - Nguyen et al. (2013) (20) - Serrano et al. (2011) (4)
4-n-nonylphenol				2
4-tert-butylphenol				2
4-tert-octylphenol				2
17β-estradiol				2
17β-estradiol-acetate		2		
17β-ethinylestradiol				8
Azithromycin			1	
Bisphenol A				2
Caffeine			1	
Carbamazepine				13
Celestolide				1
Diazepam				2
Diclofenac		10		
Erythromycin	8			
Estriol				2
Estrone				8
Fenoprop		2		
Fluoxetine				2
Galaxolide				1
Gemfibrozil		2		
Ibuprofen		10		
Ketoprofen		2		
Metronidazole		2		
Naproxen		10	1	
Ofloxacin			1	
Paracetamol		2	1	
Pentachlorophenol		2		
PFOA		3		
PFOS		3		
Primidone		2		
Roxithromycin	8			
Salicylic acid		2	1	
Sulfamethoxazole		11		
Theophylline			1	
Tonalide				1
Triclosan				2
Trimethoprim				8

The other clusters (A, B, and D) are characterised by a greater heterogeneity in terms of included studies and compounds as well as a higher number of included observations (Table 4.5). Clusters A and B are characterised by the highest and the lowest average charge value (0.9 and –0.9, respectively). In particular, cluster B includes observations regarding mainly anionic compounds, grouping the majority of them (59 out of 62) among the whole dataset. In detail, the datapoints grouped in B refer to the anionics sulfamethoxazole (11 values), diclofenac (10), ibuprofen (10), naproxen (10), PFOA (3), PFOS (3), 17β-estradiol-acetate (2), fenoprop (2), gemfibrozil (2), ketoprofen (2), pentachlorophenol (2), salicylic acid (2) but also the neutrals metronidazole (2), primidone (2), and paracetamol (2). On the contrary, cluster A grouped only cationic substances, including erythromycin (8 values) and roxithromycin (8), which represent the majority of cationic substances-related observations in the dataset (16 out of 27). Finally, cluster D mainly grouped neutral or zwitterionic compounds (48 observations out of 57 of the whole dataset), with the only exception of the neutral/cationic trimethoprim (8 values), and the cationic fluoxetine (2). The compounds included in D refer to carbamazepine (13), 17β-ethinylestradiol (8), estrone (8), 4-n-nonylphenol (2), 4-tert-butylphenol (2), 4-tert-octylphenol (2), 17β-estradiol (2), bisphenol A (2), diazepam (2), estriol (2), triclosan (2), celestolide (1), galaxolide (1), and tonalide (1) (Table 4.4). This cluster is not only characterised by the neutral average charge, but also for the highest logD_{ow} (= 3.3, Table 4.4), which drove its partitioning. The stratification of charge is clearly visible in Figure 4.1a, 4.1b, and 4.1c, in which PC1 is displayed. It is also interesting to observe that for similar values of charge, cluster B and D are well differentiated by their logD_{ow} values represented by PC4 (Figure 4.1c).

4.3.3. Regression analysis

The results of the regression analysis are reported in Table 4.6 and Table 4.7.
It emerged that, considering the dataset in which all the observations except the seven provided by Asif et al., (2020) were included (for a total of 139 observations), the removal of OMPs in MBR coupled with PAC was significantly correlated to their charge (p = 0.038 < 0.05). Here, also logD_{ow} appears to be important in the *phenomenon*, albeit the corresponding coefficient estimate appears weakly significant (p = 0.069 < 0.10). According to the coefficients' estimates, a +1 increase in logD_{ow} determines a variation of +2.23 in average removal, whilst a +1 variation in charge corresponds to a change equal to +3.13 in the response. No significance was observed for MW and all the operational conditions-related variables (p > 0.1) (Table 4.7).
The results of the regression analysis conducted considering the dataset in which the 123 observations of cluster B and D revealed that, when excluding the charge variable, the logD_{ow} has a strongly significant effect on the removal (p < 0.001), and MW gains importance in the *phenomenon*, although its regression coefficient is weakly significant (p = 0.065<0.10). The expected variation of removal when logD_{ow} and MW increase by one is +4.16 and -7.36 respectively. None of the three operational

condition-related variables resulted to significantly affect the removal of OMPs in MBR coupled with PAC ($p > 0.1$).

However, given the small values of the coefficients of determination, the results of the regression analysis should be evaluated prudently because the goodness-of-fit of the model is low. This may be because other explanatory variables not included in the model could be more important than those considered as predictors of removal. Another possible reason for the low goodness-of-fit could be the non-linear relationship between the variables under study and the consequent wrong specification of the model.

Table 4.6. Coefficients of the regression analysis for the dataset including the all the observations with the exception of the 7 provided by Asif et al. (2020). Residual std. error: 11.87 on 132 degrees of freedom. Multiple R-squared: 0.1677; adjusted R-squared: 0.1299. F-statistics: 4.433 on 6 and 132 DF, p-value: 0.0004063

Variable	Estimate	Std. Error	t value	Pr(>|t|)
intercept	93.7872	3.4320	27.327	$<2\cdot10^{-16}$***
x123 SRT	-0.7731	1.2224	-0.632	0.5282
x123 PAC ret time	-0.3360	1.0331	-0.325	0.7455
x123 PAC dose	23.0931	14.5542	1.587	0.1150
x123 logD_{ow}	2.2281	1.2168	1.831	0.0693*
x123 charge	3.1386	1.4969	2.097	0.0379**
x123 MW	1.1031	1.3666	0.807	0.4210

*Significance codes: *** = 0.01; ** = 0.05; * = 0.10*

Table 4.7. Coefficients of the regression analysis for the dataset including the all the observations related to cluster B and D. Residual std. error: 12.39 on 117 degrees of freedom. Multiple R-squared: 0.1354; adjusted R-squared: 0.0984. F-statistics: 3.663 on 5 and 117 DF, p-value: 0.004083

Variable	Estimate	Std. Error	t value	Pr(>|t|)
intercept	90.4219	4.1447	21.816	$<2\cdot10^{-16}$***
X23 SRT	-0.9713	1.3277	-0.732	0.465931
x23 PAC ret time	0.6618	1.2317	0.537	0.592103
x23 PAC dose	25.4606	16.0979	1.582	0.116438
x23 logD_{ow}	4.1640	1.1287	3.869	0.000343***
x23 MW	-7.3643	3.9616	-1.859	0.065551*

*Significance codes: *** = 0.01; ** = 0.05; * = 0.10*

4.4 Discussion

4.4.1. Influence of the operational conditions

Taken together, the collected results provide interesting insights regarding the main factors involved in the removal of OMPs during wastewater treatment by MBR coupled with PAC.

The high average removal efficiency of the datapoints grouped in cluster C (97%) suggests that PAC dosage may play an important role in OMPs removal, especially in the case of particularly high quantity added in the bioreactor (20 g/L, as in the case of Asif et al., (2020). Indeed, it is well known that the presence of PAC improves the physicochemical properties of the sludge (i.e., it promotes floc growth and structure strength) entailing an increased adsorption and, potentially, biodegradation (Alvarino et al., 2020; Hu et al., 2015). On the other hand, the variability in the average removal obtained by more commonly adopted values of PAC dosages (0.03 to 1 g/L) ranging between 84% (cluster B) to 98% (cluster A) seems to downsize the relevance of such a factor.

Moreover, the results of the regression analysis conducted taking into account all the datapoints with the exception of those of cluster C, considered as outliers, showed that selected PAC dosages do not significantly influence the removal of OMPs during the treatment (p = 0.115, Table 4.7). This result may be due to different factors. Although different studies highlighted that PAC dosage is a crucial operational condition with respect to OMPs removal (among them Alvarino et al., (2017) and Li et al., (2011), its activity may be influenced by (i) PAC addition timetable (and therefore PAC aging in the reactor); (ii) wastewater matrix effect (as it affects OMPs saturation rate and the floc biological activity (Alvarino et al., 2018b; Paredes et al., 2018); (iii) characteristics of the selected PAC (mainly: pores size, specific surface area, bulk density (Alves et al., 2018; Mailler et al., 2016); and (iv) OMPs physicochemical characteristics (Alvarino et al., 2018b). Furthermore, despite not found in the selected studies, also (v) PAC potential losses due to excess sludge withdrawal, and vi) PAC addition point (e.g., in the anoxic tank as done by Remy et al., (2012), or in the aerobic one as Asif et al., (2020) and Echevarría et al., (2019), to name just a few), may influence the sorption on PAC surface. Therefore, the sum of all these factors makes it difficult to statistically discuss the significance of PAC dosage on OMP removal efficiency.

Nevertheless, dedicated works (among them Çeçen and Aktas (2011), Loos et al., (2013), Yu et al., (2014)) highlighted that strongly limiting the influence of the six abovementioned factors, the positive influence of PAC dosage becomes statistically significant. In this regard, Mailler et al., (2016) observed that the positive correlation between PAC dosage and removal efficiency follows a logarithmic pattern. Therefore, the addition of particularly high dosages of PAC may not entail proportional benefits. In accordance with the findings of different studies (among them Alvarino et al., (2017), Löwenberg et al., (2014) and Wei et al., (2016), PAC retention time appeared

to be non-significantly correlated to the removal of the investigated OMPs in both the regression analysis conducted (p = 0.745 considering the whole dataset with the exception of cluster C, and p = 0.592 considering only neutral and anionic substances of clusters B and D). Briefly, once PAC is added in the bioreactor, its porous surface is entirely available, while after a period of time, its active sites start being occupied by the sorbed OMPs and the competitor DOM, present in the mixed liquor. This leads to a decrement of PAC potential sorption capacity, but at the same time, it provides an environment suitable for the development of a microbial community in the sludge flocs where PAC is embedded. More complex and heterogeneous microbial communities can potentially enhance biodegradation processes (Baresel et al., 2019). In other terms, the removal mechanisms of the substances may differ based on PAC age, promoting the removal of recalcitrant compounds that are more prone to be sorbed in/on fresh PAC (e.g., carbamazepine), or those which are more likely to be sorbed and biodegraded in PAC-sludge floc complex. As a result, the effect of PAC retention time on the removal of OMPs strongly depends on their corresponding physicochemical properties. In this regard, to achieve a good performance of PAC during the treatment for both cited types of substances which are more prone to be sorbed or bio-transformed, Alvarino et al., (2017) recommend a dosage of 0.2 g/L added every 35 days.

Similar considerations may be applied to SRT. As shown by Ng et al., (2013), low SRT values (i.e., 10 days) implies addition of fresh PAC, providing a higher sorption of compounds which are prone to be sorbed on PAC surface. On the contrary, high SRTs (> 100 days) promote the development of different species in the biomass, entailing a better biotransformation of the compounds (Alvarino et al., 2018a). In accordance with these considerations, both the regression analysis conducted showed that SRT is not significantly correlated with the removal (p > 0.465). Nevertheless, except for the 7 observations related to Asif et al., (2020) in which SRT was 30 days, SRTs in the dataset are always particularly high (from 92 in Alvarino et al., (2017) to 288 days in Serrano et al., (2011) compared to those expected in common conditions adopted in MBR reactors (20-50 days, Metcalf & Eddy (2014)). As a matter of fact, compounds with low biodegradability are not expected to increase their removal at high SRTs (Yu et al., 2014) and therefore an exhaustive conclusion cannot be provided due to the lack of heterogeneity of the values.

4.4.2. Influence of physicochemical characteristics of the micropollutants

Concerning physicochemical characteristics of the compounds, it is interesting to observe that the highest and the lowest average removal efficiencies refer to the observations grouped in cluster A and B respectively (98% and 84%). These are also distinguishable by the highest and the lowest average charge values. This evidence suggests that the removal of OMPs is positively correlated to their corresponding charge.

Though this may seem counterintuitive, as the surface of the PAC added in the experiments is generally neutral to positively charged at pH higher than 7, this fact was observed in many studies (among them Boehler et al., (2012); Loos et al., (2013); Mailler et al., (2016); Margot et al., (2013)). This can be explained bearing in mind that the covering of DOM, typically negatively charged at neutral pH, on PAC surface entails a consistent decrease of its overall charge (Yu et al., 2014). As a result, a high *adsorption* (indicating the potential of electrostatic interactions, according to Ternes et al., (2004), of positively charged OMPs (i.e., cationic) and the negatively charged PAC-DOM complex surface is expected, as well as for repulsion in the case of anionic compounds (de Ridder et al., 2011).

The reduced average removal efficiency (84%) characterising the observations grouped in cluster B is not surprising, as it mostly refers to anionic compounds which are, additionally, also characterised by a low log$D_{ow,}$ and therefore characterised by a low lipophilicity. Hereinafter they are referred to as compounds with low *absorption* potential (Ternes et al., 2004). However, for these compounds, removal may be driven by biotransformation and can be enhanced by the presence of compounds' specific functional groups which interact between the PAC-DOM complex, explaining an average removal of 84% (Alvarino et al., 2017).

On the contrary, even if the particularly high average removal efficiency characterising the observations of cluster A seems to reflect the same behaviour, this might also be due to other reasons. Indeed, cluster A grouped the observations related to 2 substances (namely, erythromycin and roxithromycin) which have been demonstrated to be readily biodegradable in bioreactors in which high nitrification is reached, making their removals only slightly influenced by PAC addition in such reactors (Alvarino et al., 2017).

The results of the regression analysis confirmed the importance of the role of the charge in the removal of OMPs during wastewater treatment. Excluding the 7 observations related to the study by Asif et al., (2020), the removal of the compounds under study showed to be significantly correlated to their charge (p = 0.037).

Despite this, as mentioned above, the sorption of OMPs on the PAC surface is not only driven by adsorption due to electrostatic interactions by their functional groups and the PAC surface. On the contrary, especially in the case of non-charged substances, the adhesion of the OMPs in the PAC-sludge floc complex may be also due to absorption, and therefore to compound lipophilicity (Mailler et al., 2015).

The results of the statistical analysis conducted confirm these considerations. A relatively high average removal efficiency was found for the observations grouped in cluster D (91%) in which the high presence of non-charged compounds is counteracted by a high average value of logD_{ow} (= 3.3, Table 4.4). In addition, it is interesting to observe that, considering the whole dataset, with the exception of cluster C, the removal efficiencies did not appear to be significantly correlated to logD_{ow} (p = 0.069), while considering only the observations related to neutral and anionic compounds (cluster B and D) it is (p < 0.001), confirming that in absence of

strong electrostatic interactions, the lipophilicity of a compound plays a crucial role in the sorption mechanism.

Finally, the outcomes of the statistical analysis suggest that the molecular weight does not play a crucial role in the fate of OMPs in MBR coupled with PAC. Considering the whole dataset, with the exception of cluster C, the regression analysis shows that MW is not significantly correlated to removal efficiency data (p = 0.421). Nevertheless, considering only the negative charged and neutral compounds (clusters B + D), MW gains relevance in the *phenomenon*, albeit remaining non-significant (p = 0.065). These findings are in line with those shown in the investigation conducted by Alves et al., (2018) who found that, considering weakly charged compounds, a slight positive correlation between adsorption potential and MW occurs, due to the relevance posed by the molecular size to the *phenomenon*. Furthermore, Tadkaew et al., (2011) noted that compounds with relatively high MW may be more prone to biodegradation processes, as they present more branches susceptible to be attacked by specialized microorganisms developed on the PAC-sludge floc complex, especially in the case of high lipophilic compounds.

4.5 Final remarks and further research

The statistical analysis conducted highlights and suggested interesting conclusions regarding the fate of OMPs in MBR treatments coupled with PAC.

A significant correlation between the increasing PAC dosage and the removal efficiency of the compounds considered has not been found. Nevertheless, the complexity of the factors influencing the sorption of OMPs on PAC surface during the treatment (e.g., PAC addition timetable and point, compounds characteristics, matrix effect), and the difficulty in comparing observations provided by different experimental conditions, prevent a clear view in this regard. Further research is needed to clarify the role of PAC dosage on OMP removal, as well as to investigate the good practices (e.g., timetable and point of addition) leading to better exploit the potential of PAC in the reactor, instead of the only variation of PAC dosage.

The same applies to PAC retention time, whose relevance appears to be strongly related to micropollutant physicochemical properties. The adoption of a short PAC retention time may enhance the removal of those substances which are more prone to be sorbed on PAC-sludge flocs complex, while a long PAC retention time may entail an increased biotransformation of the compounds due to more complex and heterogeneous microbial community in the reactor.

Inconclusive results were found for SRT as it generally varied between very high values (92 and 288 days) and it was not possible an exhaustive interpretation for all the expected values.

Considering the physicochemical properties, the charge demonstrated to be significantly correlated to the removal of OMPs in MBR coupled with PAC. This can be explained by the electrostatic interactions between the positively charged substances and the negatively charged surface of PAC covered by DOM.

In addition, $\log D_{ow}$ showed to be significantly correlated to the removal of neutral and anionic substances, suggesting that the absence of electrostatic interactions, or even the repulsion to the flocs for the anionic compounds, is counteracted by the high relevance of the compounds' lipophilicity.

Similar behaviour was observed concerning the MW of the substances, which showed to gain importance for neutral and anionic compounds, although not being statistically significant as $\log D_{ow}$.

Overall, the results of this study suggest that the variation of the defined operational conditions (i.e., SRT, PAC retention time, and PAC dosage) does not always entail a better removal efficiency of a broad spectrum of OMPs. On the contrary, confirming the scientific literature on the topic, the specific physicochemical characteristics (in particular, charge and $\log D_{ow}$) of each compound seems to play the most important role in such a complex mechanism.

Nevertheless, precise management of the operational conditions may significantly entail the removal of specific OMPs or groups of them.

The results obtained may provide a better understanding of the role played by the selected factors in the removal of micropollutants in MBR coupled with PAC.
It is important to underline that most of the observations included in the dataset referred to lab scale studies and synthetic wastewater. This implies that the useful considerations suggested by the results of the current statistical analysis should be strengthened by dedicated experiments in full scale plants according to O'Flaherty and Gray, (2013).
The findings mentioned above may help in the management of such advanced biological treatment in view of achieving a higher removal efficiency of the compounds considered in this study, as well as others not included but exhibiting similar physicochemical characteristics, and thus behaviour. In addition, this study showed that basic statistical means and exploratory data analysis applied to the results of different investigations may be an effective tool to elucidate the influence of the main parameters involved in the complex *phenomena* behind the removal of OMPs in MBR systems coupled with PAC.

4.6 References

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Chapter 5

HYBRID MBR IN THE REMOVAL OF PHARMACEUTICALS FROM HOSPITAL WASTEWATER. AN IN-DEPTH INVESTIGATION ON A FULL-SCALE PLANT

TABLE OF CONTENTS

Summary of the chapter, in a nutshell

- The potential enhancement in the removal efficiencies of a selection of OMP from wastewater (mainly hospital effluent) was assessed in a hybrid system consisting of full-scale MBR coupled to PAC added at two different doses (0.1 g/L and 0.2 g/L) inside the biological tanks.
- A set of 232 OMPs were identified and quantified by UHPLC-QTOF-MS. Their frequency of detection and concentration and loads in hospital wastewater, as well as WWTP influent and effluent were reported over a year time. A environmental risk assessment was conducted to evaluate the impact of the release of these contaminants in the receiving water body.
- The treatment efficiency of the MBR alone and the MBR coupled to PAC was assessed by comparing the OMP removal efficiencies and the total loads. Results show that the addition of PAC was particularly beneficial for the therapeutic classes of antibiotics and psychiatric drugs, whereas for certain compounds (e.g., iopromide) or classes (analgesics/anti-inflammatories) the addition of PAC did not imply a further increase in their already high removal in the MBR. Moreover, increasing the PAC concentration from 0.1 g/L to 0.2 g/L reduced the environmental impact in the receiving water body to a higher extent.
- The information displayed in this chapter refers to unpublished data, and thus it should be approached as a showcase of the efforts made during the PhD thesis and the corresponding data produced in lieu of a concluded work.

Results shown in this chapter are part of a manuscript in preparation.

5.1 Introduction

WWTPs are considered the main point source of OMPs in the environment, which can be found in the range from ng/L to µg/L (Verlicchi et al., 2012). The inefficacy of conventional treatments in the removal of OMPs has raised concern about their continuous release into the environment and the potential risks they may pose to aquatic life. At the present, there is no European Union legislation that includes limits to their occurrence or removal efficiencies in WWTPs, but national initiatives have arisen (STOWA, 2021). At the moment, the only country in Europe that regulates the release of OMPs in the environment is Switzerland, by ensuring a minimum removal of 80% for a set of target OMPs (Schweizer Bundesrat, 2016; Swiss Office for the Environment (FOEN), 2016, 201AD). At the European level, research is promoted to collect data on key substances included in the Watch list, periodically revised (Coimbra et al., 2021; Rizzo et al., 2019). The Watch List aims to better assess risks from contaminants found in surface water, by requesting Member states to monitor the listed substances at least once per year for up to four years. By October 2022, a proposal for a revision of the Urban Wastewater Treatment Directive (UWWTD) was announced (European Commission, 2022). In this proposal, additional actions for the reduction of OMPs, in particular pharmaceuticals and personal care products, were included to contribute to the achievement of the good ecological and chemical status of EU water bodies. Among the measures proposed, new limits for a set of OMPs and quaternary treatments are established progressively for facilities above 10,000 PE, following precautionary and risk-based approaches. Being said that the upcoming UWWTD will consider not only the domestic but also the non-domestic pollution that enter in the urban WWTPs and is discharged into water bodies.

Among the different sources of wastewater arriving at the urban WWTPs, hospital wastewater has been considered a hotspot for OMPs, being on many occasions found at higher concentrations than in urban wastewater (Verlicchi et al., 2015). Hospital wastewater can include a wide variety of active principles of drugs and their metabolites, disinfectants, and iodinated contrast media, among others (Kovalova et al., 2013, 2012). Although it is still considered the same pollutant nature of urban wastewater, it has been an object of study in research around the globe (Verlicchi et al., 2015), and *in situ* dedicated advanced treatments have been developed (McArdell et al., 2011). Among them, membrane bioreactors (MBRs) applied to wastewater have been widely developed and implemented in the last decades as they offer a better-quality effluent over conventional activated sludge (Radjenovic et al., 2008; Verlicchi et al., 2015; Xiao et al., 2019). Despite this, they are not designed for OMPs removal and therefore during these last years upgrades by combining MBR with innovative technologies have appeared, calling them "hybrid MBRs"(Rizzo et al., 2019). One of the most promising improvements is the use of activated carbon, available in different shapes: powdered activated carbon (PAC) or granular activated carbon (GAC). Its high specific surface area leads to a high adsorption capacity, and it does not generate toxic by-products (Rizzo et al., 2019).

Adsorption of OMPs onto PAC can be done by adding it to the biological tank or the secondary effluent. When used as a post-treatment for the secondary effluent, additional filtration is needed to reduce the release of suspended PAC into the environment (Kovalova et al., 2013; Margot et al., 2013). Instead, the sorption of OMPs onto PAC in the biological tank of the MBR results in a combination of biological processes and adsorption that provide several advantages, as PAC may be incorporated onto the sludge floc and act as a surface for bacteria attachment and growth (Pan et al., 2016).

In our previous work (Gutiérrez et al., 2021), we evaluated the state of the art on hybrid MBRs coupled to activated carbon for the removal of OMPs. Most of the investigations discussed were conducted at laboratory- or pilot- scale MBRs using synthetic wastewater, where OMPs were spiked at environmental concentrations. In that review, we discussed the necessity of investigating the efficiency of activated carbon under real conditions, to validate the results obtained from the referenced studies. In comparison with other hybrid systems, PAC addition is easy to implement and operate, especially when it is added inside the biological reactor since there is no need for the installation of an additional contact tank. However, special attention must be paid to assure that the concentration of PAC inside of the reactor is maintained constant and that there is enough fresh PAC that ensures the adsorption of the most recalcitrant compounds (Alvarino et al., 2017).

For all the above-mentioned reasons, we decided to perform our experiments in a full-scale MBR treating mainly hospital wastewater (75% of the flowrate) with the addition of PAC inside the biological reactor. Previous studies with the same treatment configuration as the present work used a range of PAC concentrations between 0.05 and 2 g/L (Alvarino et al., 2017, 2016; Echevarría et al., 2019; Li and Gao, 2011; Nguyen et al., 2013; Remy et al., 2012; Serrano et al., 2011; Yang et al., 2010; Yu et al., 2014). We selected the PAC doses based on the conclusions drawn in our previous work (Gutiérrez et al., 2021), where we compared the average removal efficiencies of 48 OMPs pertaining to 13 different classes from the abovementioned studies, and concluded that a PAC dose of 0.1 g/L is sufficient to achieve an 80% of removal for most of the tested compounds.

The present study has three main objectives. First, we aim to provide data on the frequency of detection and occurrence of a wide selection of OMPs (232) in hospital wastewater and in the influent of a WWTP to which the hospital wastewater represents 75% of the flowrate. Then focus is placed on three experiments where we compare the removal efficiencies of the OMPs and performance of the MBR in the absence and presence of PAC added inside the biological reactor (two doses tested, 0.1 g/L and 0.2 g/L). Finally, an environmental risk assessment of the treated wastewater effluent (in two scenarios) and the receiving water body is performed based on risk quotients (RQ) and occurrence, persistence, bioaccumulation and toxicity (OPBT) approach. The results are presented and discussed from the micro-level (compound-specific) to the macro-level (overall loads) to address the efficiency of the system at different levels.

5.2 Material and Methods

5.2.1. WWTP under investigation

A full-scale WWTP located in north-eastern Italy was selected (4000 PE, average dry weather flow of 700 m^3/d) to conduct the experiments (Figure 5.1). The core treatment of the WWTP is an MBR equipped with UF membranes. Specifically, the WWTP consists of a pre-treatment (screening and degritting), an MBR, including P removal (100 m^3), denitrification (250 m^3), nitrification (350 m^3) and membrane tanks (72 m^3), followed by a tertiary treatment with UV radiation for the disinfection of the permeate before its release to an irrigation ditch. Consequently, the final effluent is indirectly reused for irrigation.

The WWTP treats hospital wastewater (HWW) and urban wastewater (UWW), where HWW represents 75% of the flow rate entering the WWTP. The hospital is one of the main ones in the area (900 beds) and it has several wards (anaesthetics, dermatology, endocrinology, forensics, gastroenterology, genetics, geriatrics, gynaecology, haematology, infectious disease, neurology, nuclear medicine, oncology, paediatrics, traumatology and surgery) and services (clinical analysis, dialysis, pharmacology, radiology). The hospital is located in a small urban settlement close to a larger town (150,000 inhabitants). The HWW is directly discharged into the combined sewage network, and once it reaches the WWTP, it is treated in the same treatment line as the UWW. The UWW represents 25% of the influent flow rate of the WWTP and it corresponds to households and small businesses in the vicinity of the hospital.

Although the HWW flow is quite constant throughout the year, the WWTP possesses an accumulation tank (180 m^3) that contributes to minimizing the potential daily variations in the influent flow (i.e., strong rainfall events). The accumulation tank is installed prior to the pre-treatments and is able to collect both HWW and UWW arriving to the WWTP in case of significant increase of the flow. Then, the collected wastewater is gradually sent back to the UWW line to avoid the stress on the membranes. In this way, the effect of flood events are minimized, and a very stable influent flowrate is achieved. According to the operators of the WWTP, after a strong rainfall, the accumulation tank is on average emptied in 4 – 5 days and is able to maintain the permeate flux of the membranes in its optimal range. Yet, the climatic conditions during the monitoring and experimental periods of this study were predominantly stable, with very few and light rainy events.

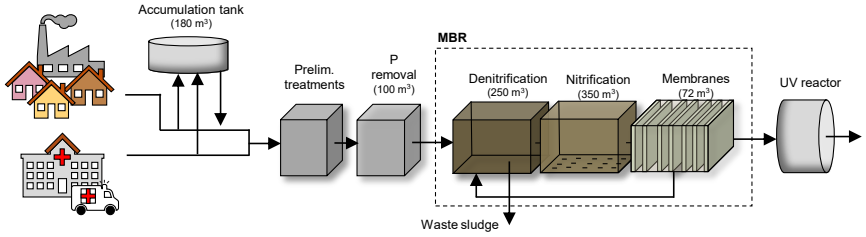

Figure 5.1. Description of the WWTP and the related sources (urban and hospital wastewater).

Regarding the WWTP operational conditions, the average hydraulic retention time (HRT) was 24 h, and the sludge retention time (SRT) was between 24 and 40 days (with an average of 27 days). For the calculation of SRT, we considered the concentration of TSS in the aerated tanks (i.e., nitrification and membrane tanks). The resulting equation (eq. 1) is a modification from Metcalf & Eddy. (2014),

$$SRT = \frac{TSS_N V_N + TSS_M V_M}{Q_W TSS_W} \quad \text{eq. 1}$$

where TSS_N, TSS_M and TSS_w are the TSS concentration in the nitrification tank, membrane tank and waste sludge, respectively (kg/m^3). In the same way, V_N and V_M are the volumes of nitrification and membrane tanks (m^3), while Q_w is the waste sludge flow rate (m^3/d).

In the studied WWTP, the waste sludge is removed from the denitrification tank (Fig. 5.1). The variation of the SRT comes from the fact the experiments are conducted in a real WWTP, where the TSS concentration is adjusted to allow an optimal operation of the membranes with low membrane fouling.

Mixed liquor concentration in the nitrification tank was on average 6.7 ± 1.3 g/L. The WWTP operates at a food-to-microorganism ratio (F/M) (eq. 2) of 0.039 gBOD$_5$/gSSV·d. The F/M ratio was calculated according to Eq. 2, where Q_{INF} refers to the influent flow, $BOD_{5,\,INF}$ to the influent BOD_5 and VSS_N to the mixed liquor biomass concentration in the nitrification tank (measured as volatile suspended solids, VSS). Wastewater from the membrane tank was recycled to the denitrification tank (2100 m^3/day) and the excess sludge amount accounts for between 0 – 43.6 m^3/d (average of 16.3 m^3/d). The average operating temperature was 23°C and the pH of the final effluent was 7.1. Oxygen concentration in the nitrification tank was maintained at 1.5 ± 0.3 mg/L.

$$\frac{F}{M} = \frac{total\ applied\ substrate\ rate}{total\ microbial\ mass} = \frac{Q_{INF}\,(m^3/d) \cdot BOD_{5,INF}(g/m^3)}{V_N(m^3) \cdot SSV_N(gSSV/m^3)} \quad \text{eq. 2}$$

The MBR is equipped with submerged ultrafiltration hollow fiber membranes (UF) (Koch Separation Solution, Italy) with a nominal pore size of 0.05 µm. The membranes were equipped with 8 modules, with a surface area of 500 m^2 per membrane (total surface area of 4000 m^2). The optimal permeate flux was 25 L/m^2/h and the maximal permeate flux was 50 L/m^2/h.

5.2.2. WWTP plant operation

Three operation periods were considered: In the first period, the MBR worked without PAC addition (March-August 2021); in the second period, a concentration of 0.1 g/L of PAC was maintained inside the bioreactor (September – November 2021), and in the third period, the concentration of PAC within the bioreactor was of 0.2 g/L (April – May 2022). The three operation periods are henceforth considered three

treatments (i.e., *noPAC* as a control, *0.1PAC* and *0.2PAC*) for the assessment of the potential enhancement in the removal efficiencies of the selected OMPs and conventional pollutants with the addition of PAC.

Due to the presence of the UF membranes in the MBR (diameter of 0.05 μm), the final effluent was free of PAC during the experimental campaigns (average TSS_{EFF} = 5.3 mg/L), and the PAC particles was solely removed from the system with the excess sludge (see Fig. 5.1). PAC concentration within the bioreactor was maintained stable through periodical and controlled additions of PAC. On the first day of *0.1PAC* and *0.2PAC* experimental campaigns, a fixed amount of PAC was distributed among MBR tanks until the desired PAC concentration was reached. Then, periodical PAC additions were made to counterbalance the PAC losses associated with the withdrawal of sludge in the WWTP, regularly monitored. By adjusting the addition of PAC according to the excess sludge, PAC concentrations varied by less than 10% from the nominal concentrations. Average PAC concentrations were therefore 0.1 ± 0.01 g/L for *0.1PAC* treatment and 0.2 ± 0.02 g/L for *0.2PAC* treatment. The daily concentration of PAC loss from the system (PAC_w) was calculated according to eq. 3,

$$PAC_w(kg/d) = \frac{PAC_{MBR}\ (kg/m^3)}{WAS\ (m^3/d)} \qquad \text{eq. 3}$$

where PAC_{MBR} is the PAC concentration inside the MBR (kg/m^3) and *WAS* is the wasted activated sludge (i.e., excess sludge) removed from the system (m^3/d). *WAS* was manually adjusted according to the desired TSS concentration in the nitrification tank by using an intermittent pump (flow of 5 L/s). Estimation of the daily PAC losses (PAC_w) allows the calculation of the real PAC concentration within the MBR during the experimental campaigns and the prediction of the successive additions of PAC. PAC removed from the system was further treated together with the excess sludge from the MBR.

5.2.3. Selected compounds and activated carbon

A total of 232 OMPs (Table S1 of the Supporting Information) were considered in the present study. Compounds pertain to 21 different classes: Analgesics/anti-inflammatories (29); antiarrhythmic agents (5), antibiotics (40), antifungals (3), antihistamines (2), antihypertensives (1), antiparasitics (6), antiseptics (1), beta-blockers (3), calcium channel blockers (1), diuretics (1), drug metabolites (26), hormones (9), illicit drugs (6), plastic additives (2), psychiatric drugs (63), receptor antagonists (2), stimulants (8), UV filters (1), veterinary drugs (22) and X-Ray contrast media (1). A set of non-target analyses were also conducted to further qualitatively determine the presence of a total of 87 compounds (without quantification). The list of non-targeted OMPs is found in Table S2 of the Supporting Information, although the results on their frequency of detection in the analysed samples are not shown in this Chapter (in preparation).

PAC was purchased from Comlet S.p.A (Cernusco sul Naviglio, Milano, Italy). Several activated carbon manufacturers and providers were contacted prior to the selection of PAC. Selection of the activated carbon was made according to its physicochemical characteristics, so the purchased PAC is comparable to the literature data (Gutiérrez et al., 2021). Table 5.1 summarizes the characteristics of the PAC used in the investigations.

Table 5.1. Physicochemical characteristics of the activated carbon provided by the manufacturer.

Analysis	Value	Analytical method
Iodine number (mg/g)	750	ASTM D4607
Methylene blue (mL)	12	Cefic – DAB VI
BET specific surface area (m^2/g)	850	ASTM D3663
Bulk density (kg/m^3)	430	ASTM D2854
Ash content (%)	10	ASTM D2866
Humidity (%)	5	ASTM D2867
pH	alkaline	ASTM D3838

5.2.4. Sampling and chemical analyses

Sampling and chemical analyses for conventional parameters were the result of a close collaboration with HERA company. Sampling was organized in advance with the help of HERA technicians and managers, resulting in calendars like the one shown in Table S3 of the Supporting Information. In this way, PAC additions, wastewater and mixed liquor sampling days were already established before the beginning of the experiments, and only slight variations from the original plan were made.

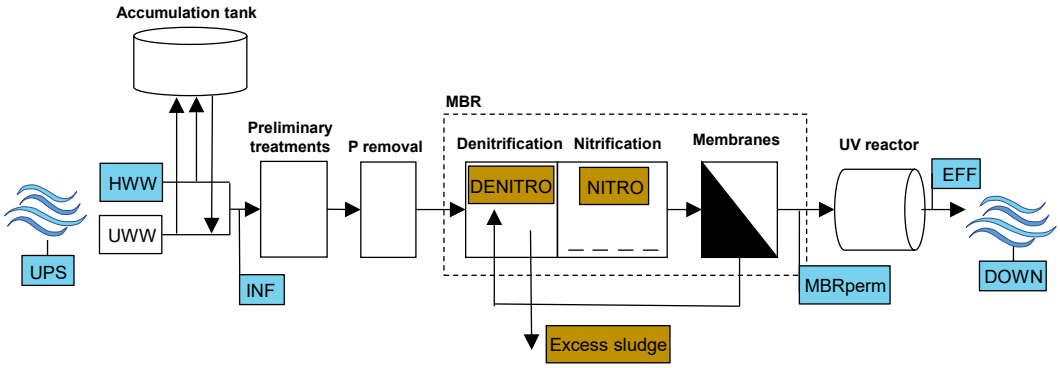

Figure 5.2. Sampling points of wastewater (in blue) and mixed liquor/sludge (brown). Wastewater samples were taken in six sampling points: hospital wastewater (HWW); WWTP influent (INF); MBR permeate (MBRperm), final effluent (EFF) and in the irrigation ditch, both upstream (UPS) and downstream (DOWN) the WWTP.

Wastewater samples were taken in six sampling points (Figure 5.2), hospital wastewater (HWW); WWTP influent, that is the mixture of urban and hospital wastewater (INF); MBR permeate (MBRperm), final effluent after the UV treatment (EFF) and in the irrigation ditch, both upstream (UPS) and downstream (DOWN) the

WWTP. During the *0.1PAC* campaign, a set of conventional parameters were periodically monitored, namely COD, BOD_5, DOC, UV_{254}, TSS, VSS, NO_3^-, NO_2^-, NH_4^+, total nitrogen (Ntot) and total phosphorous (Ptot). Samples for conventional parameters were taken in the influent (HWW and INF) and effluent (EFF) once every week. DOC and UV_{254} were also analysed in the nitrification tank (twice a week). Anionic, cationic and total surfactants concentration, together with *E. coli* concentration measurements and *D. magna* ecotoxicity tests were carried out every month to evaluate the water quality in the HWW, INF and EFF. Mixed liquor samples for total suspended solids (TSS) and sludge volume index (SVI) were monitored twice a week during the experimental period in 3 different sampling points (Fig. 5.2), namely denitrification tank (DEN), nitrification tank (NITRO) and excess sludge.

During the second experimental campaign (*0.2PAC*), TSS, DOC and UV_{254} were monitored every two weeks in HWW, INF and EFF, while TSS from the nitrification tank was analysed every week to monitor and adjust, if necessary, the load of excess sludge and the subsequent PAC additions.

24-h time proportional composite samples were used for the analysis of conventional wastewater parameters, while grab samples were taken of the mixed liquor and sludge (NITRO, DEN, recirculation and excess sludge sampling points). Table 5.2 shows the analytical methods used for the analysis of conventional parameters in wastewater and mixed liquor, conducted in HERA laboratories.

Data on dissolved oxygen concentration and temperature in the nitrification tank, as well as pH values from the EFF, were collected from the sensors installed to regularly monitor the WWTP operation.

For OMP analysis, three sampling campaigns took place: MBR without PAC addition (i.e., *noPAC*) (n = 16) MBR with 0.1 g/L of PAC (i.e., *0.1PAC)* (n=40) and MBR with 0.2 g/L of PAC (i.e., *0.2PAC*) (n = 20). 24-h time proportional composite wastewater samples were taken once a week by automatic samplers in HWW, INF, MBRperm and EFF sampling points (for the MBR permeate, the hydraulic retention time was considered). For UPS and DOWN sampling points, grab samples were taken during the last day of experimentation of the second campaign. Wastewater samples were collected in polycarbonate bottles (500 mL), which are more suitable than glass for water sampling and storage because some organic compounds tend to adsorb to glass. Samples were frozen immediately after sampling and stored at -20 °C until analysis. Refrigeration between 0 and 4 °C (only a few days) and freezing at -20 °C (longer periods) are the most common preservation methods for organic samples that cannot be analysed immediately after sampling. Before analysis, water samples were thawed and then filtrated through 0.2 μm PTFE filters. Ultrapure laboratory water samples were always processed in parallel with the environmental water samples (procedural blanks).

Table 5.2. Conventional parameters and the corresponding analytical methods used in the present study.

Parameter	Unit	Analytical method
Wastewater		
COD	mg/L	ISO 15705 par 10.2:2002
BOD_5	mg/L	APHA Standard Methods for the Examination of Water and Wastewater ed 23rd 2017 5210 D
DOC	mg/L	APHA Standard Methods for the Examination of Water and Wastewater ed 23rd 2017 5310 B
UV_{254} absorbance	ABS/cm	APHA Standard Methods for the Examination of Water and Wastewater ed 23rd 2017 5910 A B
Total suspended solids (TSS)	g/L	CNR IRSA 1A Q 64 Vol 2 1984
Volatile suspended solids (VSS)	% of TSS	CNR IRSA 1A Q 64 Vol 2 1984
$N\text{-}NH_4^+$	mg/L	APAT CNR IRSA 4030 A1 Man 29 2003
$N\text{-}NO_3^-$	mg/L	APAT CNR IRSA 4020 Man 29 2003
$N\text{-}NO_2^-$	mg/L	APAT CNR IRSA 4050 Man 29 2003
Total nitrogen	mg/L	UNI EN 12260:2004
Total phosphorous	mg/L	UNI EN ISO 6878:2004
Anionic surfactants (MBAS assay)	mg/L	M10R759.0 rev. 0 2015
Non-anionic surfactants (BIAS procedure)	mg/L	M10R759.0 rev. 0 2015
Cationic surfactants	mg/L	M10R759.0 rev. 0 2015
Total surfactants	mg/L	M10R759.0 rev. 0 2015
Acute Toxicity Test with *Daphnia magna*	Mortality (%)	APAT CNR IRSA 8020 B Man 29 2003
Escherichia coli	UFC/100 mL	M10P509.0 rev 4 2015 and APAT CNR IRSA 7030 D Man 29 2003
Mixed liquor		
Total suspended solids (TSS)	g/L	CNR IRSA 1A Q 64 Vol 2 1984
Volatile suspended solids (VSS)	% of TSS	CNR IRSA 1A Q 64 Vol 2 1984
Sludge volume index (SVI)	mL/g	CNR IRSA 7 Q 64 Vol 2 1984
Settable solids (30 mins)	mL/L	APAT CNR IRSA 2090 C Man 29 2003
DOC	mg/L	APHA Standard Methods for the Examination of Water and Wastewater ed 23rd 2017 5310 B
UV_{254} absorbance	ABS/cm	APHA Standard Methods for the Examination of Water and Wastewater ed 23rd 2017 5910 A B

Once the results of the OMP analysis were obtained, the average OMP occurrence per sampling point and treatment was calculated by conducting the arithmetic mean of the individual concentrations per sampling day. If the OMP concentration was below the corresponding limit of detection (LOD) of the instrument, 1/2 LOD was assumed, and thus overestimation of the average concentration was avoided. The average concentration of each OMP class was obtained by the addition of the individual OMPs concentrations pertaining to the respective class per sampling day and then performing the arithmetic mean. To evaluate the daily removal efficiency of each OMP, eq. 4 was used,

$$Removal\ efficiency\ (\%) = \frac{C_i Q_i - C_e Q_e}{C_i Q_i} \cdot 100 \qquad \text{eq. 4}$$

where C_i and Q_i are the influent concentration (µg/L) and flow (m^3/d), C_e and Q_e are the MBR permeate or effluent concentration (µg/L) and flow (m^3/d), as both MBR permeate removal (without UV reactor) and WWTP removal (including UV reactor) were studied. Given that the operation of the MBR was very stable during the experimental period and there was almost no difference between influent and effluent flow both Q_i and Q_e terms can be neglected, resulting in eq. 5,

$$Removal\ efficiency\ (\%) = \frac{C_i - C_e}{C_i} \cdot 100 \qquad \text{eq. 5}$$

Note that in this study the term removal refers to the difference in the concentration of a given substance in the effluent compared to the influent, regardless of whether it is mineralized, transformed, or even formed in the system (Kovalova et al., 2013). In case either the C_i or C_e of an OMP is lower than the LOD, 1/2LOD is assumed as the concentration to calculate the corresponding removal efficiency. If both C_i and C_e are below the LOD, the removal was not calculated.

5.2.5. UHPLC-QTOF-MS

232 OMPs were determined by UHPLC–QTOF–MS, using the direct injection method, in the four wastewater sampling points previously described (Table S4 of the Supporting Information). Samples were analysed at the Central Water Management Laboratory of Croatian Waters in Zagreb, Croatia. The liquid chromatography (LC) analyses were performed using an Agilent Series 1290 UHPLC system (Santa Clara, CA, USA) equipped with a Waters RP column ACQUITY UPLC, HSS T3 (150mm x 2.1mm, 1.8 µm).

The mobile phase consisted of both 10 mM ammonium formate in water (solvent A) and methanol (solvent B). Elution began with a 17-minute gradient from 95% A to 95% B, which was maintained for 6 minutes, followed by a 0.1 min linear gradient back to 95 % A. The analytes were separated at a temperature of 40 °C. The flow rate was 0.35 mL/min with an injection volume of 100 µL for all analyses. The analyses were performed in positive ion mode. The analytes were detected using a 6550 i-Funnel Q-TOF–LC/MS (Agilent Technologies, USA) at a 4 GHz detector rate. The resolution power for ESI(+) was 52,296 at 922.009798 m/z and 21,801 at 118.086255 m/z, and 2 ppm accuracy. Ions were generated using a dual AJS ESI (Agilent Jet Stream) ion source. Operation conditions in ESI(+) mode were as follows: sheath gas temperature 350 °C, gas temperature 160 °C, heat gas 12 L N_2/min, drying gas 14 L N_2/min, capillary voltages 4000V, fragmentor 250 V, and nebulizer 30 psi.

Correction during measuring for any possible drift in the mass axis was done automatically with lock 2 mass ion software. Analyses were performed using MS and

MS/MS (Allions mode) with fixed collision energy (0, 20, 40 V) and in a mass range of 50 – 1000 m/z. Data were further processed with Agilent MassHunter Workstation software (Quantitative Analysis version B.10.00/Build 10.0.707.0 for QTOF, Agilent Technologies, USA). The calibration curve was created using triplicate standard solutions at 7 concentration levels ranging from 1 to 1000 ng/L.
The LOD for all compounds ranged from 0.26 to 5.07 ng/L and LOQ ranged from 1.64 to 29.92 ng/L. LOD values for each OMP are listed in Table 5.6.

5.2.6. Risk quotients and OPBT scores

The potential risk of the analysed OMPs was evaluated via the calculation of their risk quotients (RQs). RQs were calculated as the ratio between their measured environmental concentration (MEC) for each treatment (i.e., *noPAC*, *0.1PAC* and *0.2PAC*) and the Predicted No-Effect Concentrations (PNEC) in freshwater (eq. 6). The PNEC is defined as the concentration of a compound below which adverse effects will most likely not occur. In our study, we consider four different MECs: The average concentration in the irrigation ditch upstream and downstream of the WWTP (sampling points UPS and DOWN, respectively), the average concentration in MBR permeate (MBRperm) and in the final effluent (EFF). For the two last cases, we assume that the irrigation ditch is completely dry and there is no dilution effect. To evaluate the potential risk, the ranking criterion commonly used: (i) RQ < 0.1, minimal risk to aquatic organisms; (ii) 0.1 ≤ RQ <1 medium risk and (iii) RQ ≥ 1 high risk (Verlicchi et al., 2012a). PNEC values were obtained from NORMAN database (https://www.norman-network.com/) and they represent the lowest values obtained, either experimentally or predicted by QSAR models, from the most sensitive freshwater species analysed in long-term exposure (among them: bacteria, algae, invertebrates, and fish).

$$RQ = \frac{MEC}{PNEC} \qquad \text{eq. 6}$$

Occurrence, persistence, bioaccumulation and toxicity (OPBT) analysis was conducted on the MBRperm for each experimental campaign (*noPAC*, *0.1PAC* and *0.2PAC*) as prioritization methodology to determine the potential compounds to monitor in the future. Every OMP has been assessed in the four OPBT categories, and ranked with a score from 1 to 5.
The *criterium* used to evaluate the occurrence was the average concentration of the target OMP in MBR permeate. The thresholds of 0.01, 0.1, 0.5 and 1 µg/L were chosen according to the effluent concentrations found in the studies under review by Gutiérrez et al. (2021). In that review, an effluent with a concentration of 0.01 µg/L was considered of very good quality, and 1 µg/L was set as a threshold to evaluate the efficiency of the treatments under study. If the compound concentration was below the LOD, a score of 1 is assumed.

The persistence criterion was set as the average removal efficiency of a target compound in the MBR permeate (calculated as shown in eq. 5). Compounds with very high persistence, and thus resistance to the treatment, show removal efficiencies lower than 20% (score of 5). Thresholds of 20, 40, 60 and 80% were set according to Daouk et al. (2015). A score of 3 (that is, 40% < rem ≤ 60%) was attributed to missing data where OMPs were undetected in both influent and MBR permeate, and therefore we were unable to calculate their removal efficiencies.

logK_{ow} was defined as the criteria for bioaccumulation since it indicates the tendency of a substance to be solubilized in tissues from an aqueous medium. logK_{ow} data was obtained from J Chem for Office (20.11.0, ChemAxon, https://www.chemaxon.com).

Toxicity scores were defined according to PNEC values obtained from the NORMAN database as previously described. As for persistence, PNEC thresholds of 0.1, 1, 10, and 100 µg/L were chosen following Daouk et al. (2015) criteria. A safety score of 5 was given to OMPs for which there were no available PNEC values, assuming they possess inherent toxicity.

Criteria thresholds and corresponding scores used for OPBT analysis are shown in Table 5.3. The final score of each OMP was the result of the addition of the scores for each category. In this way, OMPs can reach a maximum score of 20, and a minimum of 4.

Table 5.3. Criteria selected for OPBT analysis.

Categories	Occurrence	Persistence	Bioaccumulation	Toxicity
Criteria → / Score ↓	Av. conc. MBRperm (µg/L)	Av. Rem MBRperm (%)	logK_{ow}	PNEC (µg/L)
1	c <0.01	R > 80	logK_{ow} < 1	PNEC > 100
2	0.01 ≤ c < 0.1	60 < R ≤ 80	1 ≤ logK_{ow} < 2	10 < PNEC ≤ 100
3	0.1 ≤ c < 0.5	40 < R ≤ 60	2 ≤ logK_{ow} < 3	1 < PNEC ≤ 10
4	0.5 ≤ c < 1	20 < R ≤ 40	3 ≤ logK_{ow} < 4.5	0.1 < PNEC ≤ 1
5	c ≥ 1	R ≤ 20	logK_{ow} ≥ 4.5	PNEC ≤ 0.1

5.3 Results and discussion

The full-scale MBR under study is characterized by treating mainly HWW and, due to the lower influence of the UWW, it was considered almost an *in situ* dedicated advanced treatment of hospital effluent. The HWW was characterized together with the WWTP influent (INF), where both urban (UWW) and HWW flows come in contact at different ratios. The overall performance of the WWTP in terms of conventional parameters and OMPs was monitored, and the potential enhancement in the removal efficiencies of these latter was tested by adding PAC within the MBR. OMPs frequencies of detection, occurrence, total loading, as well as removal efficiencies are reported in this section. Different approaches of the OMP analysis were made to assist the reader: general level (including all OMPs), class level and compound-specific level. Finally, an environmental risk assessment by risk quotient (RQ) and occurrence-persistence-bioaccumulation-toxicity (OPBT) analysis was carried out to determine the compounds which may be of greater importance for the evaluation WWTP effluent and the potential effects they may have.

5.3.1. Biological reactor performance

WWTPs are regularly monitored to ensure that the quality of the effluent complies with the limits and regulations set at the regional and national levels, depending on its final purpose. In Italy, the Decreto Ministeriale 185/2003 (D.M. 185/2003) establishes the rules for the direct reuse of wastewater, while the Decreto Legislativo 152/2006 (D. Lgs. 152/2006) limits the emissions and discharge of contaminants in the environment, including the discharge of WWTP effluents in surface water. In this study, the WWTP effluent is discharged in a water ditch that ends up in the Adriatic Sea, and it is indirectly used for irrigation. Accordingly, the effluent quality must meet the D. Lgs. 152/2006 discharge limits. During the sampling campaigns, the performance of the biological reactor was monitored to ensure that the experiments were conducted under stable conditions and samples of conventional parameters were regularly taken to evaluate whether the addition of a low concentration of PAC may improve the overall quality of the effluent. Table 5.4 reports basic water quality parameters, namely COD, BOD_5, TSS, total nitrogen, NH_4^+ and total phosphorous in the effluent, together with the minimum, maximum and average removal achieved during the MBR operation alone (i.e., *noPAC*) and with 0.1 g/L of PAC (i.e., *0.1PAC*). Results show that both treatments comply with the discharge limits set up by D. Lgs. 152/2006. During *0.1PAC* treatment, the removal efficiencies of all the measured parameters increased except for N-NH_4^+, which was slightly reduced from 97% to 93% on average. In many studies, the addition of PAC has little to no effect on the removal of organic matter and nutrients, since MBRs already provide very good effluent quality (Alvarino et al., 2018; Cho et al., 2011; Gao et al., 2016). However, at times the presence of activated carbon may slightly improve the removal of organic matter (Johir et al., 2016; Remy et al., 2012) and nutrients, especially with regard to

the total nitrogen and/or nitrate. PAC has been shown to increase biological denitrification in the bioreactor since it provides anoxic zones in the microbial biofilm attached to the PAC surface. In this way, denitrification occurs not only in the denitrification tank but within the granules of sludge that incorporate the PAC. In our study, the removal of total nitrogen increased from 64% to 73% on average, improving the quality of the effluent (from 9.9 mg/L to 7.1 mg/L).

Regarding total phosphorous (Total P), Asif et al., (2020) noticed a 10% increase in the removal of this nutrient due to the increase in the abundance of polyphosphate accumulating organisms (PAOs) in the MBR coupled to PAC. In our study, the removal of total P increased by 15% during *0.1PAC* treatment. However, the effluent concentration was maintained at around 3.2 mg/L in both treatments. In activated sludge systems, phosphorous is usually removed from wastewater by precipitation and or adsorption, with insignificant amounts used for cell metabolism and growth (Radjenovic et al., 2008). Since the WWTP under study possesses a precipitation tank for the removal of phosphorous, the P concentration in the effluent is ensured within the limits established at the national level. The conclusions drawn by Asif et al., (2020) regarding the changes in the microbial community are of great interest, although the experimental conditions of the study (20 g/L of PAC) are no nearer to ours (0.1 g/L PAC). A potential matter of great interest for future investigations could be the study of the relative abundance of microorganisms at different dosages of PAC.

Table 5.4. Effluent concentration (EFF) and removal efficiencies for the main conventional parameters in the WWTP under *noPAC* and *0.1PAC* treatment. Discharge limits set by the Italian government (D. Lgs. 152/2006) are also listed.

		noPAC					0.1PAC				
	D. Lgs. 152/2006 limits (mg/L)	n	EFF (mg/L)	Min rem. (%)	Max rem. (%)	Average rem. (%)	n	EFF (mg/L)	Min rem. (%)	Max rem. (%)	Average rem. (%)
COD	125	2	29 ± 5.7	68	88	78 ± 14	10	22.5 ± 7	79	95	87 ± 5
BOD_5	25	2	12 ± 2.8	80	87	83 ± 5	8	10	78	90	87 ± 4
TSS	35	2	6 ± 1.4	88	92	90 ± 3	7	5.4 ± 0.53	91	95	93 ± 2
$N\text{-}NH_4^+$	15	2	< 1	96	98	97 ± 1	7	2.2 ± 1.52	86	97	93 ± 4
Total N	N.A.	2	9.9 ± 0.3	53	75	64 ± 16	7	7.1 ± 2.05	53	85	73 ± 14
Total P	10	2	3.3 ± 1.1	0	9	4 ± 6	7	3.2 ± 0.37	0	56	19 ± 24

Considering TSS (Figure 5.3), the concentration between experimental campaigns did not have significant differences, but a small increment was observed during *0.2PAC* treatment. In the same way, DENITRO and NITRO tanks presented similar TSS concentrations during both campaigns. As expected, UF membranes retained most of the solids, with a final average concentration of 5.4 ± 0.7 mg/L.

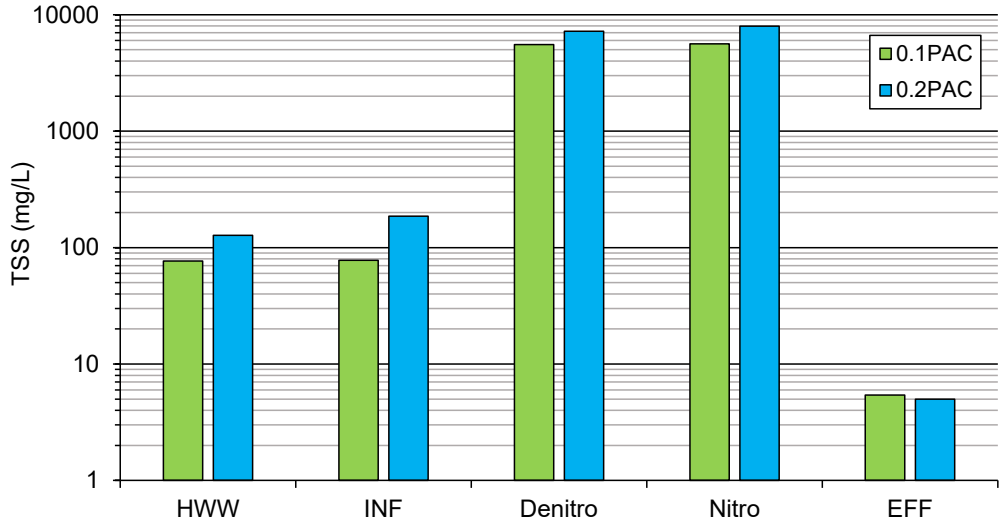

Figure 5.3. Concentration of total suspended solids (TSS) in HWW, INF and EFF, together with the DENITRO and NITRO MBR compartments. Green and blue colours correspond to the concentrations of *0.1PAC* and *0.2PAC* experimental campaigns, respectively.

The presence of dissolved organic matter (DOM) has a great influence on hybrid systems where the adsorption onto PAC is one of the main removal mechanisms of OMPs. Usually measured as dissolved organic carbon (DOC), DOM limits the removal of OMPs by competing for the available adsorption sites of PAC and causing pore blockage (de Ridder et al., 2011). This is particularly important at low PAC dosages, where the competition for adsorption sites may be higher. DOM is constituted by multiple fractions (biopolymers, humic substances, low molecular weight organics…) that present different sorption capacities onto the PAC. In general, it is considered that low molecular weight organics are the main competitors of OMPs during PAC adsorption (Guillossou et al., 2020; Zietzschmann et al., 2014). Since the analytical techniques to analyze DOM constituents are still expensive and time-consuming, alternative surrogates that may be used for regular monitoring have been investigated in the last years (Altmann et al., 2016; Zietzschmann et al., 2014). In this way, UV_{254} has been suggested as a surrogate to monitor the removal of aromatic compounds, and subsequently OMPs, in technical PAC applications. Positive correlations between OMPs removal and UV_{254} abatement have been found, independently of the wastewater origin (Altmann et al., 2016).

Figure 5.4 shows the DOC concentration and UV_{254} absorbance in different WWTP compartments for both *0.1PAC* and *0.2PAC* treatments. Data from the MBR working without PAC addition (*noPAC*) is lacking since these parameters are not commonly monitored in WWTPs. As expected, DOC concentration and UV_{254} absorbance decrease as follows: HWW, INF, NITRO and EFF. HWW provides most of the organic loading to the WWTP, which is then consumed and diluted within the bioreactor. DOC and UV_{254} present higher values in HWW and INF during the second experimental campaign (*0.2PAC*), resulting also in higher values in NITRO and EFF sampling points. While DOC removal did not show significant differences between the two PAC

dosages, UV_{254} absorbance exhibited better results with *0.2PAC* treatment by increasing its removal efficiency by 15% (from 46 to 61% on average). Indeed, while the range of UV_{254} removal varied greatly in *0.1PAC* treatment (27% - 61%), it was maintained between 54% and 65% for *0.2PAC*. The decrease of UV_{254} is directly related to the removal of recalcitrant compounds with aromatic rings and unsaturated bonds of both OMPs and DOM constituents (Altmann et al., 2016). Although DOC removal does not seem to improve with the increasing dose of PAC, recalcitrant compounds seem to be removed to a greater extent.

Many authors have suggested normalizing the PAC dose to the respective DOC (g PAC/g DOC), commonly referred to as specific PAC dosage, to estimate the required PAC dose to achieve a certain OMP removal (Streicher et al., 2016; Zietzschmann et al., 2014). Siegrist et al. (2018) recommended a specific dose of 2 − 3 g PAC/g DOC when it is added directly onto the biological treatment, and 1.5 g PAC/g DOC when used as a post-treatment. In our study, the DOC concentrations in the nitrification tank are 6.2 ± 1.2 mg/L for *0.1PAC* treatment and of 7.9 ± 1 mg/L for *0.2PAC*. In this way, the resulting PAC normalized doses are 16 g PAC/g DOC and 25 g PAC/g DOC for *0.1PAC* and *0.2PAC*, respectively. Since the DOC concentrations were in the range of 4.7 – 9.1 mg/L during the whole experimental period, the specific PAC dosages used were much higher than the ones found in the literature (Altmann et al., 2014; Streicher et al., 2016). Following the Swiss Approach recommendations, the PAC concentration in the nitrification tank should be between 9 and 27 mg/L.

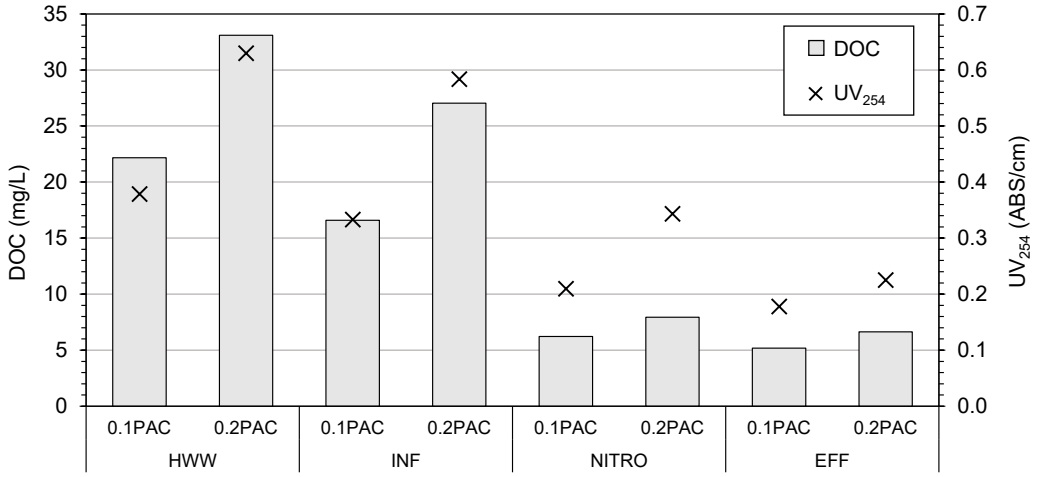

Figure 5.4. Average DOC concentration and UV_{254} absorbance in HWW, INF, NITRO and EFF during *0.1PAC* and *0.2PAC* treatments.

5.3.2. Characterization of the hospital wastewater and WWTP influent

The variation of the flowrate, and the corresponding contribution of HWW and UWW, are depicted in Figure 5.5. The figures were produced with the data obtained from the WWTP sensors in an approximately 2-year time frame (2021–2022), showing the seasonal variations. In Fig. 5.5a, the contribution of the accumulation tank, in terms of flow rate, is also depicted. The accumulation tank can collect the overflow that arrives from either HWW or UWW pipes to release it later slowly into INF within 4-5 days. As a matter of fact, it collects the wastewater mainly from strong rainy events, maintaining the operation of WWTP stable. This fact has great importance concerning the removal efficiencies for the selected OMPs and conventional parameters, as explained in the following sections. On average, the WWTP treats 641 m^3/day, from which 158 m^3/day are from UWW and 482 m^3/day from HWW, representing 25% and 75% of the total flow, respectively. Since the hospital has a capacity of 900 beds, the corresponding specific consumption is 536 L/bed, in agreement with other hospitals in the area (Verlicchi et al., 2012a).

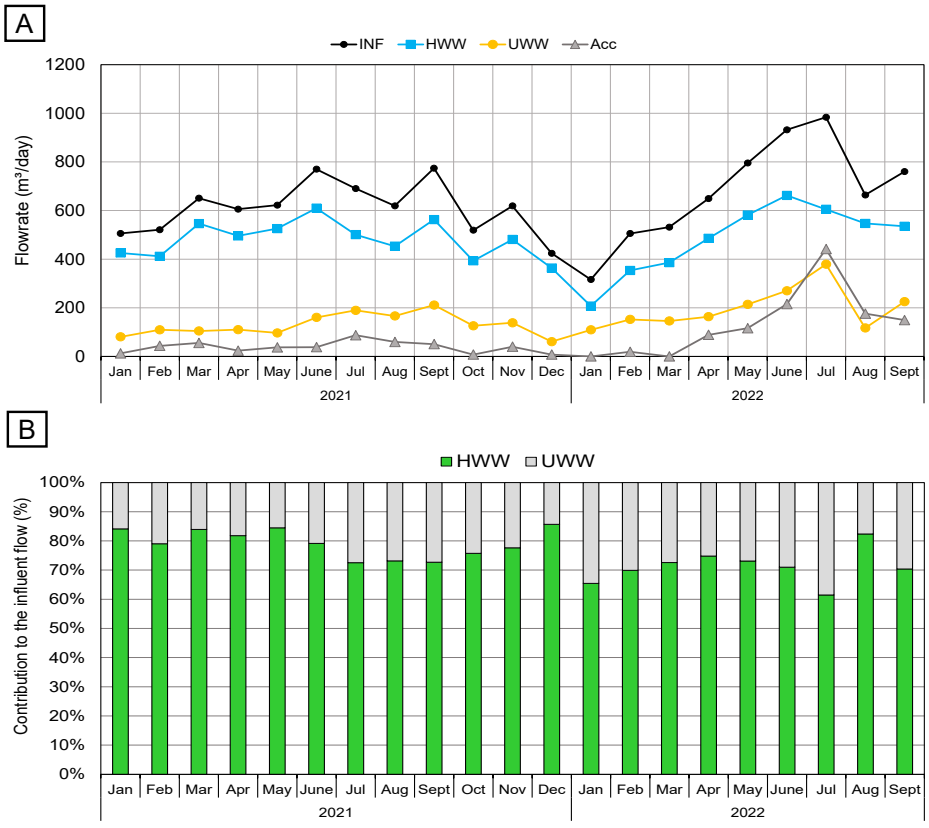

Figure 5.5. Description of the flowrate entering the WWTP: a) Flowrate (m^3/day) of the urban wastewater (UWW), hospital wastewater (HWW), and accumulation tank (Acc) entering the WWTP (INF) (sum of UWW and HWW). Note that the Acc flowrate represents a mixture of HWW and UWW entering the WWTP in case strong rainy events take place. b) Ratio (%) of HWW and UWW contributing to the WWTP influent flow.

Table 5.5 shows the characterization of HWW and INF during the whole experimental period (*noPAC*, *0.1PAC* and *0.2PAC* treatments) in terms of conventional parameters. Samples were taken for a year time at different seasons (autumn, spring and summer), avoiding strong rainy events that may cause a dilution effect for the assessed parameters. Wastewater influent was predominantly stable throughout the year, with no particular intervention in the WWTP operation by HERA technicians apart from routine monitoring and maintenance. As it is previously mentioned, 75% of the flow rate arriving at the WWTP comes from HWW. All parameters were found at higher concentrations in HWW compared to INF, except for TSS, which implies there is a dilution effect when HWW meets UWW.

Table 5.5. Characterization of the hospital wastewater arriving at the WWTP (HWW) and WWTP influent for a set of conventional parameters (INF).

	HWW				INF			
Parameter	n	Min	Max	Average	n	Min	Max	Average
COD (mg/L)	10	131	351	225.5 ± 65.1	12	104	242	178.7 ± 38.1
BOD_5 (mg/L)	8	50	135	92.1 ± 27.6	10	46	105	79.3 ± 20.5
TSS (mg/L)	10	35	188	92 ± 43.1	12	42	330	102.9 ± 74.3
VSS (% TSS)	7	79	90	83.7 ± 3.5	7	38	89	76.2 ± 18.2
DOC (mg/L)	13	15	69	27.5 ± 14.6	13	12	40	19 ± 7.3
UV_{254} (ABS/cm)	13	0.28	0.737	0.44 ± 0.14	13	0.262	0.665	0.39 ± 0.12
$N\text{-}NO_3^-$ (mg/L)	7	< 0.5	< 0.5	< 0.5	7	< 0.5	< 0.5	< 0.5
$N\text{-}NH_4^+$ (mg/L)	7	24	43	32.4 ± 7.1	9	23	42	32.4 ± 6.7
Total N (mg/L)	7	21	39	29.2 ± 6.5	9	21	39	29.3 ± 6.7
Total P (mg/L)	7	2	4	3.5 ± 0.7	9	2	6	4.1 ± 1.4
Anionic surfactants (mg/L)	5	1	3	2 ± 1	5	2	3	2.4 ± 0.6
Non an. surfactants (mg/L)	5	1	2	1.4 ± 0.5	5	1	2	1.1 ± 0.2
Cationic surfactants (mg/L)	5	0	0	0.4 ± 0.1	5	0	1	0.4 ± 0.1
Total surfactants (mg/L)	5	3	6	3.7 ± 1.1	6	2	5	3.6 ± 1
D. magna (% mortality)	3	7	20	12.2 ± 7	3	0	20	7.8 ± 10.7
E. coli (UFC/100 mL)	3	580,000	980,000	756,667 ± 204,042	3	910,000	1,000,000	946,667 ± 47,258

The frequency of detection of OMPs presented in the following figures refers to the number of times a compound is detected above the limit of detection (LOD). According to the frequency of detection (Figure 5.6), out of the 232 OMPs analysed, the compounds may be categorized into four main groups: Highly detected (Freq > 75%), moderately detected (25% < Freq ≤ 75%), slightly detected (0% < Freq ≤ 25%) and non-detected (Freq = 0%). Each group accounts for roughly one-quarter of the total number of compounds, with a similar distribution of frequencies in both hospital wastewater and WWTP influent. This result is not surprising since it is expected that the main input of OMPs to the WWTP comes from the hospital wastewater, with some compound-specific exceptions related to household or commercial activities from the surrounding urban settlement. Note that 28% of the compounds are not detected in both HWW and INF. In most cases, the compounds under the LOD are the same in both HWW and INF, with a few exceptions. The total number of compounds not detected in either HWW or INF is 73, which can be found underlined in Table 5.6.

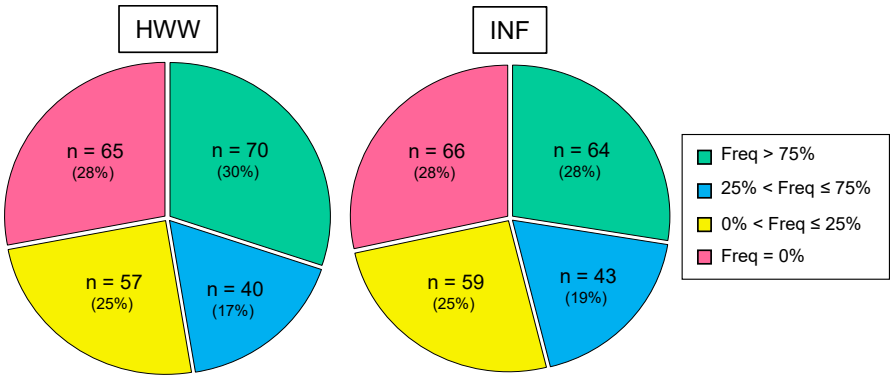

Figure 5.6. Frequency of detection (Freq) of the 232 OMPs analysed in the hospital wastewater (HWW) and WWTP influent (INF), categorized into four groups: Freq > 75% (green); 25% < Freq ≤ 75% (blue); 0% < Freq ≤ 25% (yellow) and Freq = 0% (pink). *n* indicates the number of compounds for each group, with the percentage they represent in between brackets.

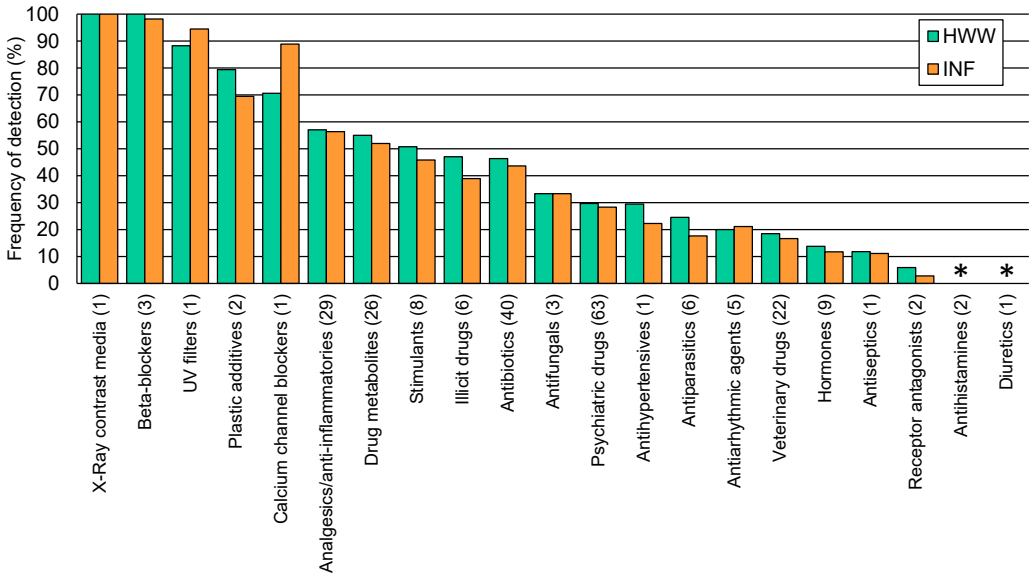

Figure 5.7. Frequency of detection (in percentage) of each OMP class in WWTP influent (INF) and hospital wastewater (HWW). In between brackets, the number of compounds for each class. Two classes, namely antihistamines and diuretics, were not detected in both HWW and INF (marked as *).

Although the frequencies of detection were easily classified into four groups with a similar distribution of data, not all the OMP classes were equally detected (Figure 5.7). In general, the frequency of detection was higher in HWW than in the INF for all therapeutic classes apart from two: UV filters and calcium channel blockers. These two classes had only one compound in their category, Octyl methoxycinnamate as a UV filter and verapamil as a calcium channel blocker. Most of the compounds found in wastewater emanate from the hospital, but the fact that these two are more detected in the INF (and at a higher concentration) implies that they are frequently used in the household area in the vicinity of the hospital. This may be explained since UV filters are used on a daily basis as a personal care product, whereas the

pharmaceutical verapamil is used to reduce blood pressure, and it may have been prescribed for daily consumption to the inhabitants of the urban settlement.

Among all the OMPs tested, three of them, corresponding to antihistamines and diuretics classes, were never detected. The most frequently detected classes were X-ray contrast media, beta-blockers, plastic additives, UV filters and calcium channel blockers. These classes included a low number of compounds, which would imply that the individual frequencies of detection of these OMPs were also high. Indeed, iopromide (x-ray contrast media), benzotriazole (plastic additive), atenolol and bisoprolol (beta-blockers) had a detection of frequency of 100%; followed by the beta-blocker metoprolol (≥94%), the UV filter octyl methoxycinnamate (≥88%) and the calcium channel blocker verapamil (≥88%). P-toluenesulfonamide was the only compound with lower detection of frequency (≥39%), pertaining to a highly detected class (plastic additives).

Some OMP classes had the highest number of compounds but with a low to medium frequency of detection. They correspond to psychiatric drugs (63 compounds), antibiotics (40), analgesics/anti-inflammatories (29), drug metabolites (26) and veterinary drugs (22). The distribution of frequencies of the OMPs within analgesics/anti-inflammatories, antibiotics and drug metabolites classes was quite homogeneous, leading to a medium average frequency of detection. On the contrary, most of the compounds pertaining to psychiatric and veterinary drug classes had a low frequency of detection. For instance, sulfadoxine and diaverine are the only compounds among veterinary drugs with a high frequency of detection (100% and 94%, respectively). Carbamazepine, venlafaxine, desvenlafaxine, gabapentin, lamotrigine and quetiapine were the compounds detected in 100% of the samples among psychiatric drugs.

Table 5.6 shows the frequency of detection, together with the minimum, maximum and average concentration of the OMPs analysed and classified by class in both HWW and INF considering all the samples. It emerges that 11 compounds show an average concentration higher than 1 μg/L in the INF, namely iopromide (7.14 μg/L), acetaminophen (4.99 μg/L), benzotriazole (4.64 μg/L), gabapentin (3.38 μg/L), azithromycin (3.08 μg/L), caffeine (2.64 μg/L), naproxen (2.09 μg/L), ketoprofen (1.68 μg/L), ciprofloxacin (1.27 μg/L), ofloxacin (1.21 μg/L) and diclofenac (1.04 μg/L), all of them with a frequency of detection of 100% except naproxen. Some of them reached maximum concentrations above 10 μg/L (i.e., iopromide (44.48 μg/L), naproxen (19.62 μg/L), diclofenac (15.49 μg/L) and benzotriazole (10.50 μg/L)). No great differences between the concentration in HWW and INF were found for most of the compounds. However, on some occasions, the concentration was unexpectedly high in the INF compared to the HWW, as for diclofenac (1.04 μg/L *versus* 0.08 μg/L, respectively) and amisulpride (0.12 μg/L *versus* 0.08 μg/L).

Apart from the assessment of the occurrence of OMPs in HWW and INF, the quantification of loads of OMPs discharged from the hospital and entering the WWTP is a great source of information. To this end, OMPs loadings in HWW and INF were calculated, and results are shown in Table S5 of the Supporting Information. OMPs

load refers to the concentration of the contaminant divided by the wastewater flow rate (HWW or INF), to obtain the mass of contaminant per unit of time (in our case mg or g per day). Given that the present study is performed in a full-scale MBR, daily variations of the flow rate are expected, which may cause a discrepancy between the concentrations and the mass loadings found in the OMPs tested.

A total of ten OMPs stood out by their high average loads (> 1 g/d) in the INF: three analgesics/anti-inflammatories, namely acetaminophen (4.4 g/d), naproxen (2.2 g/d) and ketoprofen (1.4 g/d); three antibiotics, azithromycin (2.4 g/d), ciprofloxacin (1.1 g/d) and ofloxacin (1 g/d), one plastic additive: benzotriazole (4.2 g/d); one psychiatric drug, gabapentin (3 g/d); one stimulant, caffeine (2.2 g/d), and the contrast media iopromide (6.4 g/d). By comparing their average loads in HWW and INF, all compounds except iopromide were found at higher loads in the INF, indicating that they are also used in the urban settlement. In the case of iopromide, its presence is solely attributed to the radiology ward of the hospital, where it is used as an X-ray contrast media for medical exams. For this reason, it is not surprising a dilution effect is caused by the inclusion of UWW in the INF, reducing the average load from 7.2 g/d (HWW) to 6.4 g/d (INF).

Table 5.6. Minimum, maximum and average concentration (μg/L) of the 232 OMPs analysed in hospital wastewater (HWW) (n=17) and WWTP influent (INF) (n=18) during the whole experimental campaign. Compounds are divided according to their class and the limit of detection (LOD) and frequency of detection (%) of each compound are also reported.

		HWW				INF			
Compound	**LOD (μg/L)**	**Freq (%)**	**Min conc. (μg/L)**	**Max conc. (μg/L)**	**Average conc. (μg/L)**	**Freq (%)**	**Min conc. (μg/L)**	**Max conc. (μg/L)**	**Average conc. (μg/L)**
Analgesics/anti-inflammatories									
Acetaminophen	0.0051	100	0.134	6.504	5.156 ± 1.806	100	0.095	7.256	4.985 ± 1.91
Acetylsalicylic acid	0.0034	100	0.136	1.212	0.516 ± 0.272	100	0.053	0.776	0.506 ± 0.24
Alfentanil	0.0008	35	<LOD	0.040	0.007 ± 0.012	28	<LOD	0.065	0.006 ± 0.015
Aminopyrine	0.0038	53	<LOD	0.725	0.243 ± 0.257	56	<LOD	1.299	0.312 ± 0.391
Betamethasone 17,21-dipropionate	0.0025	59	<LOD	0.026	0.009 ± 0.008	56	<LOD	0.033	0.01 ± 0.009
Buprenorphine	0.0010	82	<LOD	0.185	0.089 ± 0.052	67	<LOD	0.180	0.078 ± 0.064
Carisoprodol	0.0031	6	<LOD	0.195	0.013 ± 0.047	6	<LOD	0.091	0.007 ± 0.021
Codeine	0.0017	100	0.059	0.417	0.258 ± 0.093	100	0.076	0.407	0.248 ± 0.105
Dextromethorphan	0.0016	0	<LOD	<LOD	<LOD	6	<LOD	0.008	<LOD ± 0.002
Dextropropoxyphene	0.0051	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Diclofenac	0.0009	100	0.026	0.207	0.082 ± 0.048	100	0.050	15.491	1.040 ± 3.607
Etodolac	0.0017	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Fentanyl	0.0011	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Hydrocodone	0.0017	88	<LOD	0.390	0.212 ± 0.115	94	<LOD	0.380	0.220 ± 0.109
Hydromorphone	0.0017	100	0.045	0.371	0.153 ± 0.096	100	0.041	0.327	0.138 ± 0.086
Ibuprofen	0.0018	94	<LOD	1.092	0.579 ± 0.361	100	0.067	1.449	0.596 ± 0.406
Ketoprofen	0.0040	100	0.520	2.340	1.55 ± 0.519	100	0.659	3.828	1.683 ± 0.729
Lidocaine	0.0013	100	0.105	0.403	0.223 ± 0.090	100	0.084	0.384	0.211 ± 0.100
Meloxicam	0.0020	6	<LOD	0.002	<LOD ± 0	0	<LOD	<LOD	<LOD
Morphine	0.0017	100	0.045	0.371	0.155 ± 0.095	100	0.041	0.327	0.139 ± 0.085
Naproxen	0.0012	18	<LOD	23.256	1.929 ± 5.960	17	<LOD	19.621	2.091 ± 6.090
Oxycodone	0.0016	82	<LOD	0.058	0.027 ± 0.018	83	<LOD	0.044	0.021 ± 0.013
Oxymorphone	0.0020	94	<LOD	0.066	0.034 ± 0.016	94	<LOD	0.081	0.038 ± 0.023
Pentazocine	0.0013	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Pethidine	0.0012	18	<LOD	0.008	0.002 ± 0.002	22	<LOD	0.010	0.002 ± 0.003
Phenylbutazone	0.0017	18	<LOD	0.019	0.004 ± 0.007	11	<LOD	0.029	0.003 ± 0.007
Procaine	0.0013	94	<LOD	0.235	0.039 ± 0.059	89	<LOD	0.135	0.038 ± 0.045
Tolfenamic acid	0.0013	6	<LOD	0.007	<LOD ± 0.002	6	<LOD	0.007	<LOD ± 0.002
Tramadol	0.0010	100	0.047	0.452	0.292 ± 0.104	100	0.210	0.482	0.299 ± 0.079
Antiarrhythmic agents									
Amiodarone	0.0027	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Digitoxin	0.0062	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Propafenone	0.0010	100	0.018	0.111	0.056 ± 0.034	94	<LOD	0.201	0.043 ± 0.044
Strophanthidin	0.0040	0	<LOD	<LOD	<LOD	6	<LOD	0.069	0.006 ± 0.016
Strophanthin	0.0044	0	<LOD	<LOD	<LOD	6	<LOD	0.203	0.013 ± 0.047
Antibiotics									
Amoxicillin	0.0020	94	<LOD	0.447	0.101 ± 0.099	89	<LOD	0.219	0.082 ± 0.059
Azithromycin	0.0028	100	1.379	10.483	4.005 ± 2.213	100	1.064	9.873	3.082 ± 2.043
Cinoxacin	0.0011	18	<LOD	0.006	0.001 ± 0.002	17	<LOD	0.008	0.002 ± 0.003
Ciprofloxacin	0.0032	100	0.345	2.884	1.639 ± 0.802	100	0.236	2.834	1.266 ± 0.733
Clarithromycin	0.0023	100	0.013	0.562	0.245 ± 0.148	100	0.026	0.498	0.178 ± 0.112
Doxycycline	0.0015	59	<LOD	2.533	0.639 ± 0.823	61	<LOD	1.947	0.484 ± 0.569
Enoxacin	0.0027	24	<LOD	0.653	0.064 ± 0.164	17	<LOD	0.529	0.065 ± 0.155
Erythromycin	0.0027	100	0.068	1.897	0.565 ± 0.426	89	<LOD	1.441	0.396 ± 0.353
Flumequine	0.0018	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Furazolidon	0.0017	0	<LOD	<LOD	<LOD	6	<LOD	0.010	<LOD ± 0.002
Lomefloxacin	0.0024	76	<LOD	0.185	0.086 ± 0.062	72	<LOD	0.169	0.085 ± 0.062
Metronidazole	0.0015	94	<LOD	0.883	0.304 ± 0.269	100	0.008	0.556	0.152 ± 0.145
Minocycline	0.0035	76	<LOD	0.473	0.204 ± 0.143	56	<LOD	0.787	0.201 ± 0.224
Nalidixic Acid	0.0035	6	<LOD	0.026	<LOD ± 0.006	6	<LOD	0.036	0.004 ± 0.008

Table 5.6 (continued)

		HWW				INF			
Compound	**LOD (µg/L)**	**Freq (%)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Freq (%)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Norfloxacin	0.0024	76	<LOD	0.317	0.075 ± 0.078	61	<LOD	0.284	0.061 ± 0.076
Ofloxacin	0.0037	100	0.494	2.485	1.304 ± 0.561	100	0.504	1.922	1.213 ± 0.490
Oleandomycin	0.0021	76	<LOD	1.481	0.538 ± 0.458	78	<LOD	1.176	0.472 ± 0.419
Oxolinic Acid	0.0015	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Oxytetracycline	0.0043	65	<LOD	0.600	0.112 ± 0.146	50	<LOD	0.315	0.089 ± 0.108
Penicillin G	0.0090	6	<LOD	0.102	0.010 ± 0.024	6	<LOD	0.163	0.013 ± 0.037
Pipemidic acid	0.0032	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Roxithromycin	0.0042	94	<LOD	0.991	0.477 ± 0.312	89	<LOD	1.236	0.469 ± 0.286
Silvadene	0.0023	35	<LOD	1.167	0.149 ± 0.363	44	<LOD	1.075	0.096 ± 0.267
Spiramycin	0.0079	47	<LOD	4.439	1.240 ± 1.505	39	<LOD	2.668	0.752 ± 1.036
Sulfabenzamide	0.0032	47	<LOD	1.524	0.464 ± 0.554	39	<LOD	1.677	0.501 ± 0.676
Sulfadimethoxine	0.0021	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Sulfadimidine	0.0020	18	<LOD	0.060	0.010 ± 0.020	17	<LOD	0.097	0.013 ± 0.029
Sulfafurazole	0.0038	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Sulfaguanidine	0.0014	24	<LOD	0.226	0.033 ± 0.066	22	<LOD	0.142	0.027 ± 0.051
Sulfamerazine	0.0020	35	<LOD	1.766	0.206 ± 0.568	28	<LOD	1.370	0.135 ± 0.390
Sulfamethizole	0.0037	12	<LOD	0.132	0.011 ± 0.032	17	<LOD	0.087	0.011 ± 0.024
Sulfamethoxazole	0.0018	100	0.151	1.315	0.505 ± 0.302	100	0.108	1.230	0.417 ± 0.259
Sulfamethoxydiazine	0.0038	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Sulfamethoxypyridazine	0.0011	6	<LOD	0.055	0.004 ± 0.013	6	<LOD	0.006	<LOD ± 0.001
Sulfanilamide	0.0033	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Sulfaphenazole	0.0026	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Sulfapyridine	0.0017	94	<LOD	0.320	0.070 ± 0.079	83	<LOD	0.211	0.057 ± 0.058
Sulfathiazole	0.0017	65	<LOD	0.361	0.141 ± 0.135	50	<LOD	0.441	0.161 ± 0.179
Tinidazole	0.0021	6	<LOD	1.208	0.072 ± 0.293	6	<LOD	1.567	0.088 ± 0.369
Trimethoprim	0.0011	100	0.070	0.541	0.211 ± 0.125	100	0.065	0.388	0.172 ± 0.087
Antifungals									
Sulfacetamide	0.0017	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Terbinafine	0.0015	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Tiabendazole	0.0007	12	<LOD	0.003	<LOD ± 0.001	6	<LOD	0.003	<LOD ± 0.001
Antihistamines									
Diphenhydramine	0.0018	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Promethazine	0.0030	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Antihypertensives									
Clonidine	0.0003	29	<LOD	0.002	0.001 ± 0.001	22	<LOD	0.002	0 ± 0.001
Antiparasitics									
Albendazole	0.0014	41	<LOD	1.972	0.132 ± 0.476	17	<LOD	0.031	0.003 ± 0.008
Flubendazole	0.0033	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Levamisole	0.0032	24	<LOD	0.146	0.019 ± 0.045	17	<LOD	0.101	0.016 ± 0.034
Mebendazole	0.0013	24	<LOD	1.489	0.092 ± 0.360	11	<LOD	0.031	0.003 ± 0.007
Praziquantel	0.0026	59	<LOD	0.206	0.056 ± 0.062	61	<LOD	0.172	0.065 ± 0.059
Triclabendazole	0.0010	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Antiseptics									
Nitrofural	0.0021	12	<LOD	1.453	0.096 ± 0.352	11	<LOD	1.686	0.105 ± 0.397
Beta-blockers									
Atenolol	0.0012	100	0.196	0.600	0.438 ± 0.130	100	0.155	0.841	0.524 ± 0.184
Bisoprolol	0.0026	100	0.057	0.152	0.097 ± 0.027	100	0.051	0.165	0.101 ± 0.034
Metoprolol	0.0016	100	0.007	0.214	0.086 ± 0.065	94	<LOD	0.221	0.084 ± 0.072
Calcium channel blockers									
Verapamil	0.0012	71	<LOD	0.113	0.046 ± 0.042	89	<LOD	0.112	0.047 ± 0.035
Diuretics									
Torasemide	0.0024	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD

Table 5.6 (continued)

		HWW				INF			
Compound	**LOD (µg/L)**	**Freq (%)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Freq (%)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Drug metabolites									
10-Hydroxycarbazepine	0.0013	82	<LOD	1.663	0.619 ± 0.526	78	<LOD	1.503	0.602 ± 0.469
2-NP-AOZ	0.0020	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
4-Acetylaminoantipyrine	0.0019	82	<LOD	0.193	0.052 ± 0.054	94	<LOD	0.176	0.054 ± 0.048
4-FormylAminoAntipyrine	0.0012	88	<LOD	0.147	0.044 ± 0.040	94	<LOD	0.134	0.050 ± 0.040
6-Acetylmorphine	0.0013	88	<LOD	0.686	0.099 ± 0.215	72	<LOD	0.665	0.068 ± 0.172
7-Aminoclonazepam	0.0008	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
7-Aminoflunitrazepam	0.0008	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Acetylcodeine	0.0019	41	<LOD	0.017	0.005 ± 0.006	33	<LOD	0.019	0.005 ± 0.006
Benzoylecgonine	0.0019	100	0.071	0.421	0.242 ± 0.114	100	0.104	0.403	0.267 ± 0.083
Buprenorphine glucuronide	0.0037	47	<LOD	0.414	0.122 ± 0.147	33	<LOD	0.528	0.107 ± 0.177
Cocaethylene	0.0005	53	<LOD	0.099	0.035 ± 0.040	44	<LOD	0.111	0.029 ± 0.038
Cotinine	0.0022	100	0.424	0.701	0.553 ± 0.095	100	0.434	0.838	0.626 ± 0.114
Desalkylflurazepam	0.0009	12	<LOD	0.006	0.001 ± 0.001	6	<LOD	0.006	<LOD ± 0.001
Ecgonine methyl ester	0.0038	100	<LOD	0.485	0.096 ± 0.148	100	<LOD	0.253	0.048 ± 0.074
EDDP	0.0008	94	<LOD	0.085	0.030 ± 0.019	89	<LOD	0.067	0.022 ± 0.016
Morphine-6-β-D-glucuronide	0.0012	35	<LOD	0.153	0.032 ± 0.052	22	<LOD	0.156	0.022 ± 0.049
N-Desmethylclozapine	0.0025	12	<LOD	0.013	<LOD ± 0.003	6	<LOD	0.010	<LOD ± 0.002
Norbuprenorphine	0.0049	59	<LOD	0.576	0.059 ± 0.136	50	<LOD	1.139	0.089 ± 0.266
Norfentanyl	0.0012	94	<LOD	0.105	0.029 ± 0.026	89	<LOD	0.085	0.026 ± 0.020
Norpethidine	0.0017	88	<LOD	0.076	0.030 ± 0.019	78	<LOD	0.074	0.023 ± 0.019
Norpropoxyphene	0.0017	6	<LOD	0.024	0.002 ± 0.006	0	<LOD	<LOD	<LOD
O-Desmethyltramadol	0.0012	100	0.058	0.436	0.198 ± 0.144	100	0.108	0.479	0.265 ± 0.120
Ritalinic acid	0.0023	29	<LOD	0.228	0.033 ± 0.070	44	<LOD	0.108	0.02 ± 0.034
α-Hydroxyalprazolam	0.0026	6	<LOD	0.018	<LOD ± 0.004	6	<LOD	0.024	<LOD ± 0.005
α-Hydroxymidazolam	0.0007	100	0.005	0.052	0.014 ± 0.012	100	0.004	0.043	0.013 ± 0.009
α-Hydroxytriazolam	0.0018	12	<LOD	0.109	0.009 ± 0.027	11	<LOD	0.042	0.004 ± 0.010
Hormones									
Fludrocortisone-Acetate	0.0038	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Flumethasone	0.0030	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Hydrocortisone	0.0016	88	<LOD	0.357	0.126 ± 0.128	83	<LOD	0.438	0.101 ± 0.138
Methylprednisolone	0.0051	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Mometasone furoate	0.0020	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Prednicarbate	0.0038	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Prednisolone	0.0065	12	<LOD	0.187	0.019 ± 0.048	0	<LOD	<LOD	<LOD
Triamcinolone	0.0010	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Triamcinolone Acetonide	0.0019	24	<LOD	0.155	0.029 ± 0.055	22	<LOD	0.215	0.032 ± 0.063
Illicit drugs									
Cocaine	0.0030	29	<LOD	0.053	0.012 ± 0.019	44	<LOD	0.073	0.017 ± 0.023
Ketamine	0.0020	18	<LOD	0.021	0.003 ± 0.006	17	<LOD	0.018	0.003 ± 0.005
MDA	0.0036	100	0.022	2.234	0.790 ± 0.787	78	<LOD	2.293	0.911 ± 0.790
MDEA	0.0017	59	<LOD	0.117	0.017 ± 0.028	44	<LOD	0.033	0.008 ± 0.011
MDMA	0.0014	76	<LOD	0.198	0.027 ± 0.049	50	<LOD	0.289	0.037 ± 0.074
Phencyclidine	0.0038	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Plastic additives									
Benzotriazole	0.0017	100	1.212	9.191	4.847 ± 2.181	100	0.891	10.500	4.643 ± 2.724

Table 5.6 (continued)

		HWW				INF			
Compound	**LOD (µg/L)**	**Freq (%)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Freq (%)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
p-Toluenesulfonamide	0.0025	59	<LOD	0.386	0.068 ± 0.096	39	<LOD	0.233	0.036 ± 0.062
Psychiatric drugs									
Alprazolam	0.0016	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Amisulpride	0.0015	53	<LOD	0.080	0.013 ± 0.021	83	<LOD	0.937	0.117 ± 0.298
Amitriptyline	0.0013	47	<LOD	0.190	0.022 ± 0.05	39	<LOD	0.149	0.011 ± 0.035
Amoxapine	0.0019	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Bromazepam	0.0019	0	<LOD	<LOD	<LOD	11	<LOD	0.490	0.028 ± 0.115
Carbamazepine	0.0008	100	0.043	0.264	0.129 ± 0.058	100	0.106	0.290	0.192 ± 0.062
Chlordiazepoxide	0.0022	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Chlorprothixene	0.0033	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Citalopram	0.0024	100	0.020	0.098	0.031 ± 0.018	89	<LOD	0.054	0.023 ± 0.013
Clobazam	0.0014	12	<LOD	0.005	<LOD ± 0.001	0	<LOD	<LOD	<LOD
Clomipramine	0.0017	18	<LOD	0.036	0.005 ± 0.010	11	<LOD	0.136	0.010 ± 0.032
Clonazepam	0.0024	0	<LOD	<LOD	<LOD	6	<LOD	0.020	<LOD ± 0.005
Clorazepate	0.0032	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Clozapine	0.0012	41	<LOD	0.059	0.011 ± 0.018	33	<LOD	0.036	0.006 ± 0.010
Desipramine	0.0040	6	<LOD	0.170	0.012 ± 0.041	0	<LOD	<LOD	<LOD
Desvenlafaxine	0.0010	100	0.014	0.070	0.034 ± 0.016	100	0.029	0.103	0.054 ± 0.020
Dexametasone	0.0032	18	<LOD	0.405	0.053 ± 0.127	6	<LOD	0.304	0.018 ± 0.071
Diazepam	0.0015	6	<LOD	0.006	<LOD ± 0.001	0	<LOD	<LOD	<LOD
Dothiepin	0.0024	24	<LOD	0.130	0.023 ± 0.043	17	<LOD	0.104	0.016 ± 0.035
Doxepin	0.0017	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Felbamate	0.0018	6	<LOD	0.173	0.011 ± 0.042	6	<LOD	0.204	0.012 ± 0.048
Fluoxetine	0.0018	76	<LOD	0.038	0.016 ± 0.010	78	<LOD	0.029	0.016 ± 0.010
Flupentixol	0.0016	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Flurazepam	0.0010	0	<LOD	<LOD	<LOD	6	<LOD	0.009	<LOD ± 0.002
Fluvoxamine	0.0014	65	<LOD	0.103	0.033 ± 0.034	56	<LOD	0.102	0.031 ± 0.035
Gabapentin	0.0009	100	0.501	5.065	2.611 ± 1.375	100	1.259	5.332	3.376 ± 1.226
Haloperidol	0.0012	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Imipramine	0.0005	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Lamotrigine	0.0011	100	0.051	0.324	0.187 ± 0.095	100	0.131	0.435	0.262 ± 0.098
Lorazepam	0.0020	82	<LOD	0.166	0.088 ± 0.053	72	<LOD	0.132	0.072 ± 0.048
Maprotiline	0.0010	88	<LOD	0.082	0.027 ± 0.019	89	<LOD	0.062	0.019 ± 0.014
Medazepam	0.0030	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Memantine	0.0019	88	<LOD	0.068	0.016 ± 0.015	94	<LOD	0.057	0.021 ± 0.016
Mianserin	0.0015	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Mirtazapine	0.0021	59	<LOD	0.018	0.007 ± 0.006	50	<LOD	0.019	0.007 ± 0.007
Naltrexone	0.0024	18	<LOD	0.024	0.004 ± 0.008	17	<LOD	0.026	0.005 ± 0.008
Nitrazepam	0.0030	47	<LOD	0.097	0.029 ± 0.032	39	<LOD	0.097	0.027 ± 0.035
Nordiazepam	0.0011	6	<LOD	0.004	<LOD ± 0.001	11	<LOD	0.004	<LOD ± 0.001
Nortriptyline	0.0015	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Olanzapine	0.0034	35	<LOD	0.148	0.027 ± 0.043	33	<LOD	0.069	0.018 ± 0.025
Opipramol	0.0013	12	<LOD	0.022	0.003 ± 0.006	11	<LOD	0.017	0.002 ± 0.005
Oxazepam	0.0011	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Oxcarbazepine	0.0018	71	<LOD	0.141	0.025 ± 0.035	56	<LOD	0.055	0.016 ± 0.018
Paliperidone	0.0014	6	<LOD	0.158	0.010 ± 0.038	6	<LOD	0.114	0.007 ± 0.027
Paroxetine	0.0030	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Phenazepam	0.0025	24	<LOD	0.426	0.053 ± 0.116	11	<LOD	0.441	0.031 ± 0.105
Phenytoin	0.0049	65	<LOD	0.210	0.061 ± 0.060	67	<LOD	0.165	0.073 ± 0.061
Pipamperone	0.0021	6	<LOD	0.009	<LOD ± 0.002	6	<LOD	0.009	<LOD ± 0.002
Prazepam	0.0012	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Promazine	0.0039	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Protriptyline	0.0012	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Quetiapine	0.0015	94	<LOD	0.048	0.023 ± 0.010	100	0.007	0.040	0.020 ± 0.010
Risperidone	0.0015	47	<LOD	0.107	0.025 ± 0.042	33	<LOD	0.127	0.025 ± 0.046
Secobarbital	0.0017	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Sertraline	0.0028	6	<LOD	0.006	<LOD ± 0.001	0	<LOD	<LOD	<LOD
Temazepam	0.0019	35	<LOD	0.032	0.006 ± 0.009	39	<LOD	0.048	0.008 ± 0.012
Topiramate	0.0023	6	<LOD	0.054	0.004 ± 0.013	11	<LOD	0.032	0.003 ± 0.007

Table 5.6 (continued)

		HWW				INF			
Compound	**LOD (µg/L)**	**Freq (%)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Freq (%)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Trazodone	0.0019	94	<LOD	0.076	0.033 ± 0.019	94	<LOD	0.084	0.030 ± 0.019
Triazolam	0.0012	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Trimipramine	0.0030	6	<LOD	0.249	0.016 ± 0.060	6	<LOD	0.058	0.005 ± 0.013
Venlafaxine	0.0008	100	0.015	0.086	0.046 ± 0.025	100	0.026	0.119	0.056 ± 0.026
Zolpidem	0.0011	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Zopiclone	0.0038	6	<LOD	0.032	<LOD ± 0.007	0	<LOD	<LOD	<LOD
Receptor antagonists									
Atropine	0.0020	6	<LOD	0.009	<LOD ± 0.002	0	<LOD	<LOD	<LOD
Flumazenil	0.0039	6	<LOD	0.016	<LOD ± 0.003	6	<LOD	0.014	<LOD ± 0.003
Stimulants									
Amphetamine	0.0020	94	<LOD	11.258	1.27 ± 3.264	100	0.025	1.634	0.287 ± 0.402
Caffeine	0.0015	100	1.652	3.976	2.301 ± 0.594	100	1.648	5.971	2.637 ± 1.221
Cannabinol	0.0045	35	<LOD	0.057	0.013 ± 0.018	28	<LOD	0.024	0.005 ± 0.006
Methadone	0.0032	47	<LOD	0.085	0.016 ± 0.022	33	<LOD	0.056	0.012 ± 0.017
Methamphetamine	0.0010	6	<LOD	0.014	0.001 ± 0.003	11	<LOD	0.013	0.002 ± 0.004
Methylphenidate	0.0042	47	<LOD	0.020	0.009 ± 0.008	44	<LOD	0.023	0.009 ± 0.008
Phentermine	0.0026	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
THC	0.0029	76	<LOD	0.110	0.03 ± 0.026	50	<LOD	0.247	0.037 ± 0.061
UV filters									
Octyl methoxycinnamate	0.0017	88	<LOD	0.110	0.06 ± 0.031	94	<LOD	0.220	0.098 ± 0.053
Veterinary drugs									
Carprofen	0.0019	18	<LOD	0.135	0.013 ± 0.034	17	<LOD	0.132	0.016 ± 0.036
Diaveridine	0.0016	94	<LOD	0.773	0.378 ± 0.163	94	<LOD	0.657	0.405 ± 0.161
Difloxacin	0.0040	12	<LOD	0.022	<LOD ± 0.005	17	<LOD	0.014	<LOD ± 0.004
Dimetridazole	0.0011	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Enrofloxacin	0.0021	18	<LOD	0.013	0.003 ± 0.004	6	<LOD	0.003	<LOD ± 0.001
Flunixin	0.0018	59	<LOD	0.017	0.009 ± 0.007	50	<LOD	0.022	0.009 ± 0.009
Furaltadone	0.0028	71	<LOD	0.115	0.055 ± 0.04	61	<LOD	0.111	0.047 ± 0.041
Ipronidazole	0.0011	6	<LOD	0.006	<LOD ± 0.001	6	<LOD	0.002	<LOD ± 0
Marbofloxacin	0.0036	59	<LOD	1.462	0.297 ± 0.423	50	<LOD	0.777	0.191 ± 0.251
Monensin	0.0024	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Orbifloxacin	0.0023	0	<LOD	<LOD	<LOD	6	<LOD	0.008	<LOD ± 0.002
Oxibendazole	0.0010	6	<LOD	0.004	<LOD ± 0.001	6	<LOD	0.005	<LOD ± 0.001
Ronidazole	0.0027	6	<LOD	0.034	0.003 ± 0.008	6	<LOD	0.029	0.003 ± 0.007
Salinomycin	0.0081	6	<LOD	0.552	0.036 ± 0.133	6	<LOD	0.500	0.032 ± 0.117
Sarafloxacin	0.0039	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Sulfachlorpyridazine	0.0011	24	<LOD	0.065	0.011 ± 0.021	22	<LOD	0.049	0.008 ± 0.015
Sulfaclozine	0.0013	6	<LOD	0.046	0.003 ± 0.011	11	<LOD	0.076	0.007 ± 0.020
Sulfadoxine	0.0027	100	<LOD	<LOD	<LOD	100	<LOD	<LOD	<LOD
Sulfamonomethoxine	0.0017	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Sulfanitran	0.0022	0	<LOD	<LOD	<LOD	0	<LOD	<LOD	<LOD
Sulfaquinoxaline	0.0015	18	<LOD	0.060	0.009 ± 0.02	6	<LOD	0.152	0.009 ± 0.036
Tilmicosin	0.0038	6	<LOD	0.335	0.021 ± 0.081	6	<LOD	0.178	0.012 ± 0.042
X-Ray contrast media									
Iopromide	0.0010	100	0.294	50.728	11.896 ± 15.428	100	0.221	44.481	7.143 ± 10.26

5.3.3. Removal of organic micropollutants in MBR coupled to PAC and MBR alone

The removal of OMPs was evaluated in the three treatments tested (*noPAC*, *0.1PAC* and *0.2PAC*). In this study, the number of OMPs analysed was higher than in other studies with similar characteristics, hindering the analysis of the results obtained. For this reason, the characterization of the HWW and INF was essential to establish the criteria by which the most relevant results to expose are selected. We decided to collate and discuss the data at different levels, from the micro-level (compound-specific removal efficiencies) to the macro-level (total loads of OMPs). In this way, we were able to address the efficiency of each treatment from different perspectives.

The criteria to select the compounds and classes from which the removal efficiencies were compared was based on their frequency of detection, concentration, and literature data. For each OMP class, only compounds with a frequency of detection greater than 50% in the INF, which were present in at least two treatments were selected. In this way, we were able to compare the results of the treatments applied with a certain degree of confidence.

The abovementioned classes which had the highest frequencies of detection for all the compounds they included were considered in full (i.e., contrast-media, beta-blockers, UV filters and calcium channel blockers). For hormones, plastic additives, antiparasitics and antiarrhythmics classes, only one compound met the requirements for selection, hydrocortisone, benzotriazole, praziquantel and propafenone, respectively. The classes with compounds which were found by no means or at very low frequencies of detection were discarded for the analysis, namely antihistamines, diuretics, receptor antagonists, antiseptics, antifungals and antihypertensives. As for the remaining classes, the number of compounds selected varied: analgesics/anti-inflammatories (17 out of 29), drug metabolites (13 out of 26), antibiotics (18 out of 40), psychiatric drugs (17 out of 63), veterinary drugs (4 out of 22), stimulants (3 out of 8), illicit drugs (2 out of 6). The total number of OMPs considered at compound-level was 84. In any case, the concentrations of all the tested OMPs in each sampling point can be found in Table S6 (for *noPAC* treatment), Table S7 (for *0.1PAC* treatment) and Table S8 (for 0.2PAC treatment) on the Supporting Information, so the reader may have a glaze of the treatment efficiency for the not selected compounds.

In the following subsections, a higher OMP concentration in the effluent is sometimes found with respect to the influent concentration, leading to a negative removal. Although efforts were made to find specific answers for each OMP to this phenomenon, it is worth noting that negative removal may be caused by many factors (Kumar et al., 2022). OMP negative removal may be ascribed to the deconjugation of conjugated compounds, transformation of a metabolite or transformation product into the corresponding parent compound during the treatment, changes in the environmental conditions (i.e., significant decrease of the temperature) or desorption of the OMP attached to the particulate matter (i.e., sludge or, in this case, PAC)

(Alvarino et al., 2016; Kumar et al., 2022; Verlicchi et al., 2012b). On the other side, in the case of transformation products this phenomenon is expected, since they are formed from the partial degradation of the parent compound during the wastewater treatment. In most cases, negative removal is caused by the ion suppression during their quantification in the LC-MS, which leads to the miscalculation of the OMP concentration (Reemtsma, 2003). In this study, the direct injection of filtrated wastewater samples may have caused ion suppression of the analytes found at higher concentration or within the samples of higher complexity (i.e., INF).
Finally, as often remarked in literature, an inappropriate sampling protocol (e.g., use of grab samples, not considering the HRT), can lead to misleading results, being the flow proportional composite sampling mode the approach which brings the most reliable measurements (Verlicchi and Ghirardini, 2019). In this study, 24-h proportional composite samples of the INF and the MBR permeate were taken considering the HRT in the WWTP (= 24 h).

Analgesics/anti-inflammatories

The analgesics/anti-inflammatories group had very good results from both the MBR and PAC treatments (Figure 5.8). Six out of 17 pharmaceuticals showed no improvement in the addition of PAC since the removal efficiencies in the MBR were already very high (>90%). In this case, the differences among the treatments were less than 5%, and the compounds were therefore easily biodegraded or absorbed into the sludge. Other compounds, such as codeine, oxymorphone and buprenorphine further improved their removals with the addition of PAC even though they were already highly removed in the MBR (80% – 84%).
Nevertheless, the increase of the PAC concentration inside the reactor does not have a straightforward effect on the OMP removal efficiencies. For instance, PAC addition had a positive effect on acetylsalicylic acid removal, but it was not proportional to the PAC dose. The compound went from being released in the MBR to achieving a low to medium removal with the addition of PAC, with higher results achieved with *0.1PAC* (56%) compared to *0.2PAC* (20%). On the contrary, increasing the dose of PAC had a significant effect on procaine, lidocaine, tramadol and diclofenac. For these compounds, the addition of 0.2 g/L of PAC contributed to achieving medium removal efficiencies (43–67%), compared to very low removal or even release during the MBR operation. Diclofenac is a hydrophobic recalcitrant compound (Radjenović et al., 2009), with low removal efficiency in MBR (Alvarino et al., 2017; Wijekoon et al., 2013). Nguyen et al. (Nguyen et al., 2013) found that the removal in MBR with 0.1 g/L was approximately 15% (as in our study), whereas an increment up to 70% in the removal efficiency was observed with 0.5 g/L of PAC. Diclofenac removal seems to be influenced not only by the PAC dose but also by the presence of fresh PAC. High DCF removal efficiencies were only observed for a limited period of time without any new addition of fresh PAC in similar studies (Alvarino et al., 2017; Serrano et al., 2011). Regarding ibuprofen, a decrease in its removal efficiency was unexpectedly observed

during PAC treatments. However, the average removal was maintained high (76% - 95%) among treatments. According to previous studies, ibuprofen has a low affinity to solids and its main removal mechanism is biodegradation (Alvarino et al., 2017; Serrano et al., 2011). In these studies, no differences in the removal were observed between the biological treatment and the addition of PAC, indicating that the decrease observed in our study may not be attributed to the presence of the adsorbent.

Antibiotics

The effect of the activated carbon in antibiotics was more remarkable than for analgesics/anti-inflammatories (Figure 5.8). The removal of most compounds (11 out of 18) improved and, for seven of them, the removal efficiencies increased in the range of 33 – 89% with PAC addition. During MBR treatment, OMP release was observed for four compounds, which then reached from moderate (i.e., ofloxacin 42%, sulfathiazole 33% and lomefloxacin 59%) to high (i.e., sulfapyridine, 89%) removal efficiencies with PAC addition. Among them, sulfathiazole was the only one considerably affected by PAC concentration, with a 30% of increment between *0.1PAC* and *0.2PAC* treatments. In any case, differences among PAC treatments were not only seen for sulfadiazine. Doxycycline increased its removal by 40% in each PAC treatment, leading to a very high removal with the addition of 0.2 g/L of PAC. In particular, it went from 19% with *noPAC* to 59% in *0.1PAC* and 99% in *0.2PAC*. Instead, oxytetracycline and sulfamethoxazole needed a concentration of 0.2 g/L to see a clear impact on their removal. The removal of both compounds is ascribed to mainly biodegradation processes, with no further improvement with the addition of PAC (Alvarino et al., 2016; Alvarino et al., 2017). It seems that at low PAC concentrations (0.1 g/L) the governing removal mechanism for this compound is mainly biodegradation, whereas at higher doses the mode of degradation changes (i.e., adsorption combined to biodegradation) and sulfamethoxazole passes to be degraded on PAC surface, due to the interaction PAC-sludge (Li et al., 2011).

Nguyen et al. (2013) obtained moderate removal efficiencies for metronidazole in MBR (40%) that improved to approximately 70% with 0.1 and 0.5 g/L of PAC. In our system, we got highly variable removal in both *0.1PAC* (negative rem. – 78%) and *0.2PAC* (3% – 90%) treatments, and no explanation has been found for such results.

Azithromycin, erythromycin and roxithromycin are compounds frequently studied in the literature (Luo et al., 2014; Rizzo et al., 2019; Sipma et al., 2010; Verlicchi et al., 2012b). They present a complex structure with high molecular weight, and they have been removed from a moderate to a high range in biological treatments (Alvarino et al., 2018; Asif et al., 2020; Echevarría et al., 2019; Serrano et al., 2011). Erythromycin has shown a better removal in MBR compared to CAS systems, probably due to the higher SRTs (Echevarría et al., 2019). When PAC is added, the removal of erythromycin is probably improved because the adsorption onto PAC enhances its retention inside the reactor, and subsequently, its biodegradation in the PAC-sludge complex (Echevarría et al., 2019). Additionally, the removal has been shown to improve with the increase in the PAC dose (Alvarino et al., 2017; Echevarría et al.,

2019; Serrano et al., 2011). In this way, it seems that erythromycin is subjected to both adsorption onto PAC and biodegradation inside the MBR reactor. The same principle applies to azithromycin and roxithromycin, with results in line with the literature data (Alvarino et al., 2017; Asif et al., 2020; Serrano et al., 2011). The removal of erythromycin went from 75% in *noPAC* to 88% in *0.1PAC* and 94% in *0.2PAC*. As for azithromycin, removal was maintained above 95% in all three treatments. Finally, roxithromycin increased its removal from 72% in noPAC treatment to 82% – 92% with the addition of PAC.

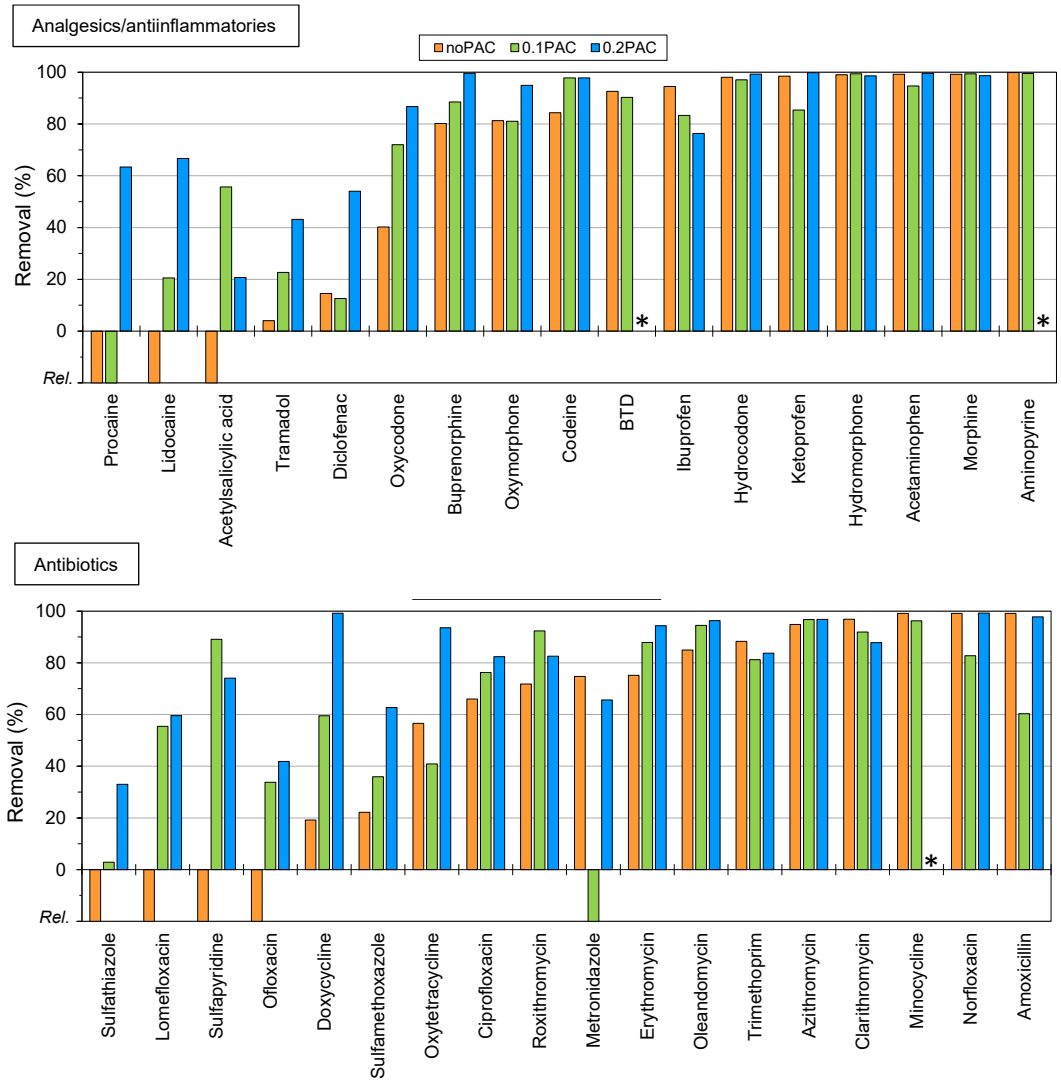

Figure 5.8. Removal efficiencies of selected OMPs pertaining to analgesics/anti-inflammatories and antibiotic classes during *noPAC* treatment (only MBR), *0.1PAC* treatment (MBR+0.1 g/L PAC) and *0.2PAC* treatment (MBR+0.2 g/L PAC). Removal is calculated as the average removal of the individual removal efficiencies in each treatment. * indicates that the removal efficiency was not calculated since the compound was undetected in both INF and MBR permeate. *Rel.* implies the compound was released from the WWTP ($conc._{MBRperm}$ > $conc._{INF}$) and therefore the removal was negative. *BTD* refers to betamethasone 17,21-dipropionate.

Drug metabolites

Drug metabolites represent a vast group of OMPs characterized by being the product of the metabolization of a parent compound (i.e., pharmaceutical) in the human body. Drug metabolites are usually a more polar and hydrophilic form of the parent compound (Fatta-Kassinos et al., 2011). Pharmaceuticals consumed in the hospital and/or at home may be completely or partially metabolized in the human body, and thus the interpretation of the results depicted in Figure 5.9 must be considered together with the corresponding parent compound. Nevertheless, most of the pharmaceuticals from which compounds of this class derive are not depicted in the rest of the figures, since they didn't meet the criteria for their selection at the compound-level discussion (i.e., their frequency of detection was less than 50% in the INF). Being said that, Table S1 of the Supp. Inf. lists the corresponding parent compound of each drug metabolite analysed in this study, and Tables S6, S7, and S8 show their concentrations in each treatment and sampling point. The fact that the corresponding parent compounds were not frequently found is probably because they were completely metabolized or degraded before arriving at the WWTP influent, empathizing the fact that it is important to consider the drug metabolites in these kinds of investigations.

It is worth highlighting that the compounds pertaining to this class may be also considered transformation products from chemical and biological reactions that take place during their transport in sewage or during the wastewater treatment (Fatta-Kassinos et al., 2011). However, they were classified in this class due to the existing information about their excretion from human metabolism, although it cannot be discarded that other studies may define them differently.

Since OMPs may undergo several transformations on their way through the human body, the sewage, the WWTP and finally the environment, little information is currently available on the drug metabolites/transformation products that can be created (Fatta-Kassinos et al., 2011). Even at environmental concentrations, they may be potentially toxic and cause potential damage to human health and the aquatic life. In this sense, adsorption onto PAC provides a great advantage over other hybrid systems since compounds adsorbed are completely removed from the wastewater (Kovalova et al., 2013).

Most of the compounds pertaining to this group improve their removal efficiencies with the addition of PAC. On a few occasions, the effect of the activated carbon was negligible or little relevant. Some compounds showed high removals (>94 %) with less than 5% of variation among treatments (i.e., benzoylecgonine, cotinine and norbuprenorphine). For O-desmethyltramadol and 10-hydroxycarbamazepine, the influence of the activated carbon was not clear, although it showed higher removal efficiencies in at least one treatment (*0.1PAC* or *0.2PAC*). For the rest of the compounds, the increase of PAC concentration inside the reactor entailed an increment in the corresponding removal efficiency of between 12% and 67%. Two compounds, norfentanyl and norpethidine, remarkably increased their removal (up to 67%) by increasing the PAC dose (0.2 g/L PAC).

4-acetylaminoantpyrine and 4-formylaminoantipyrine are two metabolites of aminopyrine. They are moderately hydrophilic compounds and have been found in MBR effluents treating hospital wastewater (Kovalova et al., 2013), with partial elimination due to PAC adsorption. In our study, 0.2 g/L of PAC was needed to achieve 19% and 45% of removal for 4-formylaminoantipyrine and 4-acetylaminoantpyrine, respectively.

Psychiatric drugs

Psychiatric drugs is the class of OMPs with the best results achieved by the addition of PAC (Figure 5.9). Considering only the biological treatment (*noPAC*), 10 out of 17 compounds were not removed at all, with higher concentrations found in the effluent compared to the influent of the WWTP. In most cases, a concentration of 0.1 g/L of PAC was enough to significantly increase the removal (e.g., amisulpride, mirtazapine). But for memantine and phenytoin, good results were solely obtained with *0.2PAC* treatment (66% and 93% increase in their removal efficiencies, respectively). Five compounds, namely fluoxetine, fluvoxamine, gabapentin, quetiapine and trazodone were well removed by the MBR, and little effect of PAC was observed. Margot et al. (Margot et al., 2013) obtained less than 20% of removal for gabapentin in a full-scale MBR coupled to PAC as a post-treatment. The authors remarked that the removal of this compound was less than 10% in the MBR and, due to its hydrophilic nature, only a 10% increase was observed by the addition of PAC. In our study, we achieved a removal of 81% in the MBR and, in agreement with Margot et al. (Margot et al., 2013), only a 10% increase in the removal efficiency was observed in both PAC treatments (up to 91%).

Carbamazepine, desvenlafaxine and venlafaxine are compounds known for their recalcitrant nature and unwillingness to biological degradation (Margot et al., 2013; Radjenović et al., 2009). For these compounds, moderate removal efficiencies (38 – 47%) were achieved with a concentration of 0.2 g/L of PAC. In previous studies, moderate removal (approx. 50%) (Nguyen et al., 2013) and high removal (87%) (Li et al., 2011) were obtained with 0.1 g/L PAC. Experiments testing 1 g/L of PAC achieved up to a 92% in their removal efficiencies (Li et al., 2011; Serrano et al., 2011). However, all these studies were conducted at laboratory scale MBRs with synthetic wastewater, causing a decrease in the DOM competition effect. Indeed, carbamazepine has proved to be greatly dependent on the presence of fresh (i.e., unsaturated) PAC, showing an abrupt increment in its removal efficiency immediately after PAC addition and a subsequent decrement over time (Alvarino et al., 2017). This compound has been suggested as an indicator of PAC saturation of the active sites for adsorption (Echevarría et al., 2019). In our study, the removal likely varied depending on the sampling day with respect to the addition of fresh PAC, resulting in a moderate average removal in *0.2PAC* treatment.

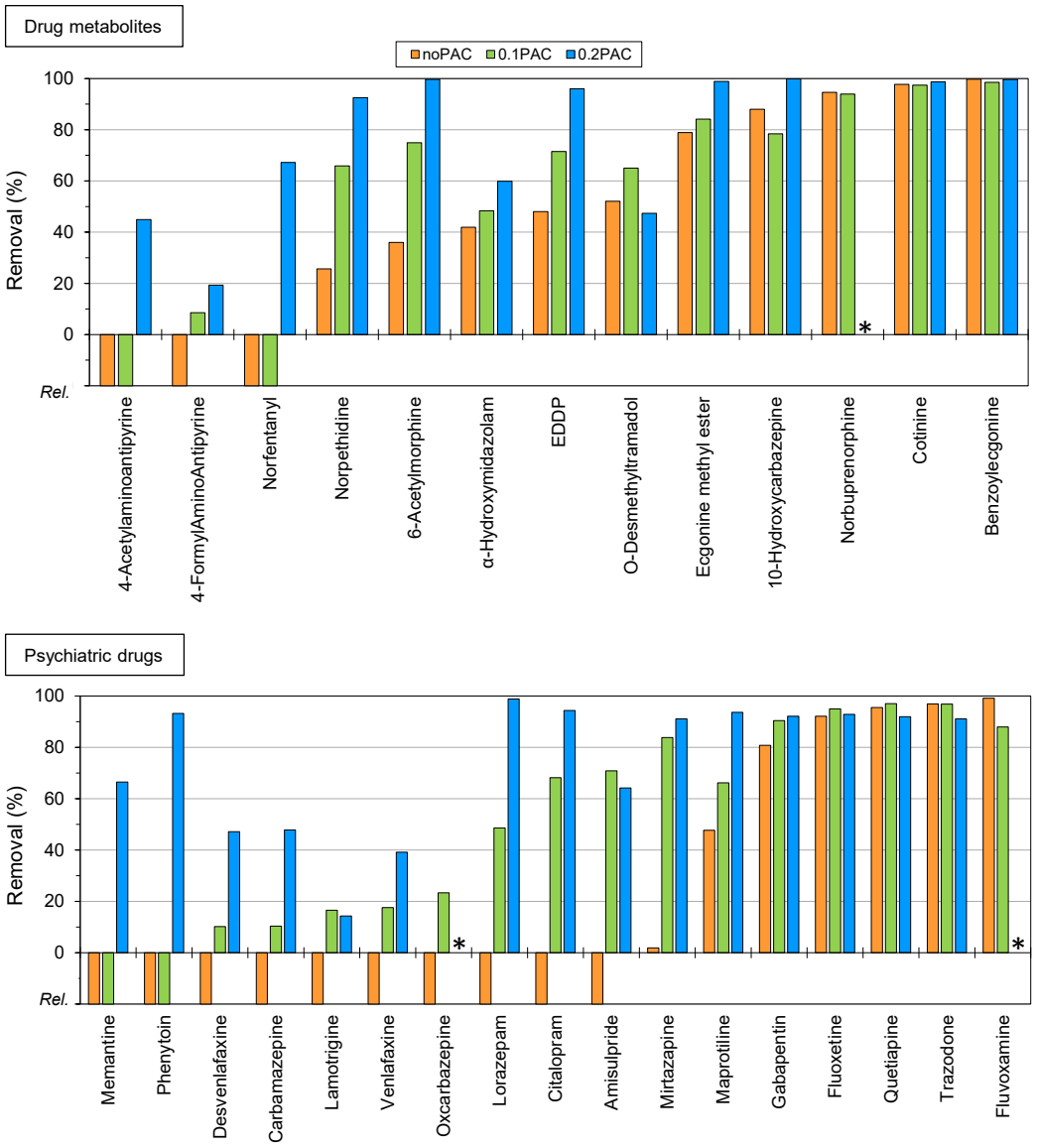

Figure 5.9. Removal efficiencies of selected OMPs pertaining to drug metabolites and psychiatric drugs during *noPAC* treatment (only MBR), *0.1PAC* treatment (MBR+0.1 g/L PAC) and *0.2PAC* treatment (MBR+0.2 g/L PAC). Removal is calculated as the average removal of the individual removal efficiencies in each treatment. * indicates that the removal efficiency was not calculated since the compound was undetected in both INF and MBR permeate. *Rel.* implies the compound was "released" at a higher concentration from the WWTP ($conc._{MBRperm} > conc._{INF}$) and therefore the removal was negative.

Other classes

Figure 5.10 shows the removal efficiencies of the OMP classes for which all or a certain fraction of the analysed compounds meet the selection criteria. They casually are the group of compounds with better results obtained in the MBR treatment (average removal of 71%), apart from three exceptions, metoprolol and flunixin, that obtained very low removal efficiencies. In this graph, 11 out of 19 compounds were not affected by the presence of PAC, while 5 of them were positively influenced (praziquantel, propafenone, MDA, MDMA, amphetamine, caffeine). Their removal efficiencies increased from moderate (57% – 67%) in *noPAC* treatment to high (79 % – 97%) in *0.2PAC* treatment.

Beta-blockers, atenolol and bisoprolol showed high removal efficiencies in all the treatments (>91%), in agreement with the literature (Echevarría et al., 2019; Kårelid et al., 2017; Kovalova et al., 2013). Metoprolol instead was removed a 20% on average in *noPAC* treatment, while for *0.1PAC* and *0.2PAC* treatments the overall removal was negative (implying a higher concentration in the permeate). Indeed, the daily removal efficiencies of this compound were highly variable, ranging from negative values up to 75% (data not shown). Margot et al. (2013) found higher concentrations of this pharmaceutical were found in the effluent of the biological treatment compared to the influent (negative removal). The possible explanations for this phenomenon were the release of the compound trapped in faeces particles, the transformation of the human metabolites back to the parent compound during the biological treatment and the formation of bacterial metabolites (Margot et al., 2013). Therefore, we can hypothesize that PAC was not able to fully adsorb metoprolol or their metabolites and, combined with the highly fluctuant concentrations, led to a negative average removal.

Compound benzotriazole, pertaining to the plastic additives class, is also used as a corrosion inhibitor (García et al., 2021). In WWTP effluents it has been found among the highest concentrations of the corresponding tested compounds (Kovalova et al., 2013; Löwenberg et al., 2014; Margot et al., 2013), showing low biodegradation. In our system, an average removal of 86% was found in MBR, which later decreased to 59% and 44% in *0.1PAC* and *0.2PAC* treatments. Benzotriazole seems to show good adsorption to activated carbon, but the literature data found only refers to PAC used as a post-treatment after the biological reactor (Boehler et al., 2012; Löwenberg et al., 2014; Margot et al., 2013). Although the water matrix was different in previous studies, the results obtained in our investigation were not expected, and thus there is no explanation for the decrement in the removal during PAC treatments.

PAC addition did not influence the removal of veterinary drugs. While marbofloxacin, diaveridine and furaltadone maintained moderate to high removal, flunixin was not removed in *noPAC* and *0.1PAC* treatments. We did not find any literature data regarding flunixin removal in WWTPs, but it appears as a compound reluctant to biodegradation and with a highly variable removal in constructed wetlands (Matamoros et al., 2008).

Finally, iopromide, pertaining to the X-ray contrast media class, showed a very high removal in both *noPAC* and PAC treatments. This compound is known for not being

degraded in biological systems and for its low tendency to adsorption (logK_{ow} = -1.74) (Carballa et al., 2004; Kovalova et al., 2013). Indeed, contrast media compounds are designed to be highly stable in the human body to serve as markers for radiology examinations (Ternes and Hirsch, 2000). Since the radiology ward conducts these types of tests only a few times a week for a reduced number of patients, this compound is irregularly discharged to the sewage, leading to a highly variable concentration in the HWW and INF (Table 5.6). In our study, high and stable removals were achieved in all the experiments, with a slight reduction of the removal efficiency in *0.1PAC* treatment (87%) compared to *noPAC* (99%) and *0.2PAC* treatment (98%). The high removal efficiencies obtained during *0.2PAC* treatment indicate that PAC does not reduce the capacity of the MBR to remove this compound. However, the results obtained during *noPAC* treatment are unexpectedly high and constant in comparison with other studies (Joss et al., 2005; Margot et al., 2013). Joss et al. (2005) found unexplained great removal variations in both CAS and MBR WWTPs. As in our experiments, the authors conducted the analysis with 24h composite samples, thus avoiding the potential mistake of taking the samples in an inappropriate sampling interval. On the other side, PAC has shown to increase the removal of iopromide from 29% (CAS) to 47% (as a post-treatment) (Margot et al., 2013). In our case, since the removal of this compound is already very high in the biological treatment, no further improvement by the addition of PAC was observed.

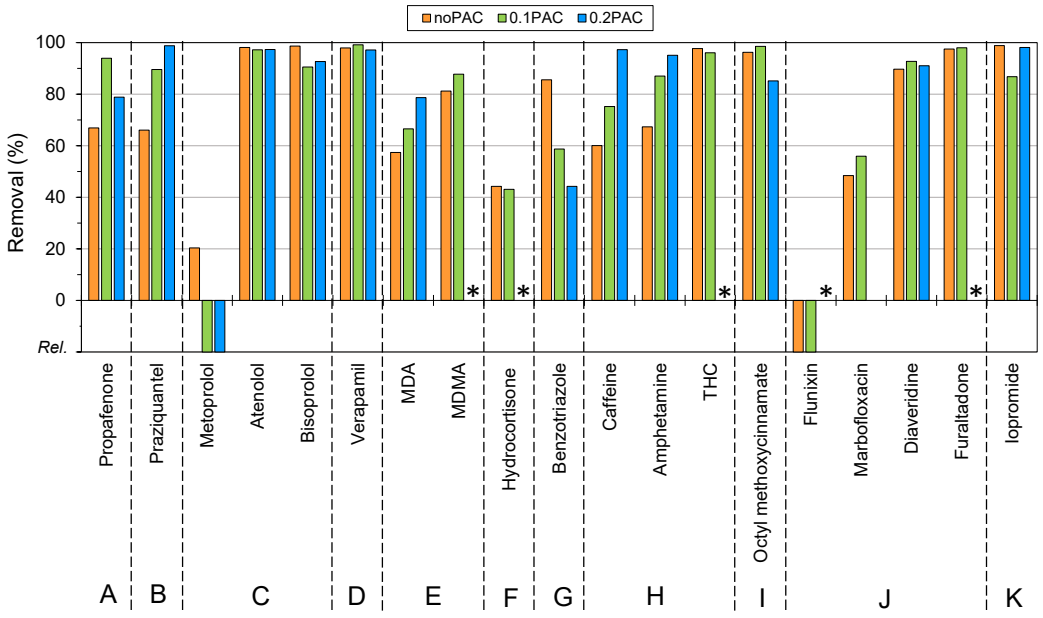

Figure 5.10. Removal efficiencies of selected compounds pertaining to several OMP classes (*A, B, C…*) during *noPAC* treatment (only MBR), *0.1PAC* and *0.2PAC* treatment. The OMP classes are **A** antiarrhythmics, **B** antiparasitics, **C** beta-blockers, **D** calcium channel blockers, **E** illicit drugs, **F** hormones, **G** plastic additives, **H** stimulants, **I** UV filters, **J** veterinary drugs and **K** X-ray contrast media. Removal is calculated as the average removal of the individual removal efficiencies in each treatment. * indicates that the removal efficiency was not calculated since the compound was undetected in both INF and MBR permeate. *Rel.* implies the compound was released from the WWTP (*conc.*$_{\text{MBRperm}}$ > *conc.*$_{\text{INF}}$) and therefore the removal was negative.

Overall removal efficiencies per OMP class

Once the removal efficiencies have been commented on at the micro-level (compound-specific), the data analysis and discussion should go up a level and assess the PAC additions considering all the OMP pertaining to the same class altogether (Figure 5.11 and Figure 5.12). In addition to that, Table S10 of the Supp. Inf. the total concentration of each therapeutic class per sampling point and treatment. Figure 5.11 shows the frequency of detection of the classes with more than 5 compounds in the MBR permeate. Results show that for all classes there is a progressive diminution of the compounds detected in the following order: *noPAC* > *0.1PAC* >*0.2PAC*, except for antibiotics. As such wise, the number of compounds that were removed to a concentration below the limit of detection increased with increasing the PAC concentration.

The average removal efficiencies of each treatment per class are shown in Figure 5.12. Analgesics/anti-inflammatories, calcium channel blockers, plastic additives, UV filters and X-Ray contrast media are the OMP classes for which there is not a clear effect of PAC addition in the MBR. All of them, except calcium channel blockers and plastic additives, already have very high removal efficiencies in MBR, and thus the potential increase in their removal due to PAC addition is not significant. On the other side, the effect of PAC on analgesics/anti-inflammatories depends on the compound analysed, which is not the case for UV filters and X-ray contrast media, with only one compound per class. Instead, the alleged decrease in the removal due to the PAC addition of calcium channel blockers was mainly due to metoprolol, for which its behaviour during the biological treatment has already been observed. In the same way, benzotriazole was the compound that mainly influenced the low removal efficiencies obtained in the plastic additives class, since the other compounds had a low frequency of detection.

Except for the abovementioned exceptions, the sixteen remaining classes increased their removal efficiencies during PAC treatments. In all cases except for illicit drugs, a correlation with PAC dose was observed, indicating that an increment of PAC dose led to better results on OMP removal. PAC is known as a suitable option for the removal of a vast set of OMPs at the same time (Boehler et al., 2012), which is confirmed by the results obtained.

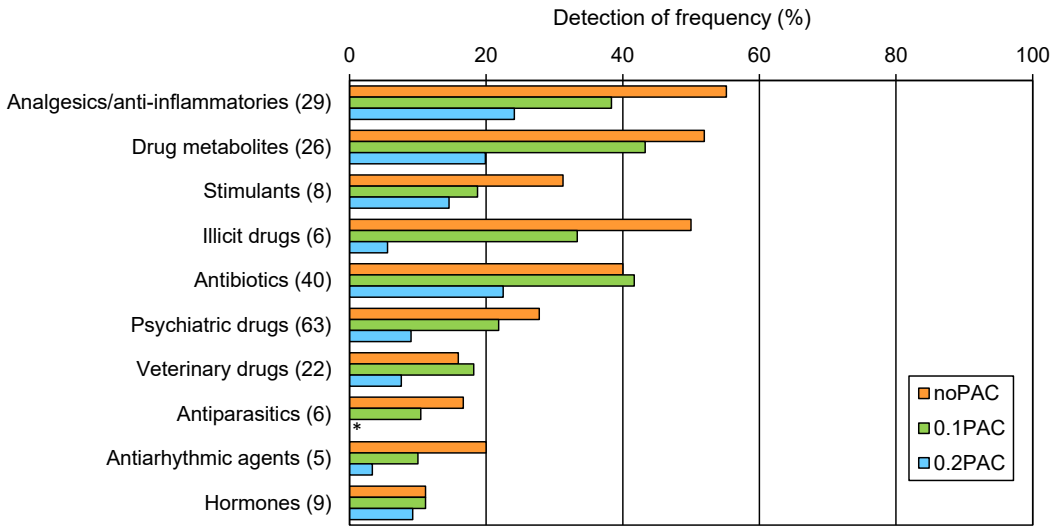

Figure 5.11. Detection of frequency (%) of the main OMP classes (number of OMPs > 5) in the MBR permeate (*MBRperm*) for MBR (*noPAC*), MBR+0.1 g/L PAC (*0.1PAC*) and MBR+0.2 g/LPAC (*0.2PAC*) treatments. In the case of the antiparasitics class, no compound was detected during *0.2PAC* treatment (marked as *).

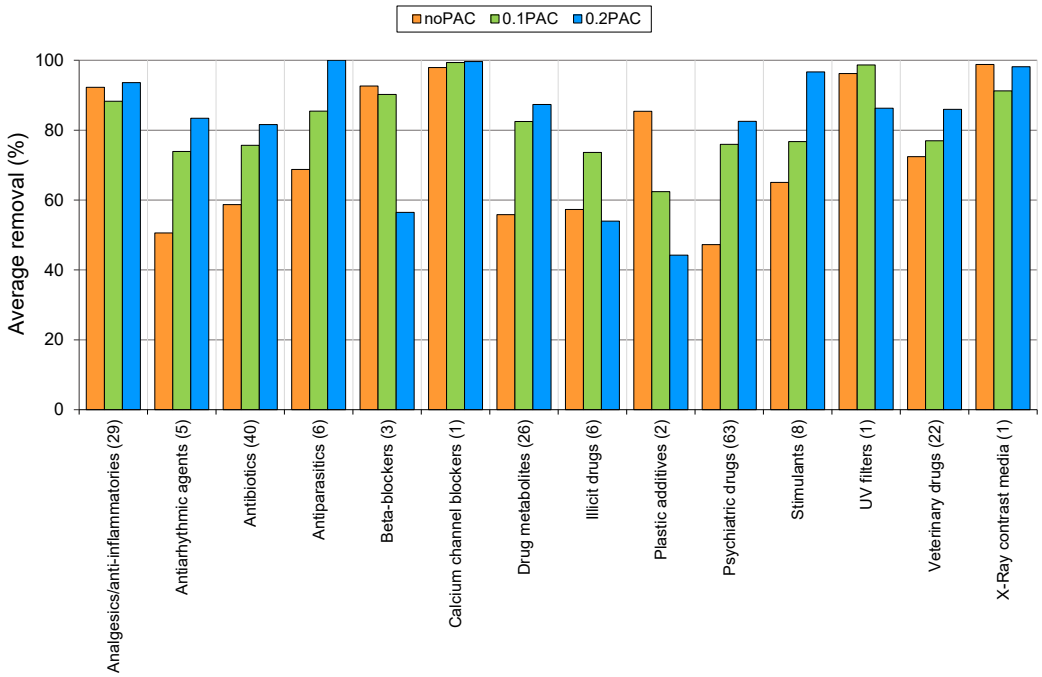

Figure 5.12. Average removal by class for each treatment: only MBR (*noPAC*), MBR + 0.1 g/L PAC (*0.1PAC*) and MBR+ 0.2 g/L PAC (*0.2PAC*) considering all the compounds pertaining to each class (in brackets, the number of compounds).

Organic micropollutants loads

The analysis and discussion on the removal of OMPs have been approached at compound and class levels, either via the frequency of detection, occurrence and removal efficiencies. However, it is pertinent to characterize wastewater and to evaluate the treatment efficiency during each treatment at a macro level. Table 5.7 shows the total loading of analysed OMPS in each sampling day and sampling treatment. Table 5.7 also depicts the contribution of the HWW to the total load in the INF. The removal efficiencies were calculated for the MBR permeate and final effluent (EFF). So far, this chapter has not discussed in detail the effect of the UV reactor on the removal of OMPs, since the main objective of the thesis was to study the effect of PAC addition to an MBRs. However, we considered showing the results of the concentrations found in EFF sampling point in Table S6, S7 and S8 of the Supp. Inf.

The first result to discuss in this subsection is the contribution of the hospital wastewater on the load of OMPs, which is on average 83%. In the previous sections, it was commented that the frequency of detection and concentrations of the OMPs under study were overall greater in the HWW compared to the INF. However, higher loads have been found in the INF (Table 5.7), and thus there is not such a dilution effect of the HWW when it is combined with the urban wastewater. We must not disregard the contribution of the OMPs used or consumed in the surrounding urban area, since they represent 17% of the total load. Nevertheless, the contribution varies depending on the sampling day. On two occasions (03/08/21 and 26/04/22), the HWW load was greater than the INF load. There are two explanations for this phenomenon. First, the higher load on the HWW corresponds to the discharge of certain pharmaceuticals that were administered during the sampling day (e.g., naproxen and iopromide). Secondly, since the HWW samples were taken from the sewage on their way to the WWTP (close to the hospital), it implies that the pharmaceuticals may be degraded on their way to the WWTP (chemically or biologically). Even if the wastewater is considered stable for some aspects (flow rate, conventional pollutants), loads of OMPs vary greatly within each treatment depending on the sampling day. The highest loads found on certain days correspond mainly to the iodinated contrast media iopromide since the radiology examinations were probably conducted during the sampling day. Considering all sampling days of each treatment, Table 5.8 shows the OMP classes and their contribution to the INF total load. Analgesics/anti-inflammatories, followed by antibiotics and iodinated contrast media were the main contributors to OMP load, followed then by plastic additives and psychiatric drugs.

Regarding the discharge of OMPs to the environment, a significant decrease in the daily loads is shown for MBRperm and EFF. An average of 13 g/day was calculated for *noPAC* treatment, which was reduced to 9 g/day during *0.1PAC* and to 4 g/day in *0.2PAC* treatments. However, as for the HWW and INF loads, MBRperm loads are subjected to great variability, with the highest loads found in the same sampling days on which the highest INF loads are also observed.

Considering all OMPs together, the removal efficiency of the MBR is on average 80%, much higher than the 26% achieved in a previous study of a pilot-scale MBR treating hospital wastewater, which provided data in the same way (Kovalova et al., 2013). However, the loads of pharmaceuticals treated in Kovalova et al., (2013) were much higher, especially with regard to iodinated contrast media, which was only removed by2% in their system. Finally, it should not be discarded that the microbial community of the WWTP of our study is adapted to the continuous load of OMPs, leading to higher biodegradation of these contaminants. With the addition of PAC, the overall removal was slightly increased (81% and 84% *0.1PAC* and *0.2PAC* treatments, respectively). This is probably because the compounds with lower loads increased the most their removal, and compounds with high loads (mainly analgesics/anti-inflammatories) were already well removed in the MBR. Indeed, this is in agreement with the previously reported data on individual loads and removal efficiencies. To conclude, it is worth noting that slightly higher values on removal efficiencies were obtained in EFF compared to the MBR permeate, which alludes to a contribution of the UV reactor to the decrease in the release of OMPs to the environment.

Table 5.7. Total loads (g/day) of OMPs in HWW, INF, MBRperm and EFF per sampling day and treatment. HWW/INF describes the ratio between HWW load and INF load. Daily removals in MBRperm and EFF are also listed. Empty values imply that the sample was not analysed, and N.A. (not applicable) that the removal efficiency could not be calculated due to the lack of data.

Treatment	Date	Exp. day	HWW (g/day)	INF (g/day)	MBRperm (g/day)	EFF (g/day)	*HWW/INF (%)*	Rem. MBRperm (%)	Rem. EFF (%)
noPAC	23/03/21	1	31	37			83	N.A.	N.A.
	27/04/21	2				10	N.A.	N.A.	N.A.
	31/05/21	3	45	52	10	6	86	81	89
	03/08/21	4	85	82	17	17	103	80	80
0.1PAC	09/09/21	3	27	43	9	7	63	78	83
	14/09/21	7	51		7	9	N.A.	N.A.	N.A.
	21/09/21	14	63	107	20	20	59	82	82
	28/09/21	28	31	35	8	8	88	78	76
	05/10/21	35	30	64	13	12	47	79	81
	12/10/21	42	57	65	8	7	88	88	90
	19/10/21	49	25	34	8	8	74	75	76
	26/10/21	56	24	30	9	9	79	71	69
	03/11/21	64		34			N.A.	N.A.	N.A.
	09/11/21	70		29	3	4	N.A.	90	88
0.2PAC	19/04/22	1	22	27	4		81	84	N.A.
	26/04/22	7	25	15	2		166	89	N.A.
	03/05/22	14	21	30	5		71	85	N.A.
	10/05/22	21	29	34	5		86	86	N.A.
	17/05/22	28	19	24	4		78	82	N.A.
	24/05/22	35	14	17	4		81	75	N.A.

Table 5.8. Contribution (%) of each OMP class to the total load in the INF during each treatment (*noPAC*, *0.1PAC* and *0.2PAC*).

	Contribution to the total load in the INF (%)		
OMP class	noPAC	0.1 PAC	0.2 PAC
Analgesics/anti-inflammatories	39	22	23
Antiarrhythmic agents	0	0	0
Antibiotics	20	22	16
Antifungals	0	0	0
Antihistamines	0	0	0
Antihypertensives	0	0	0
Antiparasitics	0	0	0
Antiseptics	0	0	0
Beta-blockers	1	1	2
Calcium channel blockers	0	0	0
Diuretics	0	0	0
Drug metabolites	4	5	5
Hormones	0	0	0
Illicit drugs	3	2	0
Plastic additives	12	7	14
Psychiatric drugs	7	9	11
Receptor antagonists	0	0	0
Stimulants	6	6	6
UV filters	0	0	0
Veterinary drugs	2	2	1
X-Ray contrast media	4	23	21

5.3.4. Impact on the receiving water body

The impact on the receiving water body was calculated by an RQ analysis and an OPBT analysis (Table 5.9 and Table S9 of the Supporting Information). Both approaches are useful tools to determine the compounds that may pose a risk to the environment. Although they were used in conjunction, the OPBT analysis was performed only on the MBRperm, while the RQ was evaluated in the MBRperm, EFF and in the irrigation ditch where the EFF is discharged, upstream (UPS) and downstream (DOWN) the WWTP. Note that the UPS and DOWN values are based on grab samples of one day during the *0.2PAC* treatment campaign (n = 1) and therefore they should be interpreted with caution.

Table 5.9 shows the frequency of detection of the times an OMP had an RQ > 1 for each campaign and sampling point evaluated. Most of the analysed OMPs were always detected at environmental concentrations below the risk (220 compounds). The total number of compounds that showed at least one time an RQ > 1 resulted in 22 (Table 5.9), meaning that their concentration entailed a high risk for the environment during that sampling day. Results show that the frequency of detection of RQ > 1 was not the same among treatments and compounds. Only one compound, amiodarone, showed a high environmental risk concentration in all sampling campaigns and sampling points (Freq = 100%). Amiodarone was not commented on in previous results since its concentration was found only one time in the MBRperm during the *0.1PAC* campaign, and thus its frequency of detection was 0% in the INF. For the RQ analysis, a concentration of 1/2 LOD was assumed in these situations. However, the PNEC value for amiodarone is extremely low (0.0011 μg/L), and thus even if its LOD was 0.00271 μg/L, the RQ was greater than 1 for all the cases.

Except for the compound amiodarone, none of the analysed OMPs were found at a high environmental risk concentration in the irrigation ditch downstream the WWTP (DOWN). Upstream the WWTP (UPS), ibuprofen was the only OMP detected at a RQ > 1. With the discharge of the WWTP effluent in the irrigation ditch, the compound was no longer found in a high risk (Freq = 0%). These results suggest that the discharge of the WWTP does not entail the release of any OMP at a concentration that would pose a significant risk for the environment. However, as mentioned before, only grab samples were taken in UPS and DOWN sampling points, and thus this conclusion should be taken with caution. On the other side, assuming that there is no irrigation ditch and the MBRperm and EFF are directly used for irrigation (i.e., no dilution effect), the number of compounds to keep an eye out for their environmental risk becomes higher. During the *noPAC* treatment, 8 compounds were always detected at high concentrations in MBRperm compared to their PNEC values (Freq = 100%). This number was reduced to 5 in 0.1PAC and no compounds were found with a RQ > 1 in all sampling days during the 0.2PAC treatment. Therefore, the overall frequency of detection of RQ > 1 was reduced by increasing the PAC concentration inside the tank. This is particularly relevant for ciprofloxacin, venlafaxine and carbamazepine (reduction of Freq up to 17% or 50%) but no for diclofenac, ibuprofen, azithromycin and ofloxacin, whose concentrations in the MBRperm were still systematically high with respect to the PNEC values in all the treatments (Freq >67%). Unfortunately, the concentrations and loads found for these latter compounds were among the highest found in the INF of the WWTP, which implies that they are frequently consumed by the patients of the hospital and inhabitants of the surrounding area, and future monitoring should be done for these compounds.

The influence of the UV reactor was also evaluated by comparing the RQ values in the MBR permeate and EFF of *noPAC* and *0.1PAC* treatments. In absence of activated carbon, the effect of the UV reactor further abating the concentration of OMPs was more relevant (MBRperm *versus* EFF in *noPAC* treatment). However, with the addition of PAC, the effect of the UV reactor is diminished, and no great differences are found between the two sampling points.

Environmental risk assessment using RQ considers only the measured concentration of the compounds with respect to their PNEC values in freshwater. OPBT analysis instead considers four criteria: the measured concentration, its removal efficiency in the system, its bioaccumulation potential (measured as K_{ow}) and toxicity (PNEC values). Since the minimum and maximum scores for each criterion are 1 and 5, respectively, the total OPBT scores range from 4 to 20 points. A threshold of 15 points (75% of the total maximum score, 20) was set to select the compounds. Table S9 shows the results obtained for each treatment. During n*oPAC* treatment, 10 compounds surpassed the threshold, namely diclofenac, carbamazepine, lorazepam, ofloxacin, α-hydroxytriazolam, mirtazapine, temazepam, trimipramine, venlafaxine and flunixin. They are characterized by having low PNEC values (<1 μg/L), high persistence (removal efficiency <20%) and a high tendency of bioaccumulation ($\log K_{ow} \geq 2$). When 0.1 g/L of PAC was added, the number of compounds was

significantly reduced (from 10 to 6). Diclofenac, amiodarone, carbamazepine, phenytoin, venlafaxine and flunixin surpassed the threshold, and four of these compounds were the same as for the *noPAC* campaign. During this second campaign, phenytoin concentrations were found higher in the MBRperm (Table S7) compared to the other campaigns (Table S6 and S8). Amiodarone, as previously commented, was only found in one sample in the MBRperm of the *0.1PAC* experimental campaign, with a concentration below the LOD in the INF, leading to negative removal. Finally, with the addition of 0.2 g/L of PAC, all the compounds decreased their rank and any of them surpassed the threshold of 15 points set.

The two approaches assessed in this study have different criteria to define the concerning OMPs to look after in this WWTP. However, it cannot be denied that the increase in the dose of PAC inside the biological reactor significantly reduced the environmental risk of the effluent of the WWTP. Moreover, although better results were obtained with the *0.2PAC* treatment, the concentrations of some OMPs may still cause a potentially harmful effect on the receiving water body considering the toxicity they have in freshwater (PNEC values). In this way, we should pay special attention to the compounds that coincide to have the higher RQ and OPBT values, namely diclofenac, carbamazepine and venlafaxine. Taking into account only RQ, the number of compounds to consider increases by including also ibuprofen, azithromycin, propafenone and ciprofloxacin. All the compounds cited have been extensively studied due to their constant presence in WWTP wastewater (Hai et al., 2018; Verlicchi et al., 2012b). The results thus are not surprising and are in accordance with previous literature about environmental risk assessment in hospital and urban wastewater (Daouk et al., 2015; Escher et al., 2011). However, it is worth highlighting that the risk assessment carried out in this study has only considered single compounds, and the effect their mixture has not been assessed. In previous studies, the combination of several OMPs has shown to increase the risk and toxicity in environmental water samples (Shao et al. 2019). Since several OMPs have been determined in the present study, it should not be discarded that some of the compounds that are not prioritized in the results of this section may pose a higher environmental risk when considered in combination with other OMPs.

According to the recent Regulation (EU) 2020/741 on water reuse (European Commission, 2020), the effluent from urban WWTPs that has been treated in accordance with Directive 91/271/EEC (UWWTD) can be used for agricultural irrigation. The minimum requirements for the reclaimed water concern only certain conventional parameters and pathogens and does not regulate the presence of OMPs in the reclaimed water. However, the direct reuse of the effluent of WWTP under investigation would require, according to the EU 2020/741, a risk management plan that addresses the identification of hazards even if they are not yet regulated. In this case, the use of environmental risk assessments such as RQ and OPBT analysis has facilitated the identification of the OMPs that could imply a high risk for the environment.

Table 5.9. Frequency of detection of RQ values > 1 of the OMPs with at least one value of RQ > 1 in one treatment, as well as their PNEC in freshwater. The colors range in an increasing intensity from white (Freq = 0%) to red (Freq = 100%).

Compound	PNEC freshwater (µg/L)	Freq. RQ UPS (%)	noPAC		0.1 PAC		0.2 PAC	Freq. RQ DOWN (%)
			Freq. RQ MBRperm (%)	Freq. RQ EFF (%)	Freq. RQ MBRperm (%)	Freq. RQ Eff (%)	Freq. RQ MBRperm (%)	
Analgesics/anti-inflammatories								
Diclofenac	0.05	0	100	100	100	89	67	0
Ibuprofen	0.01	100	100	100	100	100	67	0
Antiarrhythmic agents								
Amiodarone	0.0011	100	100	100	100	100	100	100
Propafenone	0.0036	0	100	67	22	44	0	0
Antibiotics								
Azithromycin	0.019	0	100	67	100	100	83	0
Ciprofloxacin	0.089	0	100	100	100	100	17	0
Clarithromycin	0.12	0	0	0	0	0	17	0
Doxycycline	0.46	0	0	0	33	44	0	0
Erythromycin	0.2	0	0	0	0	11	0	0
Minocycline	0.041	0	0	0	22	11	0	0
Ofloxacin	0.14	0	100	100	100	100	83	0
Roxithromycin	0.083	0	50	33	22	22	0	0
Spiramycin	0.12	0	50	0	11	11	0	0
Sulfamethoxazole	0.6	0	50	33	0	0	0	0
Drug metabolites								
Buprenorphine glucuronide	0.14	0	0	33	0	0	0	0
α-Hydroxytriazolam	0.087	0	0	33	0	0	0	0
Psychiatric drugs								
Carbamazepine	0.05	0	100	100	89	89	50	0
Lorazepam	0.096	0	0	67	0	0	0	0
Venlafaxine	0.038	0	100	67	67	67	17	0
Stimulants								
Caffeine	1.2	0	0	33	11	44	0	0
UV filters								
Octyl methoxycinnamate	0.026	0	0	33	0	0	0	0
X-Ray contrast media								
Iopromide	0.14	0	0	0	67	67	33	0

5.4 Conclusions and recommendations

In the present study, a complete characterization and evaluation of the wastewater entering a full-scale MBR treating mainly hospital effluent have been done. The potential enhancement of the removal efficiencies for a vast set of OMPs by the addition of PAC inside the biological reactor was carried out by testing two PAC doses, 0.1 g/L and 0.2 g/L. Lastly, an environmental risk assessment was conducted to find the priority OMPs to monitor regarding this specific WWTP.

The use of PAC coupled with an MBR is a novel hybrid system able to promote diverse removal mechanisms (adsorption and biodegradation) that contribute to the removal of OMPs from wastewater. Indeed, the removal efficiencies for most of the compounds improved with the addition of activated carbon. The increase was especially relevant for antibiotics and psychiatric drugs, both considered from the compound-specific level perspective and as a class. For certain compounds (e.g., iopromide, verapamil, atenolol) or classes (e.g., analgesics/anti-inflammatories) the addition of PAC was not relevant since they achieved very good results in the MBR. Moreover, increasing the concentration of PAC from 0.1 g/L to 0.2 g/L further improved the quality of the effluent, decreasing the concentration of the analysed OMPs and therefore the toxicity for the environment. By analysing the OMP concentrations and loads of the hospital wastewater, we can confirm that it represents a relevant source of OMPs, and *in situ* advanced treatments should be considered to reduce the loads of OMPs that end up in the aquatic environments. The addition of PAC inside the reactor further reduces the total load of OMPs discharged to the receiving water body, reducing therefore the potential harm caused to the living organisms. Last but not least, the addition of PAC slightly improved the MBR performance, by reducing the concentration of some conventional pollutants (nitrogen, BOD_5).

To implement the continuous use of PAC in this WWTP, upgrades in the dosing mode could improve and facilitate the operation of the WWTP technicians. Statistical analysis may be performed in order to predict the best dose of PAC according to the operational conditions of the WWTP, thus assure a certain degree of removal or a certain concentration of target OMPs in the effluent. Special attention must be paid to the compounds prioritized in the environmental risk assessment (e.g., diclofenac, carbamazepine and venlafaxine) and the effect of the mixture of several OMPs in the final effluent. Finally, a techno-economic analysis should be carried out to study the feasibility of the implementation of this hybrid technology for the removal of OMPs from the hospital (and urban) wastewater.

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The author wishes to thank HERA company, managers and technicians for the support and willingness to use their installations for the conduction of experiments, as well as for the measurements of conventional pollutants and the storage of samples for OMP analysis. The author also thanks the institution of Croatian Waters for the analysis of target and non-target OMPs. Their contribution was essential for the accomplishment of the chapter.

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Chapter 6

BATCH ADSORPTION OF THREE ORGANIC MICROPOLLUTANTS IN POWDERED ACTIVATED CARBON

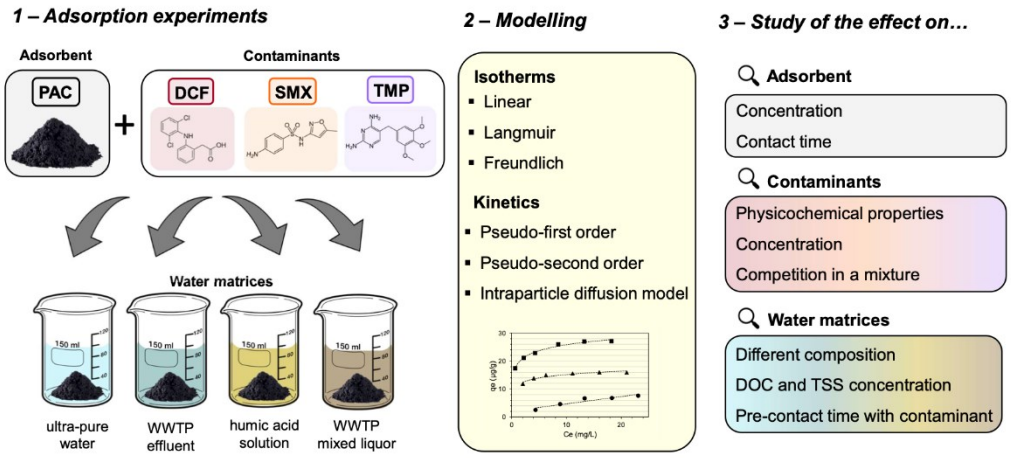
TABLE OF CONTENTS

Summary of the chapter, in a nutshell

- The influence of the wastewater matrix on the adsorption of three OMPs onto PAC was studied through batch adsorption experiments under four different water matrices: ultra-pure water, humic acid solution, MBR permeate and mixed liquor of a WWTP.
- The adsorption affinity onto PAC was primarily defined by the pharmaceutical physicochemical properties (i.e., charge and hydrophobicity), with better results obtained for TMP, followed by DCF and SMX. When present in a mixture, a competition effect among the three micropollutants was observed.
- Depending on the water matrix and compound, the PAC capacity and the adsorption process varied accordingly. The higher adsorption capacity was observed for diclofenac and sulfamethoxazole in humic acid solution, while better results were obtained for trimethoprim in MBR permeate. Adsorption in mixed liquor was limited, presumably due to its complex nature and the presence of suspended solids.

This chapter is part of a manuscript published in February 2022 with the title *Study of the influence of the wastewater matrix in the adsorption of three pharmaceuticals by powdered activated carbon* by Marina Gutiérrez, Paola Verlicchi and Dragana Mutavdžić Pavlović, which can be found in Appendix 2.

Graphical abstract



6.1 Introduction

Pharmaceuticals are one of the most common organic micropollutants (OMPs) found in wastewater. Among pharmaceuticals, nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics are in the spotlight due to their high consumption and/or recalcitrant nature (Luo et al., 2014; Verlicchi et al., 2010). In wastewater treatment plants (WWTPs), the core treatment is biological degradation, and even though some OMPs are highly biodegradable, their concentrations in WWTP effluent are still an issue, since WWTPs are not designed to remove them (Rizzo et al., 2019). In this way, different advanced treatments have gained interest and have been gradually implemented over the last few years (Khan et al., 2020; Mailler et al., 2016; Margot et al., 2013). These include activated carbon adsorption (in powder or granules), which offers the advantage of being able to remove a wide range of compounds. This is particularly relevant in wastewater treatment, where OMPs often occur as a "cocktail" and, tens to hundreds of substances can be found at the same time (Verlicchi et al., 2012). Indeed, the removal of many recalcitrant OMPs relies almost uniquely on sorption processes (Li et al., 2011). Powdered activated carbon (PAC) is known for being a very flexible option that can be added to existing treatments lines (i.e., addition to the biological tank) or as a polishing treatment to treat the secondary effluent (i.e., in a new contact tank) (Alvarino et al., 2017; Löwenberg et al., 2014). PAC is used to enhance the adsorption and to promote diverse removal mechanisms with the main aim of obtaining synergistic effects (such as enhanced biodegradation). Adsorption onto activated carbon that is a complex process that is not fully understood, driven by the properties of the adsorbent and absorbate as well as the water quality. When considering the application of PAC in WWTPs, the potential enhancement of the removal of pharmaceuticals depends on many factors for which the extent of their influence is challenging to consider altogether (Gutiérrez et al., 2022). Activated carbon is a porous adsorbent with adsorption capacity relying on its surface properties (specific surface area, pore volume, functional chemical groups) (Alves et al., 2018; Choi and Chung, 2014). OMPs instead depend on their physicochemical characteristics (compound charge, hydrophobicity, molecular weight, etc.) to be adsorbed, which usually leads to competition effects where some substances tend to adsorb more easily than others. Moreover, the overall adsorption process depends also on the conditions in which it occurs, such as the water matrix. The constituents of the water matrix and, more specifically, the dissolved organic matter (DOM) may influence the adsorption process. DOM is formed by many fractions that differ in size (building blocks, biopolymers, humic acids, low molecular weight organics, etc.), which may limit the adsorption of OMPs by blocking the pores on the PAC surface or by direct competition for the adsorption sites (Zietzschmann et al., 2016b, 2014). OMPs may also interact with the DOM present in the liquid phase or the adsorbed DOM onto the PAC surface. The results of the interaction may enhance or diminish the adsorption onto PAC, depending on the tested OMPs and conditions

(Guillossou et al., 2020; Hernandez-Ruiz et al., 2012; Jin et al., 2018). In this way, the use of synthetic water matrices (e.g., humic acid solution) can act as a means to understand the adsorption process under certain DOM constituents (Jin et al., 2018). Adsorption batch tests and mathematical models can be useful tools to examine the conditions under which PAC adsorption takes place and predict adsorbent response to such conditions. In previous research, the application of adsorption models has been of great value to understand the mechanisms of adsorption of certain pollutants on porous adsorbents like PAC (Behera et al., 2010). However, only a few studies have applied these models to study the effect of varying concentrations of DOC (Margot et al., 2013) and DOM constituents (Hernandez-Ruiz et al., 2012; Jin et al., 2018; Zietzschmann et al., 2014) in the adsorption of pharmaceuticals in wastewater. Indeed, the potential positive effect of these interactions between DOM and pharmaceuticals has been rarely documented and quantified (Guillossou et al., 2020; Hernandez-Ruiz et al., 2012). Considering the adsorbates, the influence of their physicochemical properties (polarity, charge and hydrophobicity) in adsorption has been the subject of study in literature (Margot et al., 2013), but rarely has the literature focused on the subsequent potential competition effect caused by their different affinity towards PAC under realistic conditions of wastewater treatment (Hernandez-Ruiz et al., 2012).

For all the above-mentioned reasons, the adsorption of three pharmaceuticals, onto PAC is investigated under different conditions using four different approaches. First, the adsorption capacity of PAC for the three target compounds is determined experimentally and the adsorption process will be described by three isotherm models (Linear, Langmuir and Freundlich) and three kinetic models (Lagergren's pseudo-first-order, pseudo-second-order and intraparticle diffusion model (IPD)). Second, the potential competition effect among pharmaceuticals due to their different physicochemical properties (charge, hydrophobicity) is evaluated. Third, the potential influence of the water matrix is assessed by comparing the adsorption process (kinetics, isotherms, experimental adsorption capacity) in ultra-pure water, humic acid solution, permeate of a full-scale MBR and mixed liquor from the nitrification tank of the same MBR. Finally, the interaction between the pharmaceuticals and the DOM on the adsorption onto PAC is studied.

6.2 Materials

6.2.1. Adsorbates

Diclofenac

Diclofenac (DCF) is a nonsteroidal anti-inflammatory drug (NSAID) used to treat pain and inflammatory disorders. It is commonly commercially available as a sodium or potassium salt. In this thesis, we used diclofenac sodium salt in adsorption experiments due to its higher solubility, thereinafter named only DCF. Diclofenac inhibits prostaglandin synthesis by hindering the conversion of arachidonic acid through two subtypes of cyclooxygenases, COX-1 and COX-2 (Sallmann, 1986). As a side effect, inhibition of cyclooxygenase enzymes causes gastrointestinal distress. DCF is also used as a veterinary drug, and its use has been associated with the vulture crisis in the Indian subcontinent, where the 95% of the vulture population deceased due to renal failure caused by the ingestion of diclofenac-treated livestock (Oaks et al., 2004). In Europe, DCF was one of the compounds selected for the first Watch List (Decision 2015/495).

DCF is a weak electrolyte (Figure 6.1), where anionic and neutral forms coexist in relative amounts depending on the pH. It is characterized by a pK_a of 4. In wastewater, DCF predominates in its anionic form (Salvestrini et al., 2020). It possesses a low human excretion rate (< 39%), but due to its high levels of consumption, it has been found up to 94.2 μg/L in WWTP influents (Luo et al., 2014). Despite being a hydrophobic compound (logK_{ow} = 4.26), the main removal mechanism seems to be biodegradation (Radjenović et al., 2009; Verlicchi et al., 2012). Compared to other NSAIDs, DCF shows inefficient and variable removal efficiencies, with great discrepancy among the literature data (Luo et al., 2014; Radjenović et al., 2009). DCF seems to show better results in MBR compared to CAS, although some authors found almost negligible removal efficiencies in MBR (Kovalova et al., 2012; Radjenović et al., 2009). As reported in Verlicchi et al. (Verlicchi et al., 2012), the type of reactor is apparently less important for the removal of DCF than other operational conditions, namely SRT, since long SRTs promote the adaptation of the microorganisms present in the reactor. The addition of PAC in MBRs has shown to be beneficial, albeit the removal efficiencies still show a great variability (32% – 99%) (Gutiérrez et al., 2021). DCF removal doesn't seem to be dependent on the PAC dose, but rather the frequency of dosage (fresh PAC versus old PAC).

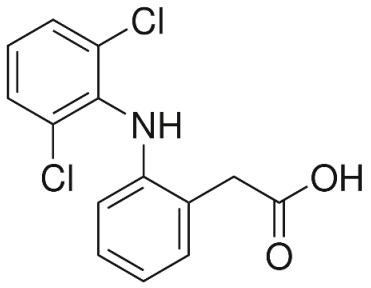


Figure 6.1. Molecular structure of diclofenac.

Sulfamethoxazole

Sulfamethoxazole (SMX) is an antibiotic that inhibits bacterial growth (i.e., bacteriostatic) belonging to the class of sulfonamides (Figure 6.2). It acts by blocking the production of folic acid in both gram-positive and negative bacteria. Specifically, it inhibits the conversion of PABA and dihydropteroate diphosphate to dihydrofolic acid. It acts in the same metabolic route as trimethoprim, by inhibiting the folic acid precursor tetrahydrofolic acid. Accordingly, it is commonly prescribed in combination with trimethoprim. In wastewater, it is found in the range of < 0.003 – 0.98 μg/L with effluent concentrations that may exceed the influent (< 0.003 – 1.15 μg/L) (Luo et al., 2014). This is due because SMX metabolites and transformation products are able to retransform into the parent compound during the biological treatment (Verlicchi et al., 2012).

SMX is an anionic compound with very low hydrophobicity (logK_{ow} = 0.79). The chemical properties of SMX make it reluctant to adsorb onto PAC or sludge and more prone to biodegradation, especially under anoxic/anaerobic redox conditions (Alvarino et al., 2018, 2017). However, the addition of PAC into the biological tank may increase the presence of anoxic and anaerobic zones of the biofilm attached to the PAC surface, enhancing the biodegradation of the SMX (Alvarino et al., 2016). Still, although direct adsorption onto PAC doesn't seem to be the main removal mechanism of SMX, batch adsorption isotherms obtained by Li et al., (Li et al., 2011) estimated maximum adsorption (q_m) of 0.017 mg/g.

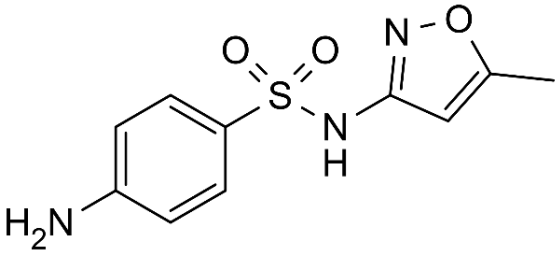


Figure 6.2. Molecular structure of sulfamethoxazole.

Trimethoprim

Trimethoprim (TMP) is a derivative of trimethoxybenzyl-pyrimidine with antibacterial and antiprotozoal properties (Figure 6.3). The mechanism of action is to inhibit bacterial dihydrofolate reductase, blocking the production of tetrahydrofolic acid. It is primarily used in the treatment of urinary tract infections, although it may be used against any susceptible aerobic bacterial species. It is usually combined with sulfamethoxazole for the treatment of mild infections. The human excretion rate is relatively high, between 40 and 69% (Luo et al., 2014). Trimethoprim is a relatively hydrophilic compound ($\log K_{ow}$ = 1.28) with a low tendency for sorption onto the sludge (Verlicchi et al., 2012). In WWTP influents, it has been found in the range of 0.06 – 6.8 μg/L with significantly varied removal efficiencies in CAS (< 0 – 81.6%) (Luo et al., 2014). It is generally classified as being moderately removable for both CAS and MBR systems (Luo et al., 2014; Verlicchi et al., 2012), with the presence of nitrifying bacteria favouring its removal (Radjenović et al., 2009; Serrano et al., 2011). Better removal efficiencies for TMP have been obtained when PAC is added inside the biological tank of a MBR in comparison to PAC used as a post-treatment (Gutiérrez et al., 2021). Trimethoprim was included on the Watch list in 2020 (Decision EU 2020/1161) and maintained in the Watch List in 2022 (Decision EU 2022/1307).

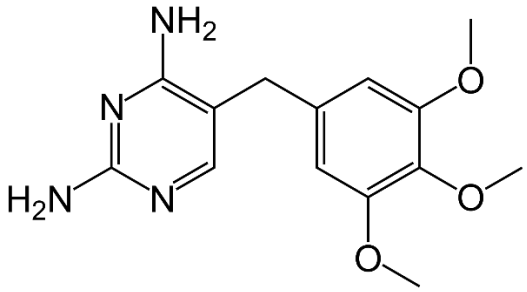


Figure 6.3. Molecular structure of trimethoprim.

The commercial information about the three OMPs used in the adsorption experiments can be found in Table 6.1. Target compounds were selected according to their physicochemical properties, listed in Table 6.2. J Chem for Office (20.11.0, ChemAxon) was used for calculating the physicochemical properties and ionization state (Figure 6.4).

Table 6.1. List of compounds used in adsorption experiments.

Target compound	CAS	Purity	Supplier
Diclofenac sodium salt	15307-79-6	≥98%	Sigma-Aldrich, St. Louis, MO, USA
Sulfamethoxazole	723-46-6	≥98%	Sigma-Aldrich, St. Louis, MO, USA
Trimethoprim	738-70-5	≥98%	Acros Organics, Thermo Fisher Scientific Inc., New Jersey, NJ, USA

Table 6.2. Physicochemical properties of the selected OMPs. J Chem for Office (20.11.0, ChemAxon, https://www.chemaxon.com, accessed on 11 June 2021) was used for calculating the physicochemical properties. Values for pK_{a1} and pK_{a2} were obtained from a) Babić et al., (2007) and b) Zrnčić et al., (2015).

Compound	Molecular formula	Molecular weight (g/mol)	logK_{ow}	pK_{a1}	pK_{a2}
Diclofenac	$C_{14}H_{10}Cl_2NNaO_2$	318.13	4.26	4.21[a]	
Sulfamethoxazole	$C_{10}H_{11}N_3O_3S$	253.28	0.79	1.83[a]	5.57[a]
Trimethoprim	$C_{14}H_{18}N_4O_3$	290.32	1.28	7.10 ± 0.02[b]	

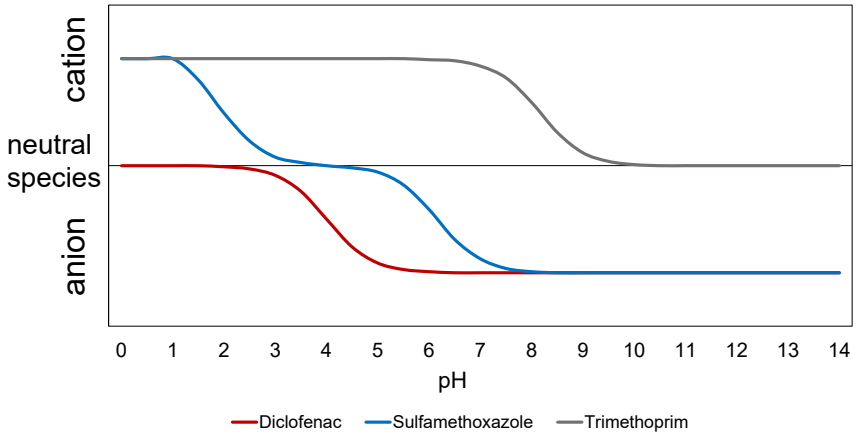


Figure 6.4. Changes in the ionization state of DCF, SMX and TMP as a function of the pH. J Chem for Office (20.11.0, ChemAxon, https://www.chemaxon.com) was used for calculating the physicochemical properties and ionization state.

6.2.2. Adsorbent

PAC (ACTISORBE 700, Brenntang S.p.a, Italy) was used for all the adsorption experiments. The PAC characteristics and their analytical methods were supplied by the manufacturer and can be found in Table 6.3. The surface properties of the selected PAC are in agreement with literature on adsorption of organic pollutants (Burchacka et al., 2021; Giannakoudakis et al., 2016; Gutiérrez et al., 2021; Mailler et al., 2015). After its purchase, the PAC was not treated, in order to emulate real conditions on which the adsorbent is directly added to the wastewater treatment line.

Table 6.3. Characteristics of the purchased PAC used in adsorption experiments.

Analysis	Value	Analytical method
Iodine number (mg/g)	750	ASTM 4607
Methylene blue (mL)	12	-
BET specific surface area (m^2/g)	850	ASTM 3663
Bulk density (kg/m^3)	430	ASTM 2854
Ash content (%)	10	ASTM D 2866
Humidity (%)	5	ASTM D 2867
pH	Alkaline	ASTM D 3838

6.2.3. Water Matrices

Four different water matrices were used to prepare OMP solutions: ultrapure water (Milli-Q), humic acid (HA) solution and effluent and mixed liquor from a WWTP.

Milli-Q water was obtained from the Millipore Simplicity UV-system (Millipore Corporation, Billerica, USA). The preparation method of each water matrix is described below.

Commercially available humic acids (CAS 1415-93-6, Sigma-Aldrich, St. Louis, MO, USA) were used to prepare the humic acid solution. HA solution used in the experiments contained 50 mg/L of HAs, with a dissolved organic carbon (DOC) concentration of 29.35 mg/L. The solution was prepared following the method of Tolić Čop et al., (2022). Briefly, to prepare a volume of 100 mL, 5 mL of 1M NH_4OH were added to a 100 mL flask. Then 0.005 g of HAs were weighted and the Milli-Q water was added to a maximum of 85 mL. The pH of the solution was then adjusted to 5.34 with 1 M formic acid and made up to the desired volume (100 mL).

The effluent and mixed liquor were collected from the permeate and the nitrification tank, respectively, of a full-scale MBR located in northern Italy. After their collection, both effluent and mixed liquor were frozen at −20 °C and transported to the laboratories in Zagreb. Both the MBR permeate and mixed liquor were autoclaved at 121ºC to reduce any potential biological activity and subsequently filtered through paper filters (Lab Expert, KEFO d.o.o, Croatia) to remove any particulate matter. Filters from the mixed liquor were air dried for 24 h and scrapped to obtain dry sludge. To ensure that all the glass beakers on which the adsorption experiments were conducted contained the same amount of mixed liquor suspended solids (MLSS), a certain amount (120 mg) of dry sludge was added to each glass beaker. The resulting MLSS concentration in the mixed liquor was 6 g/L, a concentration commonly found in real WWTPs.

6.3 Methodology

6.3.1. Batch adsorption experiments

Preliminary experiments were conducted to determine the contact time necessary to reach the equilibrium between the PAC and the target OMPs in ultra-pure water. Three different concentrations of target pollutants were tested (5, 15 and 25 mg/L). The PAC was agitated in the OMP solutions for 10, 20, 30, 40 and 50 min and 1, 2, 4, 6, 12, 18 and 24 h at constant temperature (25 °C). Two PAC concentrations (0.1 g/L and 1 g/L) were tested in each target OMP individually, while 0.1 g/L of PAC was also tested in the mixture of the three OMPs. Experiments were carried out in a volume of 20 mL of OMP solutions. The results of the preliminary experiments determined 24 hours as sufficient time to reach the equilibrium for all three compounds and the mixture. Based on the results obtained, the sorption kinetics were determined.

The batch sorption experiments were conducted in 20 mL of OMP solutions. Six different nominal concentrations (5, 7.5, 10, 15, 20 and 25 mg/L) were tested for DCF and TMP, while five concentrations (5, 10, 15, 20 and 25 mg/L) were tested for SMX to determine the sorption isotherms. PAC was added to the solutions at 0.1, 0.25, 0.5, and 1 g/L in each experiment. All experiments were performed in triplicates using an incubator shaker at 150 rpm and a constant temperature of 25 °C (Innova 4080, New Brunswick Scientific, USA), which enabled continuous contact between the compounds and the activated carbon. To avoid photodegradation, all experiments were performed in darkness.

To prepare OMP solutions, exact amounts of the target compounds were weighed and added to the corresponding water matrix. To ensure OMPs were completely dissolved, OMP solutions contained a maximum of 1% of methanol and were sonicated in an ultrasonic bath (Sonorex Digital 10P, Bandelin electronic, Berlin, Germany) for 5 minutes. Once the OMPs solutions were prepared, 20 mL of each were added to glass beakers in triplicates. PAC was then carefully added ensuring that the exact weighted mass of PAC was transferred. Glass beakers were sealed with parafilm to avoid evaporation and put into agitation for 24 h. Prior to the quantitative analysis of the OMP concentration, glass beakers were decanted, and samples were centrifuged at 3500 rpm for 5 minutes (Hettich EBA 20, Westphalia, Germany) to subsequently be filtered by a 0.45 µm Nylon syringe filter (Filter-Bio, Nantong, China). Blank samples containing the corresponding water matrices were also included in the analysis to act as controls.

Different adsorption batch experiments were conducted depending on the water matrix (Table 6.4). Firstly, all OMPs were tested individually in each water matrix to compare the effect of the DOM (measured as DOC) in the adsorption process (Experiment 1). In ultra-pure water, a second experiment (Experiment 2) was conducted with the mixture of the three target compounds at the previously selected concentrations (5, 7.5, 10, 15, 20 and 25 mg/L) to evaluate the interaction and

competition between the OMPs. Then, the HA solution was used to study the influence of a pre-equilibrium contact time between the DOM and the OMPs prior to the adsorption (Experiment 3). OMPs were added to the HA solution 24 h before the addition of PAC to simulate the interactions between the DOM and OMPs in the sewer and inside the WWTP. Mixed liquor experiment (Experiment 4) was performed with the addition of PAC and without PAC to assess the adsorption of the OMPs to the mixed liquor suspended solids (MLSS).

Table 6.4. Summary of the adsorption batch experiments.

# Experiment	Matrix	Experimental conditions
(Exp. 1). Effect of the water matrix in the adsorption of OMPs	Ultra-pure water (DOC = --)	▪ Individual solutions of DCF, SMX and TMP ▪ No pre-contact time between the pharmaceuticals and the water matrix
	Humic acid solution (DOC = 29.35 mg/L)	
	MBR permeate (DOC = 4.1 mg/L)	
	Mixed liquor (DOC = 4.7 mg/L)	
(Exp. 2). Effect of the interaction of the three pharmaceuticals in the adsorption onto PAC	Ultra-pure water (DOC = --)	▪ Individual solutions of DCF, SMX and TMP ▪ Solution of the three DCF, SMX and TMP in a mixture
(Exp. 3). Study of the influence of a pre-equilibrium contact time between the DOM and the pharmaceutical	Humic acid solution (DOC = 29.35 mg/L)	▪ Individual solutions of DCF, SMX and TMP - Condition 1. No pre-contact time between pharmaceuticals and the HA solution - Condition 2. 24 h pre-contact time between the pharmaceuticals and the HA solution
(Exp. 4). Effect of the presence of the solid phase of the mixed liquor in the adsorption of the pharmaceuticals onto PAC	Mixed liquor (DOC = 4.7 mg/L)	▪ Individual solutions of DCF, SMX and TMP - Condition 1. Adsorption in the mixed liquor without added PAC (control for sludge adsorption) - Condition 2. Adsorption in the mixed liquor with added PAC

6.3.2. Sorption kinetics models and isotherms

The sorption of OMPs onto activated carbon and correlated modelling equations are exhaustively described in the Chapter 1. Nevertheless, hereunder kinetics and isotherms models used in the present work are briefly described.

The amount of adsorbed OMP (q_t) was calculated from the difference between the initial concentration (C_0) and the remaining concentration at time t (C_e) by using eq. 1.,

$$q_t = \frac{(C_o - C_e) \cdot V}{W} \qquad \text{eq. 1}$$

where q_t (mg/g) is the amount of target OMP adsorbed at time t; C_0 and C_e are the initial and the concentration at time t (mg/L); V is the volume of the solution (L) and W the mass of adsorbent used (g).

Sorption kinetics

Sorption kinetics were determined with the data from the preliminary tests conducted to obtain the equilibrium time. Three kinetic models were tested: Lagergren pseudo-first order, pseudo-second order and intraparticle diffusion model.

Lagergren pseudo-first order

In Lagergren pseudo-first order (Lagergren, 1898) (eq. 2), the solute uptake rate changes proportionally to the difference in the saturation level of the adsorbent (i.e., q_e-q_t). Because of that, it is usually associated with the first stages of adsorption (Tran et al., 2017),

$$\frac{dq_t}{dt} = k_1(q_e - q_t) \quad \text{eq. 2}$$

where q_e and q_t are the quantity of solute adsorbed on the PAC surface (μg/g) at the equilibrium (q_e) and at time t (q_t), and k_1 is considered the constant rate (1/min). The integration from t=0 (when q = 0) to t (when q = q_t) as the following (eq. 3),

$$\log(q_e - q_t) = -\frac{k_1}{2.303}t + logq_e \quad \text{eq. 3}$$

Pseudo-second order equation

In the pseudo-second order equation (eq. 4), the sorption capacity is proportional to the number of the active sites (Mutavdžić Pavlović et al., 2018).

$$\frac{t}{q_t} = \frac{1}{k_2 q_e^2} + \frac{1}{q_e}t \quad \text{eq. 4}$$

In this equation, k_2 is defined as the constant rate for the pseudo-second order (μg/g min).

Intraparticle diffusion model

The intraparticle diffusion model is expressed by the Weber and Morris equation (Weber and Morris, J.C., 1963) (eq. 5),

$$q_t = k_{id}t^{1/2} + C \quad \text{eq. 5}$$

where k_{id} is the intraparticle diffusion rate constant (μg/g·min$^{1/2}$), intercept C provides information about the thickness of the boundary layer. In this model, if a linear relationship between $t^{1/2}$ and q_t with null intercept is observed, the adsorption is solely governed by intraparticle diffusion. Alternatively, if the intraparticle diffusion plot shows multi-linearity, the pore diffusion is not the only rate-limiting step in the adsorption process.

Isotherms

In order to describe the mechanism of DCF, SMX and TMP adsorption onto the PAC, the data obtained from the isotherms were fitted to the linear isotherm (eq. 6), Freundlich isotherm (eq. 7) and Langmuir isotherm (eq. 8),

$$q_e = K_d C_e \quad \text{eq. 6}$$

$$q_e = K_F C_e^{1/n} \quad \text{eq. 7}$$

$$\frac{1}{q_e} = \frac{1}{q_m} + \frac{1}{K_L q_m C_e} \quad \text{eq. 8}$$

where q_e is the amount of adsorbed compound per mass unit of adsorbent at the equilibrium (μg/g); C_e is the equilibrium concentration of the OMP (mg/mL); K_d is the distribution coefficient; K_F is the Freundlich adsorption constant ((μg/g) (mL/mg)$^{1/n}$); $1/n$ is the heterogeneity constant; q_m is the equilibrium sorption capacity, that is, the maximum amount of OMP to be adsorbed by the activated carbon (μg/g) and K_L is the adsorption constant for Langmuir isotherms, related to the sorption bonding energy (L/mg). Note that the term $1/n$ on Freundlich isotherm represents the intensity of adsorption; if $1/n<1$, the process is considered favorable and suggests a good affinity between the adsorbate and the adsorbent (i.e., chemisorption), while if $1/n>1$ is unfavored for the first compounds adsorbed, but it improves the adsorption of the following (i.e., physisorption).

6.3.3. HPLC analysis

Quantitative determination of target pollutants was performed by HPLC (Waters 2795 Separation Module, Alliance HPLC System, Waters Corporation, Milford, MA, USA) coupled with PDA (Waters 2996, Waters Corporation, Milford, MA, USA). The HPLC-PDA system consists of a quaternary pump, a vacuum degasser and temperature-controlled column and autosampler units. A Kinetex C18 column was used (Phenomenex, 150 × 4.6 mm, 5μm particle size, 100 Å pore size). The mobile phase contained solvent A, composed of 0.1% of formic acid in Milli-Q water, and solvent B, with 0.1% of formic acid in acetonitrile. The flow rate was 0.5 mL/min for all the experiments. The column temperature was 20 ºC. The injection volume for each sample was 20 μL.

Isocratic methods were used to determine the concentration of individual target pollutants (Table 6.5). For the solution containing the OMPs mixture (DCF, SMX and TMP) a method with gradient elution was developed (Table 6.6). The total run time was 25 mins, and the flow was kept constant at 0.5 mL/min. Peak wavelengths for each compound are listed in Table 6.5. The retention time of each compound was 6.2 mins for TMP, 12.9 mins for SMX and 20.2 mins for DCF in the gradient elution method.

Table 6.5. Isocratic method in HPLC-PDA for each target pollutant.

Method	Solvent A (%)	Solvent B (%)	Flow (mL/min)	Elution time (min)	Retention time (min)	Peak wavelength (nm)
Diclofenac	35	65	0.5	10	6.5	276.9
Sulfamethoxazole	65	35	0.5	10	6.0	269.8
Trimethoprim	85	15	0.5	10	5.6	270.8

Table 6.6. Mobile phase gradients for the mixture of DCF, SMX and TMP.

Time (min)	Solvent A (%)	Solvent B (%)	Flow (mL/min)
0	85	15	0.5
6	85	15	0.5
7	65	35	0.5
10	65	35	0.5
15	35	65	0.5
20	35	65	0.5
20.10	85	15	0.5
25	85	15	0.5

6.4 Results and discussion

6.4.1. Effect of contact time and initial concentration of OMPs

In order to determine the time needed to reach the maximum adsorption of the target OMPs onto PAC, adsorption experiments at different contact times were conducted. For this purpose, individual solutions of each OMP were tested at three concentrations (5, 15 and 25 mg/L) with two concentrations of PAC (0.1 and 1 g/L) at different contact times (10, 20, 30, 40 and 50 min and 1, 2, 4, 6, 12, 18 and 24 h). Figure 6.5 shows the removal (in terms of % of adsorption) of the three target compounds over time (10 min – 24 h) in Milli-Q water with 1 g/L of PAC. Results obtained with 0.1 g/L of PAC are found in Figure 6.6.

All target compounds reached the equilibrium within 24 h, with very little difference in the adsorption between 18 h and 24 h, indicating that no more molecules could be adsorbed. In this way, 24 h was taken as the equilibrium time for the adsorption isotherms.

TMP was almost completely removed by the adsorption onto PAC (1 g/L) at 24 h (96-99.8%), followed by DCF (88–97%) and SMX (46–99.9%). TMP was the compound with the fastest kinetics, with removal from 77% (for the initial concentration of 25 mg/L) to 90% (for the initial concentration of 5 mg/L) in the first 10 minutes of agitation. SMX instead was the compound with the lowest rates and overall adsorption by great difference, depending on the initial concentration. In the first 10 minutes, 57% of the compound was adsorbed for 5 mg/L (maximum adsorption of 99.9% after 24 h), while only 1.5% was adsorbed for 25 mg/L (at 24 h, only 46% of the compound was adsorbed).

Lower adsorption percentages were found when PAC was added at 0.1 g/L for all OMPs in all tested shaking times (Figure 6.6). At initial concentration of 5 mg/L, adsorption of 39%, 63% and 74% was obtained at 24 h for SMX, DCF and TMP, respectively. On the other hand, maximum adsorption of approximately 15% was obtained for all OMPs at 25 mg/L. By looking at Figure 6.6, it can be seen that the adsorption rate was particularly high within the first ten minutes in all tested OMPs with initial concentration of 15 and 25 mg/L. Adsorption percentage reached in 10 min was approximately the 50% of the total adsorption obtained after 24 h. As an example, the adsorption of DCF at 10 min was 7% and after 24 h, 15%. After the first ten minutes, the rate of adsorption was considerably low until it reached the equilibrium.

Note that adsorption seems to be dependent on the initial concentration of the pharmaceuticals (Figure 6.5 and Figure 6.6). Higher adsorptions were found at the initial concentration 5 mg/L compared to 15 and 25 mg/L for DCF, SMX and TMP, indicating that the adsorption of pharmaceuticals onto activated carbon is dependent on their initial concentration.

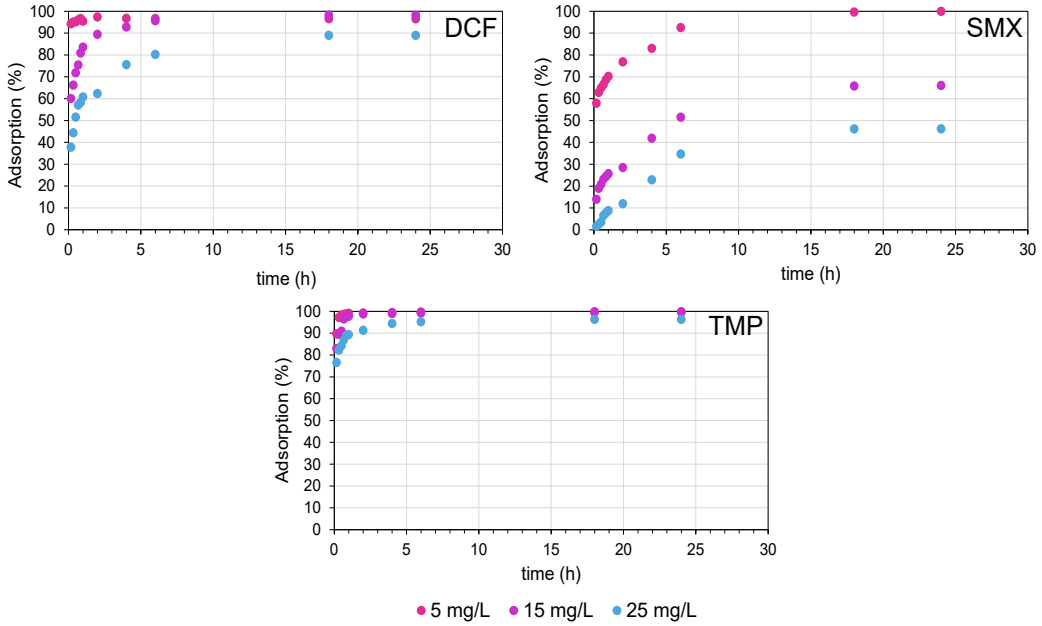


Figure 6.5. Kinetics of adsorption of DCF, SMX and TMP at three different concentrations (5, 15 and 25 mg/L) in Milli-Q water with 1 g/L of PAC at different contact times (10 min – 24 h).

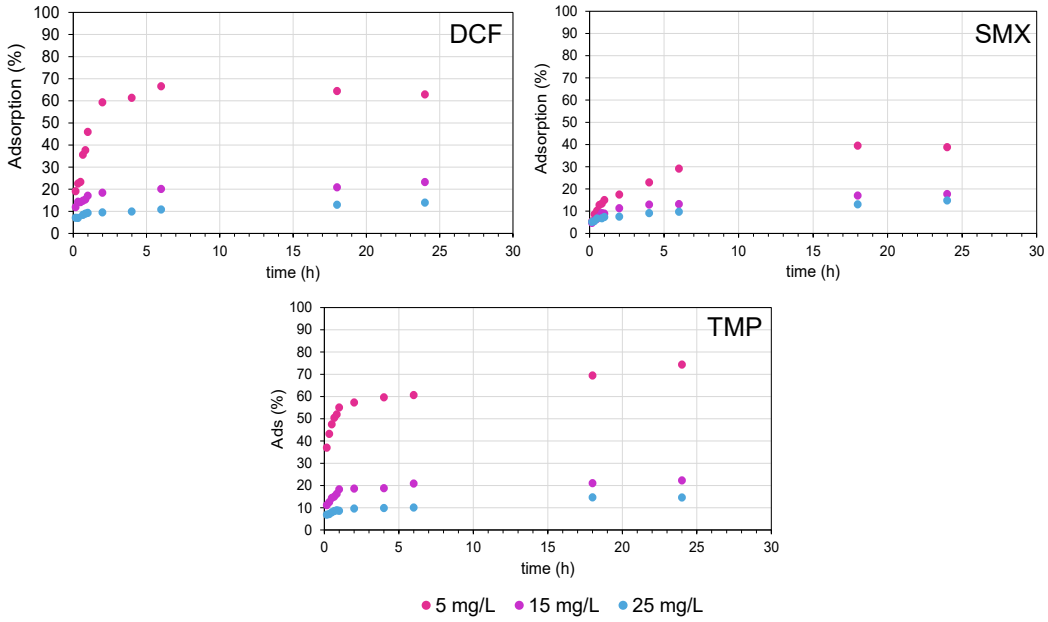


Figure 6.6. Kinetics of DCF, SMX and TMP at three different concentrations (5, 15 and 25 mg/L) in Milli-Q water with 0.1g/L of PAC (10 min – 24 h).

6.4.2. Kinetics

Sorption of the tested pharmaceuticals has proved to be a fast process overall. However, the behaviour of each compound was different presumably due to their physicochemical properties and the initial conditions of the experiments (i.e., the concentration of the adsorbent and adsorbate). To better understand the control mechanisms of the sorption process, we performed kinetics studies by applying three different kinetics models: pseudo-first order, pseudo-second order and IPD. The kinetics models were applied to all the tested concentrations of OMPs and PAC, even though the behaviour should be the same regardless the initial concentrations ratios. In this way, we cover a vast data set and we can assure the reliability of the results obtained.

The kinetics followed a pseudo-second order for the three target compounds at the two tested PAC concentrations (1 and 0.1 g/L). The sorption rate constants (k_1 and k_2), $q_{e,\ calc.}$, $q_{e,\ exp.}$ and correlation coefficients (R^2) are shown in Table 6.7 for a PAC concentration of 1 g/L and Table 6.8 in the case of 0.1 g/L of PAC. The correlation coefficients of the adjustments were very close to the unity (R^2 > 0.98) with no significant differences between the experimental q_e ($q_{e,\ exp.}$) and calculated values ($q_{e,\ calc.}$), suggesting that the sorption is governed by the number of available active sites (Delgado et al., 2019; Mutavdžić Pavlović et al., 2018). The lowest $q_{e,\ exp.}$ values were obtained by SMX in all tested concentrations. The maximum amounts of adsorbed pharmaceutical onto PAC ($q_{e,\ exp.}$) were the highest at the lowest PAC concentration and vice versa. The values obtained were in the range of 4826 – 24,083 μg/g for 1g/L of PAC and 19,398 – 37,184 μg/g for 0.1 g/L of PAC considering the three tested OMPs. As anticipated in Figure 6.5 and Figure 6.6, fastest kinetics (k_2) were obtained with the lowest OMP concentration (5 mg/L) for all the tested compounds except for TMP at 1 g/L PAC. Depending on the initial concentration, k_2 changes by at least one order of magnitude, indicating that the initial OMP concentration seems to have a significant role in the sorption kinetics.

Table 6.7. Sorption kinetics parameters of DCF, SMX and TMP in ultra-pure water with 1 g/L of added PAC. C_0 indicates the initial concentration of the OMP and $q_{e,\ exp.}$ the values of q_e obtained experimentally.

Compound	C_0 (mg/L)	$q_{e,\ exp.}$ (μg/g)	Pseudo–First Order			Pseudo–Second Order		
			$q_{e,\ calc.}$ (μg/g)	k_1 (1/min)	R^2	$q_{e,\ calc.}$ (μg/g)	k_2 (g/μg·min)	R^2
DCF	5	4826	206	$1.61 \cdot 10^{-4}$	0.135	5000	$4.00 \cdot 10^{-3}$	1.000
	15	14,729	3185	$2.07 \cdot 10^{-3}$	0.806	14,286	$6.13 \cdot 10^{-6}$	1.000
	25	22,240	11,163	$1.15 \cdot 10^{-3}$	0.851	25,000	$1.14 \cdot 10^{-6}$	0.993
SMX	5	4999	2085	$5.07 \cdot 10^{-3}$	0.987	5000	$8.16 \cdot 10^{-6}$	0.999
	15	9910	11,527	$6.91 \cdot 10^{-4}$	0.902	11,111	$8.71 \cdot 10^{-7}$	0.992
	25	11,549	23,206	$4.61 \cdot 10^{-4}$	0.877	14,286	$1.88 \cdot 10^{-7}$	0.979
TMP	5	4992	82	$2.07 \cdot 10^{-3}$	0.598	5000	$4.00 \cdot 10^{-7}$	1.000
	15	14,933	606	$1.84 \cdot 10^{-3}$	0.543	14,286	$4.90 \cdot 10^{-5}$	1.000
	25	24,083	3151	$1.15 \cdot 10^{-3}$	0.657	25,000	$8.00 \cdot 10^{-6}$	1.000

Table 6.8. Sorption kinetics parameters of DCF, SMX and TMP in ultra-pure water with 0.1 g/L of added PAC for pseudo-first order and pseudo second order. C_0 indicates the initial concentration of the OMP and $q_{e,\,exp.}$ the values of q_e obtained experimentally.

Compound	C_0 (mg/L)	$q_{e,\,exp.}$ (μg/g)	Pseudo–First Order			Pseudo–Second Order		
			$q_{e,\,calc.}$ (μg/g)	k_1 (1/min)	R^2	$q_{e,\,calc.}$ (μg/g)	k_2 (g/μg·min)	R^2
DCF	5	31,442	127,321	$6.91 \cdot 10^{-5}$	0.743	33,333	$1.13 \cdot 10^{-6}$	0.999
	15	34,852	29,971	$4.61 \cdot 10^{-4}$	0.430	33,333	$1.29 \cdot 10^{-6}$	0.996
	25	34,869	229,192	$4.61 \cdot 10^{-4}$	0.877	33,333	$6.92 \cdot 10^{-7}$	0.995
SMX	5	19,398	43,813	$2.30 \cdot 10^{-4}$	0.868	20,000	$4.55 \cdot 10^{-7}$	0.992
	15	26,490	138,038	$9.21 \cdot 10^{-5}$	0.784	25,000	$7.41 \cdot 10^{-8}$	0.996
	25	37,016	233,830	$6.91 \cdot 10^{-5}$	0.940	33,333	$3.83 \cdot 10^{-8}$	0.984
TMP	5	37,184	25,439	$4.61 \cdot 10^{-4}$	0.844	33,333	$1.13 \cdot 10^{-6}$	0.997
	15	33,416	126,765	$6.91 \cdot 10^{-5}$	0.561	33,333	$1.5 \cdot 10^{-6}$	0.999
	25	36,425	229,826	$6.91 \cdot 10^{-5}$	0.917	33,333	$6.43 \cdot 10^{-7}$	0.989

In parallel to pseudo-first and second order models, we fit the data into the intraparticle diffusion model (IPD). Previous studies (Çalişkan and Göktürk, 2010; Delgado et al., 2019; Torrellas et al., 2015) have reported that the removal of pharmaceuticals by adsorption onto PAC does not fit IPD, since the rate of adsorption is controlled by one or more stages. Nevertheless, although the model does not fit, it is known that in porous adsorbents like PAC, intraparticle diffusion plays a major role in the adsorption process (Çalişkan and Göktürk, 2010). The IPD model may be useful to predict the reaction pathways and the rate-controlling step in the transport of the OMP from the water matrix to the active sites (Tran et al., 2017). For porous adsorbents like PAC, the adsorption process is differentiated into four stages, as stated originally by Walter and Weber (1984). The first stage is the transfer of the target pollutant to the solution (bulk transport); the second is the film diffusion, in which the adsorbate is transported from the bulk phase to the external surface of the PAC; the third stage is the diffusion of the adsorbate molecules along the adsorbent surface or through the pores (i.e. intraparticle diffusion), defined as the rate-controlling step in the IPD model; and the fourth stage is when the adsorption is formed between the OMP and the active site. When the adsorption onto PAC is controlled by the intraparticle diffusion, stages 1, 2 and 4 occur very quickly and the intraparticle diffusion is the only rate-controlling step. As a result, the IPD model adjustment should show a linear relationship between t1/2 and qt with a null intercept (C = 0). In the original linear form of the IPD (eq. 5) presented by (Weber and Morris, J.C., 1963), only the second, third and fourth stages are considered, since bulk transport does not directly relate to the solid-liquid sorption process.

In this study, the q_t versus $t^{1/2}$ plot showed multilinearity with three different slopes, indicating that the adsorption process is governed by a multistep mechanism, differentiated by the three abovementioned stages (Tran et al., 2017). The fitting data for the model is shown in Table 6.9. First of all, it can be seen that the values of the rate constant (k_{id}) follow the following order: $k_{id1} > k_{id2} > k_{id3}$, for in all the samples tested. K_{id} values are also higher at increasing OMP initial concentrations. The fact that the third stage is the lowest is due to the attainment of the equilibrium state, in which intraparticle diffusion gradually slows down, the OMPs come into contact with the

active sites and the final equilibrium is reached, resulting in the corresponding plots being nearly horizontal lines (Suriyanon et al., 2013; Xiang et al., 2018). Regarding constant *C*, the results show that $C \neq 0$ in all samples tested and increasing values from C_1 to C_3 were found for DCF and TMP (and not for SMX). Constant *C* is associated with the thickness of the boundary layer, which implies that there is a higher boundary layer effect within the pores (and active sites) of the activated carbon compared to the outer surface. According to Rudzinski and Plazinski (2008), negative values of intercept *C* observed for SMX can be explained by the presence of a "subsurface" region close to the surface of PAC on which the concentration of the adsorbate is different than in the bulk phase, which affects to the rate of the surface reactions (pseudo-second-order kinetics) at the initial times.

Although the adsorption onto PAC is governed by multi-step mechanism and that intraparticle diffusion is not the only rate-limiting stage in the adsorption process, the IPD model was useful to understand that the sorption mechanisms of the three target OMPs. In general, it can be deducted that once the OMPs pass through the boundary layer from the bulk phase to the external surface of the PAC, it slowly moves from the macropores to the active sites, decreasing the adsorption rate. The adsorption also seems to be determined by a boundary layer effect that increase its relevance in the latter stages of the adsorption process.

Table 6.9 Intraparticle diffusion model constants and correlation coefficients for DCF, SMX and TMP sorption at different initial concentration, together with the respective regression coefficients (R^2).

Compound	C_0 (mg/L)	Intraparticle Diffusion								
		First Phase			Second Phase			Third Phase		
		k_{p1}, (μg/g min$^{1/2}$)	C_1	R^2	k_{p2}, (μg/g min$^{1/2}$)	C_2	R^2	k_{p3}, (μg/g min$^{1/2}$)	C_3	R^2
DCF	5	0.402	93.03	0.921	0.078	95.45	1.000	-0.006	96.75	0.979
	15	15.657	129.49	0.996	2.322	242.66	0.999	-0.013	295.08	1.000
	25	26.047	109.34	0.976	11.310	192.21	0.962	0.029	443.70	1.000
SMX	5	2.596	50.37	0.985	1.926	54.95	0.962	0.074	97.16	1.000
	15	7.479	20.77	0.977	8.644	-8.99	1.000	0.187	191.09	1.000
	25	8.524	-23.18	0.947	14.061	-97.14	0.991	0.033	229.71	1.000
TMP	5	3.813	78.36	0.889	0.348	96.39	0.995	0.020	99.15	0.781
	15	12.055	211.25	0.958	0.958	285.80	0.998	0.072	296.07	0.938
	25	15.330	337.67	0.982	3.291	420.88	0.999	0.321	470.19	0.933

6.4.3. Sorption isotherms in ultra-pure water and competition effect

OMPs concentrations tested for isotherm determination were in the range of 5 – 25 mg/L, while PAC concentration was between 0.1 and 1 g/L. The equilibrium time was set at 24 h. PAC concentrations were selected in accordance with the literature (Alvarino et al., 2016; Li et al., 2011; Nguyen et al., 2013). Instead, the OMPs concentrations were the lowest allowed by the analytical method. Due to the high adsorption capacity of the PAC, lower OMPs concentrations would be almost completely adsorbed and unable to be detected.

Equilibrium adsorption in ultra-pure water was studied by applying linear, Langmuir and Freundlich isotherms models. Figure 6.7 shows the linear sorption isotherms of DCF, SMX and TMP at the tested PAC concentrations in ultra-pure water. The sorption coefficient of the linear sorption, together with the sorption parameters derived from Langmuir and Freundlich models and regression coefficients (R^2) are listed in Table 6.10. Note that N.A indicates that the parameters could not be obtained, as the residual concentration found in the liquid phase was too low to conduct the modelling.

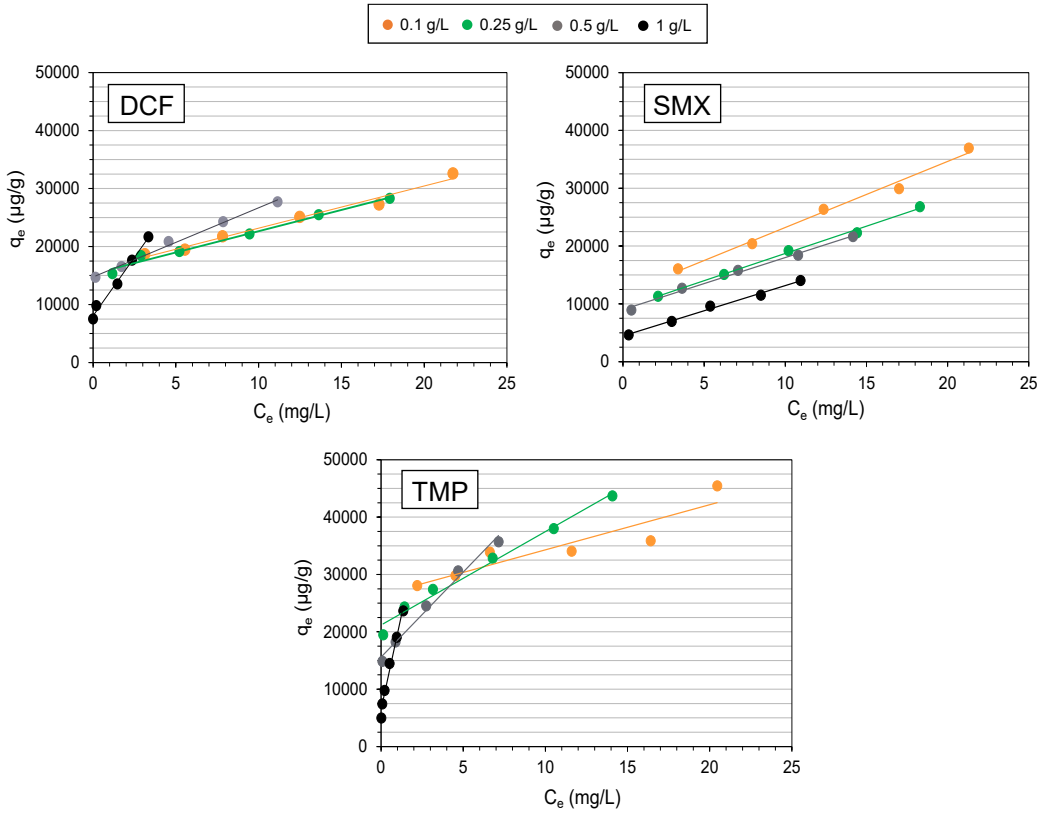


Figure 6.7. Experimental equilibrium adsorption capacity of DCF, SMX and TMP at four different PAC concentrations (0.1, 0.25, 0.5 and 1 g/L) in ultra-pure water.

From the analysis of the obtained results in Table 6.10, it emerges that regression coefficients for linear sorption (0.783 – 0.96) were significantly lower than for the Langmuir and Freundlich models ($p < 0.05$) for all three tested compounds, which means that the model does not fit the adsorption data very well. On the other hand, no significant differences were found between Langmuir and Freundlich for DCF and TMP, while Freundlich model provided better R^2 coefficients for SMX. This finding is in agreement with previous studies in the literature (Çalişkan and Göktürk, 2010; Kim et al., 2010; Torrellas et al., 2015), where very similar R^2 values were obtained, and no statistical analyses were performed to determine the best fitting equation. Langmuir and Freundlich isotherms are the most used for describing the adsorption of porous adsorbents in wastewater, but further investigation on isotherms modelling may be needed to best describe the adsorption process.

Considering K_d, q_m and K_F parameters, the results observed in the kinetic studies are confirmed once again, and the OMPs better adsorbed in PAC as follows: TMP, DCF and SMX. On the other hand, the term $1/n$ of Freundlich isotherm represents the intensity of adsorption. Since the values found for all compounds are less than 1, it can be assumed that there is a good affinity between the adsorbates and the adsorbent, and that chemical adsorption occurs.

Complex mixtures of OMPs are usually found in wastewater (Verlicchi et al., 2012). The diversity of the nature and target use of the OMPs is usually reflected in their physicochemical properties (e.g., hydrophobicity, solubility, charge, molecular weight). When PAC is used to remove pollutants in wastewater, adsorption depends on the interactions between the compound and the adsorbent surface, and the aforesaid pharmaceuticals properties listed in Table 6.2 may be the key to understanding and predicting the adsorption tendency of the compound. For these reasons, it is of great importance to understand the competitive effect between pharmaceuticals when considering adsorption onto activated carbon. The target compounds are expected to be adsorbed to varying degrees, and the competition for the adsorption sites may vary depending on the initial concentration and physicochemical properties of the compound. To evaluate the competitive effect between the three target OMPs (Experiment 2), adsorption batch experiments in a solution with a mixture of DCF, SMX and TMP at three different concentrations (5, 15 and 25 mg/L) were conducted. Moreover, kinetics studies were conducted to evaluate if the rate and mechanism of adsorption of each compound varied in comparison to individual OMPs solutions. Results are showed in Table 6.11 for adsorption isotherms (parameters and regression coefficients) and Figure 6.8. Results on the kinetic studies are found in Table 6.12.

Table 6.10. Distribution coefficient (K_d), Langmuir and Freundlich isotherms constants in different water matrices (ultra-pure water, MBR permeate, mixed liquor and humic acid solution. Results for humic acid solutions were considered without pre-contact time between the HAs and the OMPs. N.A (not applicable) indicates that the parameters could not be obtained, as the residual concentration found in the liquid phase was too low to conduct the modelling.

		Linear Sorption		Langmuir Isotherm			Freundlich Isotherm		
Compound	PAC conc. (g/L)	K_d (mL/g)	R^2	q_m (µg/g)	K_L (L/mg)	R^2	$1/n$	K_F (mg/g) (mL/mg)$^{1/n}$	R^2
Ultra-pure water									
DCF	0.1	1777.9	0.895	33,333	0.300	0.967	0.281	12,673.9	0.925
	0.25	1949.2	0.836	33,333	0.429	0.979	0.215	14,368.6	0.953
	0.5	2980.6	0.783	25,000	2.000	0.978	0.271	14,099.6	0.991
	1	7167.1	0.855	20,000	5.000	0.946	0.574	10,802.1	0.999
SMX	0.1	1896.0	0.960	50,000	0.100	0.915	0.439	8918.7	0.959
	0.25	1634.0	0.947	33,333	0.150	0.936	0.392	7972.1	0.967
	0.5	1756.3	0.902	25,000	0.444	0.956	0.380	7667.1	0.985
	1	1417.6	0.937	16,667	0.300	0.912	0.520	3947.0	0.990
TMP	0.1	2618.9	0.833	50,000	0.400	0.951	0.178	23,576.4	0.801
	0.25	3712.3	0.820	50,000	0.667	0.972	0.249	21,407.6	0.961
	0.5	5939.4	0.852	33,333	1.500	0.967	0.393	16,565.9	0.998
	1	19,820.0	0.910	25,000	4.444	0.939	N.A	N.A	N.A
Humic acid solution									
DCF	0.1	4521.6	0.941	100,000	0.125	0.908	0.457	18,012.1	0.929
	0.25	4802.4	0.783	50,000	1.000	0.994	0.280	24,760.4	0.896
	0.5	4600.6	0.768	33,333	1.500	0.984	0.200	20,607.3	0.781
	1	12,308.0	0.718	100,000	1.429	0.526	N.A	N.A	N.A
SMX	0.1	2856.7	0.878	50,000	0.250	0.919	0.263	20,426.7	0.863
	0.25	3957.7	0.792	50,000	1.000	0.983	0.141	29,673.2	0.651
	0.5	6994.4	0.801	33,333	3.000	0.983	0.273	22,606.7	0.807
	1	11,372.0	0.763	25,000	5.000	0.991	N.A	N.A	N.A
TMP	0.1	2287.9	0.860	50,000	0.286	0.975	0.212	19,150.8	0.900
	0.25	2600.1	0.791	33,333	0.750	0.992	0.189	19,424.7	0.958
	0.5	3824.5	0.720	33,333	3.000	0.994	0.196	19,358.8	0.998
	1	31,430.0	0.740	25,000	10.000	0.998	N.A	N.A	N.A
MBR permeate									
DCF	0.1	1553.7	0.880	33,333	0.150	0.978	0.416	8206.6	0.865
	0.25	1785.4	0.802	25,000	0.667	0.989	0.207	14,004.0	0.925
	0.5	3273.4	0.776	50,000	1.000	0.985	0.279	14,831.4	0.997
	1	12,011.0	0.734	25,000	1.000	0.995	N.A	N.A	N.A
SMX	0.1	1642.8	0.999	1,000,000	0.002	0.028	0.953	1843.1	0.988
	0.25	1349.2	0.962	33,333	0.100	0.924	0.498	5154.4	0.978
	0.5	1874.2	0.870	25,000	0.444	0.993	0.265	10,690.4	0.932
	1	3009.7	0.837	20,000	1.000	1.000	0.231	11,178.0	0.996
TMP	0.1	9370.2	0.875	250,000	0.057	0.225	0.810	15,532.7	0.647
	0.25	6616.8	0.690	50,000	1.000	0.974	0.282	31,351.0	0.754
	0.5	8417.5	0.535	50,000	1.000	0.937	N.A	N.A	N.A
	1	N.A	N.A	N.A	N.A	N.A	N.A	N.A	N.A
Mixed liquor									
DCF	0.1	827.9	0.993	-25,000	-0.019	0.466	1.356	299.7	0.957
	0.25	766.7	0.963	-10,000	-0.033	0.407	1.608	148.1	0.903
	0.5	235.9	0.995	50,000	0.005	0.038	0.906	296.5	0.952
	1	234.1	0.998	33,333	0.008	0.268	0.889	312.6	0.979
SMX	0.1	431.5	0.965	-3333	-0.048	0.907	1.827	55.0	0.999
	0.25	233.2	0.990	-33,333	-0.006	0.085	1.098	186.3	0.954
	0.5	84.0	0.892	2000	0.172	0.873	0.485	384.3	0.707
	1	109.4	0.858	2500	0.118	0.552	0.662	300.6	0.594
TMP	0.1	3988.7	0.976	1,250,000	0.004	0.015	1.006	4011.8	0.939
	0.25	1785.7	0.995	125,000	0.020	0.538	0.8440	2659.3	0.980
	0.5	1002.7	0.960	33,333	0.060	0.986	0.6493	2484.4	1.000
	1	822.7	0.868	14,286	0.233	0.996	0.4847	2980.3	0.967

Table 6.11. Distribution coefficient (K_d), Langmuir and Freundlich isotherms constants for the mixture of the three OMPs in ultra-pure water.

		Linear Sorption		Langmuir Isotherm			Freundlich Isotherm		
Compound	**PAC conc.** *(g/L)*	K_d *(mL/g)*	R^2	q_m *(µg/g)*	K_L *(L/mg)*	R^2	*1/n*	K_F *(µg/g) (mL/mg)$^{1/n}$*	R^2
DCF	0.1	1806.2	0.852	33,333	0.375	0.987	0.203	16,008.9	0.955
	0.25	1063.6	0.763	16,667	1.000	1.000	0.124	11,356.0	0.900
	0.5	1348.8	0.785	16,667	1.000	0.995	0.212	9531.0	0.962
	1	1390.1	0.707	12,500	1.000	0.996	0.125	9464.5	0.823
SMX	0.1	423.03	0.935	50,000	0.010	0.987	0.587	1222.7	0.423
	0.25	385.32	0.965	14,286	0.054	1.000	0.670	1012.2	0.950
	0.5	280.47	0.976	10,000	0.053	0.995	0.709	629.0	0.998
	1	162.16	0.868	3333	0.375	0.996	0.137	1783.6	0.652
TMP	0.1	2442.7	0.901	50,000	0.200	0.987	0.257	17,243.7	0.597
	0.25	2036.5	0.733	25,000	2.000	1.000	0.128	19,171.9	0.964
	0.5	2716.2	0.730	25,000	2.000	0.995	0.151	17,870.4	0.955
	1	5636.6	0.843	25,000	2.000	0.996	0.239	14,485.5	1.000

As for individual solutions, no differences between isotherm models were found, with the exception of the significantly lower R^2 of linear isotherm in the case of DCF ($p < 0.05$). Despite the lack of significance, the regression coefficients for the Langmuir isotherm are slightly higher, indicating that a monolayer adsorption on the PAC surface is assumed, and that the differences in the adsorption between pharmaceuticals depend on the affinity of the compound to the PAC surface. Although there were no differences between the maximum adsorption capacity (q_m) among the pharmaceuticals, the Langmuir adsorption constants (K_L) were significantly lower for SMX ($p = 0.018$). Similarly, K_d and K_F showed significant differences between tested compounds ($p < 0.05$), with higher coefficient values in the following order: TMP > DCF > SMX.

When comparing isotherms coefficients between individual solutions and the mixture, it was found that only K_F and K_d were significantly lower in the mixture compared to the individual solution in SMX. In this sense, although no significant differences were found for the other parameters (q_m, K_L) and compounds (DCF, TMP), higher values were found in the individual solutions, indicating that there is some competition effect, especially for SMX.

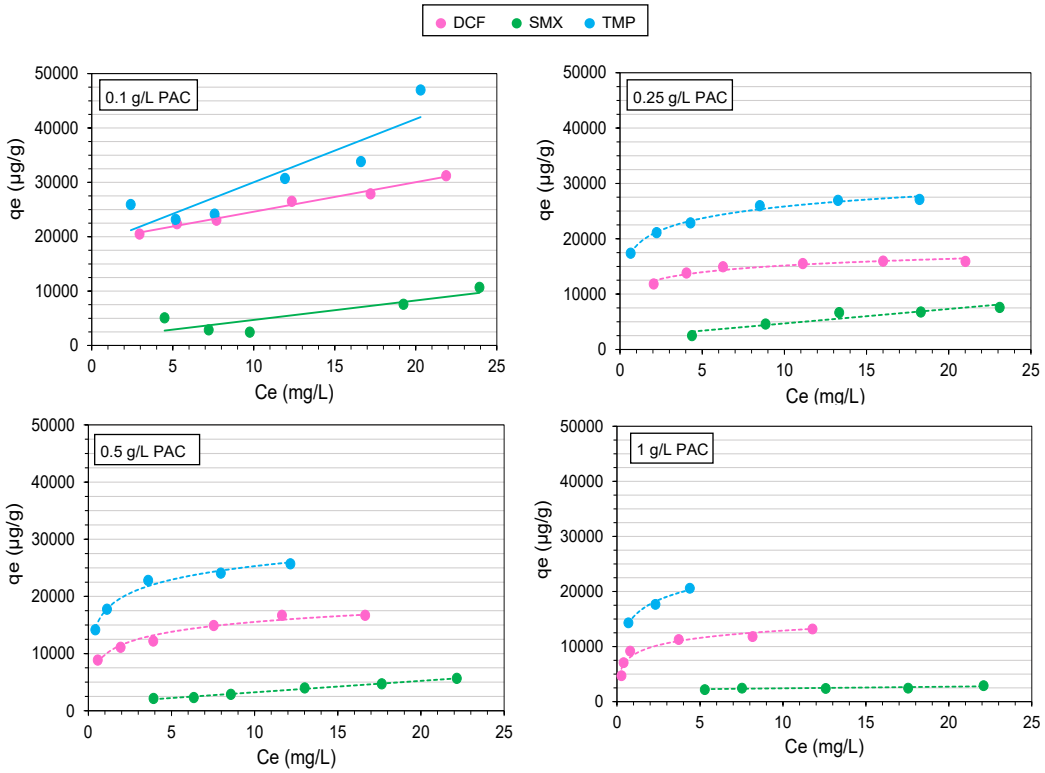


Figure 6.8. Experimental equilibrium adsorption capacity of DCF, SMX and TMP in a mixture at four different PAC concentrations (0.1, 0.25, 0.5 and 1 g/L) in ultra-pure water.

Regarding the kinetics, the compounds followed a pseudo-second order equation (Table 6.12), with no significant differences between $q_{e,\ exp}$ and $q_{e,\ calc.}$ ($p > 0.05$). Despite there were not differences between the kinetic coefficients (k_2) for the individual solutions and the mixture, both $q_{e,\ exp.}$ and $q_{e,\ calc}$. were overall greater in the individual solutions compared to the mix ($p = 0.01$). This can be also reflected by the removal efficiencies of the compounds in the liquid phase depicted in Table 6.13, which were found between 23% – 27% higher in the individual solutions at 5 mg/L in three OMPs compared to the mixture (e.g., 62.9% *versus* 36.9% for DCF).

Table 6.12. Sorption kinetics parameters for the mixture of DCF, SMX and TMP in ultra-pure water with 0.1 g/L of added PAC.

Compound	C_0 (mg/L)	$q_{e,\ exp.}$ (µg/g)	Pseudo–First Order			Pseudo–Second Order		
			$q_{e,\ calc.}$ (µg/g)	k_1 (1/min)	R^2	$q_{e,\ calc.}$ (µg/g)	k_2 (g/µg·min)	R^2
DCF	5	18,467	136,395	$9.21 \cdot 10^{-5}$	0.878	16,667	$1.33 \cdot 10^{-6}$	0.991
	15	28,362	40,272	$1.84 \cdot 10^{-4}$	0.851	33,333	$4.09 \cdot 10^{-7}$	0.993
	25	15,957	242,493	$2.30 \cdot 10^{-5}$	0.387	16,667	$1.2 \cdot 10^{-6}$	0.990
SMX	5	5716	48,865	$6.909 \cdot 10^{-5}$	0.801	10,000	$1.81 \cdot 10^{-7}$	0.890
	15	4742	147,809	$1.382 \cdot 10^{-5}$	0.633	5000	$2.72 \cdot 10^{-6}$	0.991
	25	35,771	237,684	$6.909 \cdot 10^{-5}$	0.740	33,333	$2.81 \cdot 10^{-7}$	0.997
TMP	5	25,531	32,464	$2.30 \cdot 10^{-4}$	0.820	25,000	$1.45 \cdot 10^{-6}$	0.999
	15	25,310	134,122	$4.61 \cdot 10^{-5}$	0.435	25,000	$1.23 \cdot 10^{-6}$	0.990
	25	25,948	239,111	$4.61 \cdot 10^{-5}$	0.874	25,000	$5.71 \cdot 10^{-7}$	0.941

In general, TMP was the compound that adsorbed best at PAC compared to the other two compounds. TMP is the only OMP tested that is found mainly in its cationic form at the pH of water and wastewater (pH 6 − 8) (Figure 6.4). Regardless of their other physicochemical properties, cationic compounds have been shown to be well removed on PAC hybrid systems, due to the electrostatic interactions with the negatively charged surface of most manufactured PACs (Mailler et al., 2015; Margot et al., 2013). The charge of ionizable compounds is the conducting parameter that determines their adsorption onto PAC (Gutiérrez et al., 2022). In water and wastewater, DCF and SMX are mainly present in their anionic form, so the expected removal by PAC is lower. In absence of positive electrostatic interactions, hydrophobicity (measured as K_{ow}) becomes the critical factor to predict the adsorption. SMX is an anionic compound with very low hydrophobicity ($logK_{ow}$ = 0.79), compared to DCF ($logK_{ow}$ = 4.26). Both properties are responsible the lower adsorption of SMX onto PAC in the tested conditions.

Table 6.13. Removal efficiencies in the aqueous phase (%) after 24h of contact time between individual solutions of DCF, SMX and TMP and the mixture of the three compounds at three different initial concentrations (5, 15, 25 mg/L) with 0.1 g/L of PAC.

Compound	Initial concentration (mg/L)	Removal efficiency (%)	
		Individual	Mixture
DCF	5	62.9	36.9
	15	23.2	18.9
	25	13.9	6.4
SMX	5	38.8	11.4
	15	17.7	3.2
	25	14.8	14.3
TMP	5	74.4	51.1
	15	22.3	16.9
	25	14.6	10.4

6.4.4. Influence on the water matrix

Water matrix influences the adsorption process as well as the physicochemical properties of OMPs and activated carbon. During wastewater treatment, the constituents of the wastewater change along with its quality. Briefly, in the primary treatment, a portion of organic matter and suspended solids is removed from the raw wastewater. Then, most of the biodegradable compounds and suspended solids are removed during the secondary (or biological) treatment. The final effluent has a low concentration of organic matter and nutrients (nitrogen, phosphorous) and is disinfected before its discharge. In advanced and/or hybrid systems, the quality of the wastewater is further improved by the removal of dissolved and suspended materials, such as OMPs. In this context, PAC may be used inside the biological tank (Alvarino et al., 2017) or as a polishing treatment (Kovalova et al., 2013b) at the end of the process, and thus it is necessary to study the influence of the water matrix on the adsorption of contaminants. One of the most important parameters to consider is the presence of dissolved organic matter (DOM) (Aschermann et al., 2019). DOM is constituted by fractions of different sizes (i.e., building blocks, humic and fulvic acids, biopolymers

and low molecular weight organics), that can affect adsorption at varying degrees (Zietzschmann et al., 2014). Usually, the addition of fresh PAC is required to maintain high removal efficiencies, since the PAC surface gets saturated over time due to the adsorption of the DOM present in the wastewater and the OMPs (Alvarino et al., 2017; Aschermann et al., 2019). In addition, the effect of PAC saturation is more pronounced for anionic compounds, since DOM is negatively charged at the overall pH of wastewater and can interfere with the adsorption of anionic compounds through electrostatic repulsion (Margot et al., 2013). However, the effect of the presence of DOM is still unclear. Many studies report that DOM has no significant effect or may even have a positive effect on the adsorption of some pharmaceuticals, depending on the experimental conditions (Guillossou et al., 2020; Pan et al., 2013; Zietzschmann et al., 2016a).The influence on the water matrix was studied by performing adsorption batch experiments in ultra-pure water, humic acid solution, MBR permeate and mixed liquor and comparing the obtained experimental results and isotherms modelling (Experiments 1, 3, 4 and 5). In our study, we could not to perform analyses to determine the composition of in the MBR permeate and the mixed liquor. However, we measured the total DOC concentration for the HAs solution (29.35 mg/L), MBR permeate (4.1 mg/L) and mixed liquor (4.7 mg/L). It should be noted that the DOC concentration in the MBR permeate and that in the mixed liquor are quite similar, despite their different nature. Mixed liquor possesses a high concentration of total suspended solids (6 g/L) compared to MBR permeate (5.4 mg/L). In this case, the solid phase mixed liquor was included in the adsorption experiments, since it can act as an adsorbent and influence the interactions between OMPs and PAC.

Experimental equilibrium adsorption capacities of DCF, SMX and TMP for each water matrix are depicted in Figure 6.9 (PAC concentration of 0.1 g/L and 1 g/L) and Figure 6.10 (PAC concentration of 0.25 g/L and 0.5 g/L). Sorption parameters from isotherm models and regression coefficients for each water matrix are listed in Table 6.10. The adsorption mechanisms, and therefore the isotherms models that describe them, may vary from compound to compound, as described in the literature (Mutavdžić Pavlović et al., 2022a). Similarly, they appear to depend on the water matrix in which adsorption occurs. As mentioned earlier, both the Langmuir and Freundlich models fitted the results of DCF and TMP very well, while for SMX the Freundlich model provided a better fit in ultra-pure water. Still, the regression coefficients of Freundlich model for SMX are very high ($R^2 > 0.956$). As for ultra-pure water, both Langmuir and Freundlich isotherms had very similar regression coefficients in MBR permeate, and there was not a model that fitted the results better for any of the compounds tested. None of the Langmuir parameters (K_L and q_m) differed significantly among OMPs. Instead, the Langmuir isotherm clearly fitted better the plot q_e versus C_e in the humic acid solution, while the Freundlich isotherm had significantly higher R^2 values in the mixed liquor. In the Langmuir isotherm, a monolayer adsorption on the PAC surface is assumed with a fixed number of energetically equivalent sites, while Freundlich isotherm is considered an empirical expression for multilayer adsorption with different energy in the active sites (Mutavdžić Pavlović et al., 2018). Mixed liquor is

expected to represent a much more complex matrix, since it was extracted from the biological reactor, where most of the biological and chemical transformations to remove contaminants take place. In previous studies, it has been observed that at similar DOC-pharmaceutical concentrations, the composition of DOM can cause a stronger adsorption competition effect depending on the type of water (in the study, drinking water compared to WWTP effluent) (Zietzschmann et al., 2016a). In this way, the results are not surprising, and confirm that adsorption mechanisms change depending to the experimental conditions.

Assuming that the Freundlich isotherm (eq. 7) had the best fit for all the water matrices, the higher K_F values were found as follows: humic acid solution, ultra-pure water, MBR permeate and mixed liquor. According to eq. 7, higher K_F values correspond to a higher adsorption capacity of the PAC (q_e) for the same equilibrium concentration (C_e) for all three compounds. As shown in Figure 6.9 and Figure 6.10, the higher PAC loads were obtained in the humic acid solution for DCF and SMX, followed by ultra-pure water and MBR permeate, with very similar results ($p > 0.05$). The lowest adsorption of micropollutants was found in the mixed liquor. On the other hand, PAC loads were found to be the lowest in the mixed liquor for all pharmaceuticals. For TMP instead, the best results were obtained in the MBR permeate, followed by ultra-pure water, humic acid solution and mixed liquor in all the PAC concentrations tested except 0.1 g/L. Indeed, for 1 g/L, the remaining concentrations of TMP in the solution were too low to perform the isotherm modelling. For 0.1 g/L of PAC, an unexpected increase in the adsorption capacity was achieved at higher TMP concentrations in the mixed liquor, not following the trend of the other PAC concentrations. Although the overall results are not consistent with other studies (Guillossou et al., 2020; Kovalova et al., 2013a), where adsorption capacity in wastewater was systematically lower in compared to the ultra-pure water, it is possible that positive interactions between the humic acids and MBR effluent DOM lead to an increase adsorption capacity of PAC. Moreover, in real wastewater systems, DOM is present at a concentration of 3 to 6 orders of magnitude higher than organic micropollutants (mg/L compared to µg/L – ng/L). In our experimentation, the extent of the effect of DOM may be limited or altered since the C_0 of the tested pharmaceuticals ranged from 5 to 25 mg/L. In all water matrices, the highest PAC loadings (q_e) were observed at the lowest PAC concentration (0.1 g/L) and maximum pharmaceutical concentration (25 mg/L) for all the water matrixes and compounds.

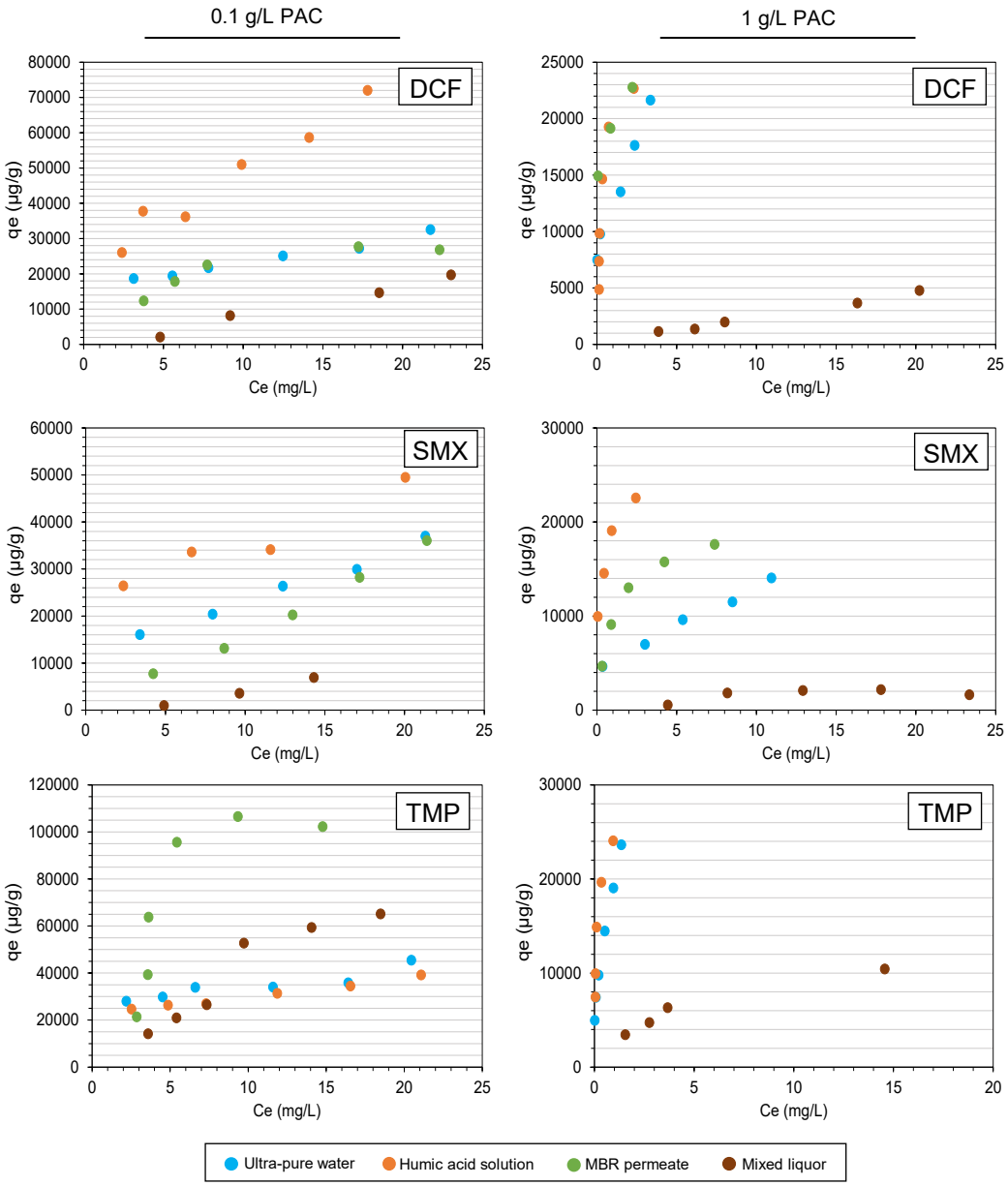


Figure 6.9. Experimental equilibrium adsorption capacity of DCF, SMX and TMP at two different PAC concentrations (0.1 and 1 g/L) in ultra-pure water, humic acid solution, MBR permeate and mixed liquor from a WWTP.

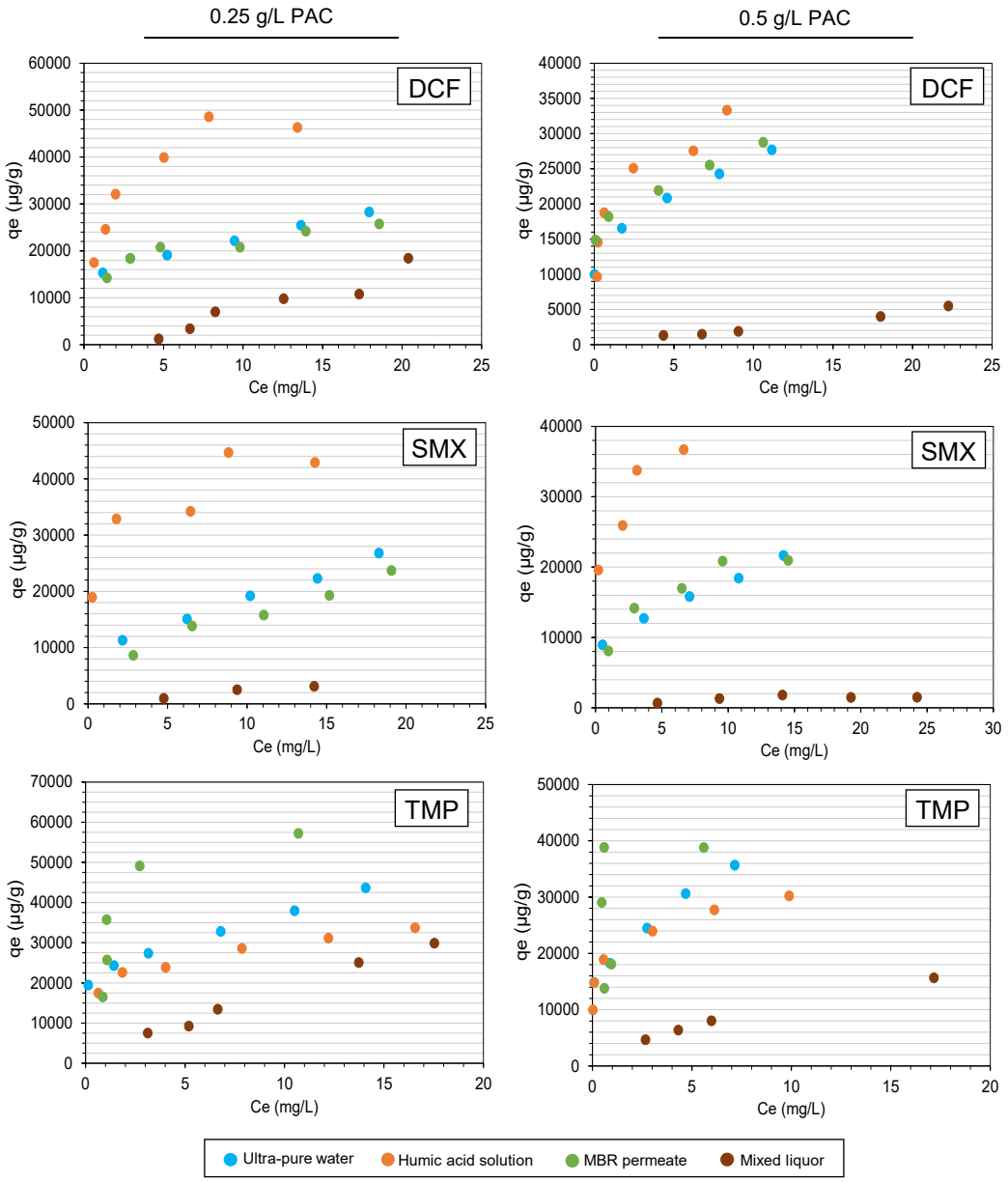


Figure 6.10. Experimental equilibrium adsorption capacity of DCF, SMX and TMP at two different PAC concentrations (0.25 and 0.5 g/L) in ultra-pure water, humic acid solution, MBR permeate and mixed liquor from a WWTP.

It has been observed that the adsorption of some OMPs is promoted by the presence of humic acid in soils and sediments, suggesting that the presence of these substances may positively influence the sorption affinity for the adsorbent (Mutavdžić Pavlović et al., 2022b). Humic substances, which are also commonly found in wastewater, are known to act as carriers of organic micropollutants (Anielak et al., 2022). Due to their mobility and ability to form complexes with organic and inorganic species, commercial HAs may contain trace elements (e.g., ions, heavy metals) that contribute to the adsorption of further organic compounds (i.e., DCF) in adsorption experiments

(Anielak et al., 2022). In another study, the formation of ciprofloxacin-HA complexes has been reported as a "*false positive adsorption*" when testing the sorption capacity of various adsorbents (Jin et al., 2018). According to Behera et al. (2010), the pharmaceutical-HA complex would be able to adsorb onto the surface of the adsorbent. These authors also suggest that the free pharmaceuticals in the solution could adsorb to the already adsorbed HA, leading to an increase in the adsorption (Jin et al., 2018). On the other hand, the high concentrations of HAs in our study (29.35 mg/L) may enhance the sorption of some pharmaceuticals, via hydrophobicity. Even if the interaction between DOM and pharmaceuticals is not expected, the presence of HAs may promote the adsorption through the PAC in solution. The adsorption of dissolved humic substances has been proved to reduce the aggregation of carbon nanotubes, thus increasing the surface area available for adsorption by two orders of magnitude, increasing the change of hydrophobic interactions between the adsorbent and SMX (Pan et al., 2013). This could explain the increased adsorption of DCF and SMX, two anionic compounds for which the electrostatic interactions with the DOM would not be primarily considered. For the aforementioned reasons, the increased adsorption capacity of PAC in the HA solution is not surprising. Although there is no single phenomenon that explains the observed results, the literature data confirm that the presence of humic substances can affect the adsorption of organic compounds such as pharmaceuticals in several ways.

In the case of the MBR permeate, the results show that the presence of DOM had no negative effect on drug adsorption, with no statistical differences from ultra-pure water for DCF and SMX ($p > 0.05$) and with an increase in the adsorption capacity of PAC for TMP ($p < 0.05$). Since the concentration of the pharmaceutical influences the experimental adsorption values (with the highest q_e values at C_0 of 25 mg/L in all water matrices), it may be that DOC is not high enough in the solution to cause a decrease in adsorption compared with ultra-pure water. In any case, the results show that the adsorption of TMP in the MBR permeate was enhanced, probably due to the above-mentioned reasons related to HAs and, in particular to the fact that TMP is positively charged, which could favor the interactions with negatively charged DOM. PAC, which was added to the effluent of two full-scale WWTPs, was shown to provide a better effluent quality (i.e., lower TMP concentration) which suggests that DOM constituents of the MBR permeate have a different effect on the adsorption of TMP onto PAC (Kovalova et al., 2013b; Margot et al., 2013). Indeed, TMP was not the only compound with lower adsorption in the mixed liquor. Even with the very similar DOC concentration, the differences in the adsorption capacity of PAC between the MBR permeate and mixed liquor indicate that the DOM constituents play a significant role in the adsorption process. While HAs appear to favor adsorption, low molecular weight organics have been shown to limit the process due to direct competition for the adsorption sites (Zietzschmann et al., 2014). However, it should be noted that the experiments conducted aimed to reproduce the adsorption process under real WWTP conditions, and therefore the solid fraction of the mixed liquor was included in the adsorption batch experiments. Since some pharmaceuticals can also adsorb to sludge

(Alvarino et al., 2016), additional adsorption experiments were performed without the addition of PAC to quantify the adsorption onto the solid phase of the mixed liquor (dried sludge). The results of the experimental q_e and C_e values were very different, and no modelling could be performed (data not shown). However, the resulting q_e values were very low compared to PAC adsorption (e.g., maximum q_e found was 530 µg/g for SMX), and thus the adsorption onto the mixed liquor can be neglected for the pharmaceuticals under study (Alvarino et al., 2016). However, the presence of additional suspended material (with a concentration of 6 g/L) could limit the ability of the pharmaceuticals to reach the PAC adsorption sites, and thus physically reduce the adsorption of pharmaceuticals.

6.4.5. Influence of the pre-equilibrium between OMPs and DOM on adsorption

The influence on the interaction between DOM and the OMPs before the adsorption onto PAC was studied by using HA solution with a DOC concentration of approximately 24 mg/L. Humic acids are one of the most common DOM fractions found in wastewater (Anielak et al., 2022), and they were chosen because of their commercial availability and ease of use in the laboratory. Since the objective was to study the interaction between DOM and the OMPs, the concentration of DOC does not have to be identical to the concentration in the biological tank of a WWTP (4.7 mg/L). In fact, the experiments were performed with the highest possible DOC concentration, to produce the largest difference between DOM and the OMP concentration. The pre-contact time between HAs and OMPs was set at 24 hours, since this time has already been tested as sufficient to evaluate the influence of the interaction between them (Guillossou et al., 2020).

The results of the adsorption capacity of the three OMPs without and with 24 h of pre-contact time with a solution of HAs are shown in Figure 6.11. Isotherm parameters and correlation coefficients are shown in Table 6.13. Langmuir isotherm is a model that better fits the results in the HA solution, and no statistical differences were found for the maximum adsorption capacity (q_m) and Langmuir coefficient (K_L) between the two conditions. As seen in Figure 6.11, a slight increment in the q_e values is observed for no pre-contact time condition in the case of DCF.

Regarding removal efficiencies (data not shown), no statistical differences were found between no- and 24 h pre-contact time with HA solution, although a slight increment was observed for the condition of no-precontact time (3% for SMX, 7% for TMP and 8% for DCF). As explained earlier, the presence of HA in the solution favoured the adsorption compared to the other water matrices for the three OMPs tested, which may be attributed to the high adsorption of the HAs and the interaction between the HA and the OMPs. However, the pre-contact time had no significant effect on the adsorption. The long shaking times of the adsorption experiments (24 h) were already sufficient to observe the potential beneficial effects of the presence of HA in the solution (e.g. formation of pharmaceutical-HA complexes, increased dispersion of

the PAC), without the need for additional pre-contact time. In this way, Guillossou et al., (2020) found that the 24 hour pre-contact time between DOM and OMPs favored adsorption at short contact times (i.e., 30 min), and had no effect once the equilibrium between the adsorbent and adsorbates was reached (i.e., 72 h).

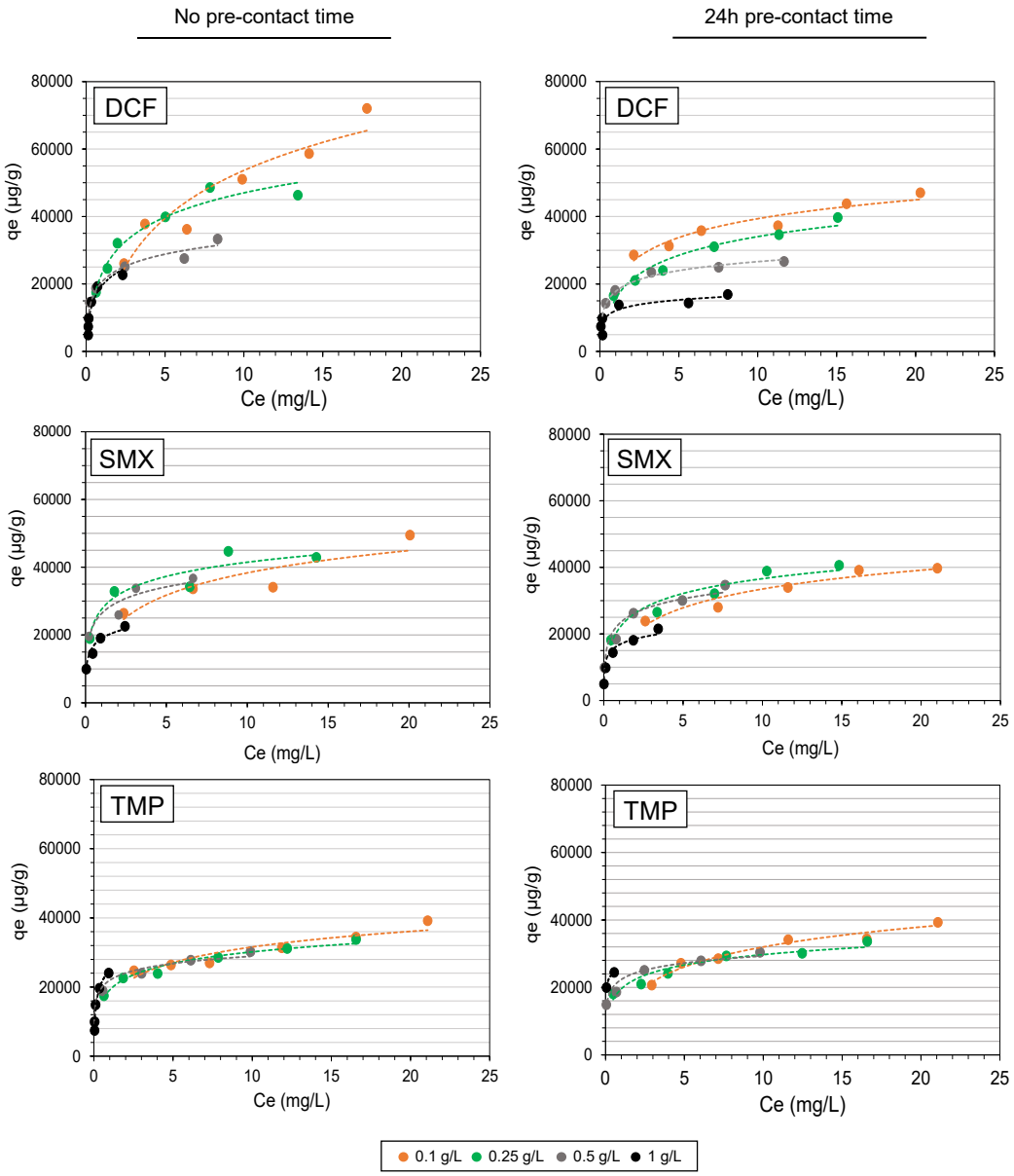


Figure 6.11. Experimental adsorption capacity of PAC at four concentrations (0.1, 0.25, 0.5 and 1 g/L) for individual OMPs (DCF, SMX and TMP) in a humic acid (HA) solution. In the left, OMPs and PAC were added at the same time to the HA solution (no pre-contact time). In the right, each OMP was added to the HA solution 24 h before the PAC addition (24 h pre-contact time).

Table 6.14. Distribution coefficient (K_d) and Langmuir and Freundlich isotherms parameters, together with the corresponding regression coefficients (R^2) for the adsorption DCF, SMX and TMP onto PAC in a humic acid solution with and without pre-contact time between the OMPs and the humic acids (24 h pre-contact time *versus* no pre-contact time). Not applicable (N.A) indicates that the parameters could not be obtained, as the residual concentration found in the liquid phase was very low to conduct the modelling.

		Linear Sorption		Langmuir Isotherm			Freundlich Isotherm		
Compound	**PAC conc.** (g/L)	K_d (mL/g)	R^2	q_m (µg/g)	K_L (L/mg)	R^2	$1/n$	K_F (mg/g) (mL/mg)$^{1/n}$	R^2
Humic acid solution: no pre-contact time									
DCF	0.1	4521.6	0.941	100,000	0.125	0.908	0.457	18,012.1	0.929
	0.25	4802.4	0.783	50,000	1.000	0.994	0.280	24,760.4	0.896
	0.5	4600.6	0.768	33,333	1.500	0.984	0.200	20,607.3	0.781
	1	12,308.0	0.718	100,000	1.429	0.526	N.A	N.A	N.A
SMX	0.1	2856.7	0.878	50,000	0.250	0.919	0.263	20,426.7	0.863
	0.25	3957.7	0.792	50,000	1.000	0.983	0.141	29,673.2	0.651
	0.5	6994.4	0.801	33,333	3.000	0.983	0.273	22,606.7	0.807
	1	11,372.0	0.763	25,000	5.000	0.991	N.A	N.A	N.A
TMP	0.1	2287.9	0.860	50,000	0.286	0.975	0.212	19,150.8	0.900
	0.25	2600.1	0.791	33,333	0.750	0.992	0.189	19,424.7	0.958
	0.5	3824.5	0.720	33,333	3.000	0.994	0.196	19,358.8	0.998
	1	31,430.0	0.740	25,000	10.000	0.998	N.A	N.A	N.A
Humic acid solution: 24h pre-contact time									
DCF	0.1	2931.5	0.848	50,000	0.400	0.983	0.219	23,435.3	0.951
	0.25	3196.9	0.871	50,000	0.333	0.980	0.334	15,739.0	0.988
	0.5	2932.1	0.700	25,000	2.000	0.999	0.096	20,854.0	0.959
	1	2403.6	0.619	16,667	6.000	0.990	0.083	13,418.6	0.614
SMX	0.1	2378.1	0.897	50,000	0.250	0.985	0.262	18,030.1	0.953
	0.25	3434.0	0.869	50,000	0.500	0.981	0.304	18,300.8	0.970
	0.5	5491.8	0.811	33,333	3.000	0.988	0.189	23,086.4	0.948
	1	7530.7	0.785	20,000	6.250	0.988	N.A	N.A	N.A
TMP	0.1	2340.0	0.872	50,000	0.250	0.989	0.293	16,000.9	0.949
	0.25	2567.3	0.791	33,333	0.750	0.991	0.227	17,667.8	0.974
	0.5	3896.4	0.728	33,333	3.000	0.996	0.137	22,092.6	0.987
	1	N.A	N.A	N.A	N.A	N.A	N.A	N.A	N.A

6.5 Conclusions

Adsorption of OMPs onto the PAC surface is a complex process that depends on many factors. In this study, we studied the influence of the OMPs characteristics and concentration, of the water matrix and the effect of the interactions these elements may have. To do so, we conducted adsorption batch tests and applied mathematical models (adsorption isotherms and kinetics), which allowed us to quantify the adsorption capacity of the PAC for each OMP and condition tested, as well as to describe the mechanisms of adsorption.

TMP was the compound with the highest affinity for PAC in all the tested conditions. Its physicochemical properties, namely its positive charge, defined its removal from the water phase and rate of adsorption onto PAC. Since DCF and SMX were anionic compounds in the tested conditions, the hydrophobicity was determinant to define the affinity towards PAC. SMX is a hydrophilic compound, the adsorption rate and affinity for PAC were the lowest among the tested OMPs. When the compounds occur in a mixture, the pattern of adsorption is the same, with better results obtained for TMP, followed by DCF and SMX. Although the kinetics of adsorption did not differ, a higher amount of OMP was adsorbed per unit mass of activated carbon. The initial concentration of the compounds as well as the concentration of activated carbon also defined the extent of the adsorption.

Sorption of tested pharmaceuticals was proved to be an overall fast process in ultra-pure water. Kinetics followed a pseudo second-order, indicating that the sorption rate is governed by the number of available active sites. The boundary layer effect seems to also determine the rate of adsorption, by reducing the adsorption rate as the OMP gradually reach the active sites at the equilibrium.

Water matrix greatly influences the adsorption of OMPs, but its effect varied from compound to compound. DCF and SMX were better adsorbed in humic acid solution, followed by ultra-pure water and MBR permeate. It seems that the presence of organic matter and, in specific, humic acids positively influences the affinity for the adsorbent in these compounds. Instead, TMP was more adsorbed in MBR permeate compared to ultra-pure water and humic acid solution. Mixed liquor gave the low adsorption capacities of PAC, presumably due to its complex nature. The adsorption isotherms also varied among water matrixes. Langmuir and Freundlich isotherm fitted very well the results of adsorption in ultra-pure water and MBR permeate, only Langmuir isotherm explained adsorption in humic acid solution and Freundlich isotherm in the mixed liquor.

DOM and specifically humic acids, proved to be beneficial for the adsorption of the selected OMPs. However, the interaction between the DOM and the OMPs prior to the addition of the adsorbent did not have any effect on the adsorption. The fact remains that the time to reach the equilibrium during adsorption experiments (24 h) was long enough to promote the adsorption in presence of humic acids.

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Chapter 7

GENERAL DISCUSSION AND CONCLUSIONS

In a context where there is an increasing awareness in the scientific community, policymakers and general public about the issue that is the presence of organic micropollutants (OMPs) in water bodies, the present Thesis has intended to contribute to the knowledge about an innovative treatment solution that could reduce their release from the wastewater treatment plant (WWTP) effluents. The innovative treatment, consisting in a hybrid system that combines an advanced biological treatment which is the membrane bioreactor (MBR) with activated carbon has been deeply studied from different approaches.

Given that the MBR technology provides a better-quality effluent compared to conventional activated sludge systems (Radjenovic et al., 2008) and the activated carbon is a well-known adsorbent whose great adsorption capacity has been extensively described in the literature (Çeçen and Aktas, 2011), the combination of these two technologies seem a promising option for promoting diverse removal mechanisms that could enhance the removal of OMPs from wastewater.

To this end, the Thesis first aimed to review the state-of-the-art and advances achieved in the removal of OMPs by this hybrid system, which resulted in a publication (Gutiérrez et al., 2021). In the publication, 66 papers were selected for qualitative analysis, from which 27 of them were used for the quantitative analysis of the OMP removal efficiencies. The selected research studies included laboratory (46%), pilot (42%) and full-scale plants (12%) using either synthetic wastewater (50%) or real wastewater(50%). The activated carbon was added inside the biological tank or in a contact tank after as a post-treatment. The collected data on the removal efficiencies, which were compared and discussed considering the treatment configuration and operational conditions, confirmed that coupling the activated carbon, either in the form of powder (PAC) or granules (GAC), implied an increase in the observed removal efficiencies. However, the discussion of these results remarked the fact that the influencing factors are manifold and there is not a leading parameter that ensures a minimum removal for all OMPs. For instance, whereas the dose of activated carbon seems to play an important role, the frequent addition of fresh PAC into the biological reactor is of great importance to ensure the removal of OMPs which rely solely on adsorption (Alvarino et al., 2017). In this way, although there is not a well-defined dose of PAC to reach a minimum removal for all the OMPs, results indicated that a concentration of 0.1 g/L of PAC inside the biological reactor can ensure an 80% of removal for most of the compounds studied under these conditions (34 of 37 OMPs).

Among the influencing parameters that were discussed in the review, the presence of dissolved organic carbon (DOM) stood out as one with the highest relevance when the activated carbon is added to the biological tank and as a post-treatment. Although it has been identified as a competitor in the adsorption process onto the activated carbon (Zietzschmann et al., 2016), the interactions between the DOM, the adsorbent and the OMPs commonly lead to synergistic effects for the removal of these contaminants (Sbardella et al., 2018). The DOM that is attached to the surface of the activated carbon is able to promote the growth of the microorganisms responsible for

the biodegradation of the OMPs. In the same way, the interactions between the overall negatively charged DOM and ionic OMPs may entail the enhancement in the removal of some compounds with, in particular, a positive charge (Margot et al., 2013). On the other side, the octanol-water distribution coefficient (D_{ow}) was found to have some relevance, although the studies do not draw clear conclusions about the correlation of this parameter with the OMP removal (Kovalova et al., 2013; Mailler et al., 2015; Rattier et al., 2012).

As a result of the review process, the OMP's physicochemical characteristics, the surface properties of the activated carbon, the operational conditions and the water matrix (i.e., DOM) were considered influencing factors for which the extent of their influence was not clearly understood. In consequence, a more rigorous approach to elaborate and interpret the data was needed to identify the main parameters affecting the removal of OMPs. In this case, a meta-analysis was carried out by means of statistical analyses, which resulted in a second publication (Gutiérrez et al., 2022). The statistical analyses, which were mainly based on exploratory methods (cluster analysis, principal component analysis) and regression analysis, were carried out to discuss the results obtained in the scientific literature that was included in the previous review, specifically with regard to PAC added inside the MBR. Although some attempts to correlate the OMP removal efficiencies with potential influencing parameters are found in the literature (Alves et al., 2018; Dickenson and Drewes, 2010; Kovalova et al., 2013; Mailler et al., 2015), these studies do not contemplate the use of data from different investigations. In our meta-analysis, the operational conditions of the studies (namely PAC dosage, PAC retention time and SRT) did not significantly influence the removal of the OMPs under treatment. The PAC dosage adopted (between 0.03 and 1 g/L, apart from one study that added 20 g/L) was not significantly correlated with the removal efficiency, and it provided overall very good results in all the investigations, with removals ranging from 84% to 98%. Among the potential explanations for these results are the PAC age, PAC surface characteristics, its addition point, the wastewater characteristics, and the characteristics of the selected OMPs (Alvarino et al., 2017; Alves et al., 2018; Li et al., 2011; Remy et al., 2012). Concerning the OMPs' physicochemical characteristics (in our study, charge, D_{ow} and molecular weight), the results of the analysis confirmed the importance of the role of the charge in the removal of the OMPs during the wastewater treatment. The removal of the compounds under study showed to be significantly correlated to their charge, with better results obtained for the compounds positively charged in comparison to neutral and anionic compounds. As mentioned above, the overall negatively charged DOM present in the wastewater under treatment covers the PAC surface, thus entailing a consistent decrease in the overall charge of the PAC-DOM complex (Yu et al., 2014). If this is the case, cationic compounds are expected to be adsorbed likewise repulsion is expected for negatively charged compounds (de Ridder et al., 2011). In the absence of positive electrostatic interactions, the compound lipophilicity (i.e., D_{ow}), especially with regard to neutral compounds, becomes important (Mailler et al., 2015).

The use of statistical tools to compare and draw general conclusions from the results found in the scientific literature was an innovative approach not frequently found in the literature. In this regard, the results obtained highlighted the importance of considering the charge and lipophilicity of the OMPs under study to estimate the removal of hybrid MBRs coupled to PAC. However, the results of the current statistical analysis should be strengthened by considering more parameters that could bring new information and knowledge to the topic. The data collected for the meta-analysis referred mainly to laboratory experiments conducted using synthetic experiments. Although the use of synthetic water has allowed overcoming the water matrix-related issues in these types of investigations, the use of pilot or full-scale plants with real wastewater should be of utmost importance to confirm the results obtained (O'Flaherty and Gray, 2013).

Bearing this in mind, the batch adsorption experiments conducted in the Faculty of Chemical Engineering and Technology of the University of Zagreb were focused on the effect of the wastewater matrix in the adsorption of OMPs. To this end, the adsorption of three pharmaceuticals, namely diclofenac, sulfamethoxazole and trimethoprim onto PAC was studied in four water matrixes of increasing complexity: ultra-pure water, humic acid solution, MBR permeate and mixed liquor. In previous research, the application of adsorption models has been of great value to understand the mechanisms of adsorption of certain pollutants onto activated carbon (Behera et al., 2010). However, there are not many studies that have applied these models when the compounds are found in a mixture (as in real wastewater) or have quantified the potential effect of the DOM interacting with the OMP and adsorbent in the wastewater (Guillossou et al., 2020; Hernandez-Ruiz et al., 2012).

The results, published recently, aimed to contribute to the knowledge of the PAC adsorption process that takes place under real conditions in WWTP (Gutiérrez et al., 2023). The application of kinetic and adsorption isotherm models allowed the definition of the adsorption mechanisms and processes that take place when OMP comes in contact with the adsorbent. In addition to that, the water matrix showed to greatly influence the adsorption of OMPs, but its effect varied from compound to compound. First of all, the complexity of the mixed liquor matrix and the presence of suspended solids in the biological tank seem to reduce the adsorption capacity of PAC, as confirmed in the literature (Boehler et al., 2012). The constituents of the DOM, which vary along with the wastewater treatment, seemed to greatly influence the adsorption process. For instance, the results showed that the presence of humic acids can contribute to better adsorption of certain pollutants, such as sulfamethoxazole. The interactions of this contaminant with the DOM constituent can lead to the adsorption of the complex pharmaceutical-humic acid in the adsorbent's surface, improving the overall performance of the PAC (Behera et al., 2010; Jin et al., 2018). In addition to that, the adsorption of dissolved humic acids has been proven to increase the area available for adsorption in carbon nanotubes by reducing their aggregation, which would increase the change of hydrophobic interactions between the adsorbent and the pharmaceutical (Pan et al., 2013).

Finally, the compound physicochemical properties showed once again to be determinant in defining the affinity of the compound to the surface of PAC at both individual solutions and mixtures. In all the water matrices tested, the cationic compound trimethoprim showed the highest rates of adsorption and removal efficiencies. Following the charge, the second parameter that influenced the most was the D_{ow}, which determined the adsorption of anionic compounds diclofenac and sulfamethoxazole.

In a context where the presence of OMPs will be potentially monitored and regulated in the following years, with a target removal of 80% set up for key OMPs and the obligation to apply a quaternary treatment in most WWTPs (European Commission, 2022). It is of utmost importance to test the innovative treatments in full-scale WWTPs. In addition to that, the upcoming new UWWTD remarks on the importance of monitoring inputs of wastewater from non-domestic origin in urban WWTPs, since they may entail a higher risk of contamination of micropollutants in the water bodies. In this context, research studies have remarked on the importance of considering hospital wastewater a hotspot for OMPs, in particular, pharmaceuticals (Verlicchi et al., 2015).

In this Thesis, the main goal was to test the addition of PAC in an MBR treating mainly hospital wastewater for the removal of OMPs, in order to reduce the potential risk of their release into the environment. In particular, the addition in the biological reactor of two concentrations of PAC was tested (0.1 g/L and 0.2 g/L). The results obtained indicate that the addition of PAC reduced the overall load of OMPs in the final WWTP effluent, and it was particularly convenient for the removal of antibiotics and psychiatric drugs. In the same way, the MBR alone showed to be efficient in the removal of the compounds pertaining to the therapeutic class of analgesics/anti-inflammatories. The increase of the PAC dose from 0.1 g/L to 0.2 g/L showed that it can reduce the impact in the receiving water bodies of the compounds that were identified as of highest risk (i.e., diclofenac, carbamazepine, venlafaxine).

The results of this investigation remark on the effectiveness of activated carbon to deal with a vast group of OMPs at the same time. The characterization of the hospital effluent confirmed that it can be a point source of pharmaceuticals arriving at the WWTP. In particular, the iodinated contrast media iopromide showed to be uniquely correlated to the hospital wastewater, since it is used for X-ray medical exams. The dedicated advanced treatment of hospital effluent may be an effective solution for reducing the impact of non-domestic sources of OMPs in urban wastewater. Finally, the addition of PAC in the biological tank of an MBR could be considered a manageable upgrade for WWTP that will deal with the removal of certain OMPs, especially when the addition of a new contact tank for the application of PAC as a post-treatment is not feasible.

For the abovementioned reasons, the present Thesis has the following conclusions:

- A hybrid system consisting of an MBR coupled to activated carbon is an effective treatment for the removal of a vast set of OMPs from wastewater. However, the removal efficiencies are greatly dependent on the organic micropollutant's nature, the activated carbon surface characteristics, the presence of dissolved organic matter in the wastewater and the interactions between these influencing factors.
- Results collected about recent literature data of hybrid MBR systems where activated carbon is added in the form of PAC to the biological reactor show that a concentration of 0.1 g/L of PAC is able to achieve an 80% of removal for most of the OMPs tested. However, there is not a well-defined PAC dose to achieve a minimum removal for all the OMPs. In the same way, literature data show that when PAC is used as an end-of-pipe treatment, there is greater variability in the OMP removal efficiencies obtained by these systems.
- In comparison with PAC, granular activated carbon (GAC) columns used as a post-treatment showed to be greatly dependent on MBR performance and effluent load. When GAC filters exhibit biological activity (i.e., biological activated carbon, BAC), only OMPs with a certain degree of biodegradability are able to achieve a fairly constant removal efficiency for long operation times. For OMPs dependent on adsorption, the operation is constricted to good management of periodical washes and column bioregeneration is essential.
- PAC is able to influence the MBR operation due to the absorbance of dissolved organic matter and the integration of sludge flocs onto a PAC-sludge complex. The presence of PAC in the sludge increases the strength of the sludge floc and improves its settling characteristics, it reduces the formation of the cake layer in the membrane and mitigates the membrane fouling.
- Results from a meta-analysis performed on a collection of published papers regarding MBR coupled to PAC suggest that the variation of the operational conditions (i.e., SRT, PAC dosage) does not always entail a better removal efficiency of a broad spectrum of OMPs. On the contrary, the physicochemical characteristics of each compound seem to play the most important role in such a complex mechanism.
- Among the physicochemical properties, the charge was demonstrated to be significantly correlated to the removal of OMPs in MBR coupled to PAC. Positively charged substances and negatively charged surfaces of PAC covered the dissolved organic matter led to higher removal efficiencies.
- Adsorption batch tests on target OMPs and the use of mathematical models (adsorption isotherms and kinetics) allow the quantification of the adsorption capacity of PAC under selected conditions and the description of the mechanisms of adsorption for such compounds.
- Sorption of tested pharmaceuticals was proved to be an overall fast process in ultra-pure water. Kinetics followed a pseudo second-order, indicating that the

sorption rate is governed by the number of available active sites. The boundary layer effect seems to also determine the rate of adsorption, by reducing the adsorption rate as the OMP gradually reaches the active sites at the equilibrium.

- In ultra-pure water conditions, TMP was the compound with the highest affinity for PAC. Its physicochemical properties, namely its positive charge, defined its removal from the water phase and rate of adsorption onto PAC. Since DCF and SMX were anionic compounds in the tested conditions, the hydrophobicity was determinant to define the affinity towards PAC.
- Adsorption batch tests on DCF, SMX and TMP showed that the adsorption batch process onto PAC is greatly dependent on the nature of the dissolved organic matter (DOM). Humic acids, in particular, proved to be beneficial for the adsorption of DCF and SMX.
- Results on a full-scale MBR with PAC added at 0.1 and 0.2 g/L show that the removal efficiencies for most of the compounds improved with the addition of activated carbon. The increase was especially relevant for pharmaceuticals pertaining to antibiotics and psychiatric drugs. Considering the results from a broad perspective, the addition of PAC inside the reactor further reduces the total load of OMPs discharged to the receiving water body, reducing therefore the potential harm caused to the living organisms. Moreover, the addition of PAC slightly improved the MBR performance, by reducing the concentration of some conventional pollutants (nitrogen, BOD_5).

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Appendix 1

Supporting Information of Chapter 5

Table S1. List of the selected OMPs according to their Anatomical Therapeutic Chemical (ATC) classification.

Compound	ATC	Anatomical main group	Therapeutic subgroup
Analgesics/anti-inflammatories			
Acetaminophen	N02BE01	Nervous system	Analgesics
Acetylsalicylic acid	N02BA01	Nervous system	Analgesics
Alfentanil	N01AH02	Nervous system	Anesthetics
Aminopyrine	N02BB03	Nervous system	Analgesics
Betamethasone 17,21-dipropionate	A07EA04	Alimentary tract and metabolism	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents
Buprenorphine	N02AE01	Nervous system	Analgesics
Carisoprodol	M03BA02	Musculo-skeletal system	Muscle relaxants
Codeine	R05DA04	Respiratory system	Cough and cold preparations
Dextromethorphan	R05DA09	Respiratory system	Cough and cold preparations
Dextropropoxyphene	N02AC04	Nervous system	Analgesics
Diclofenac	M01AB05	Musculo-skeletal system	Anti-inflammatory and antirheumatic products
Etodolac	M01AB08	Musculo-skeletal system	Anti-inflammatory and antirheumatic products
Fentanyl	N01AH01	Nervous system	Anesthetics
Hydrocodone	R05DA03	Respiratory system	Cough and cold preparations
Hydromorphone	N02AA03	Nervous system	Analgesics
Ibuprofen	M01AE01	Musculo-skeletal system	Anti-inflammatory and antirheumatic products
Ketoprofen	M01AE03	Musculo-skeletal system	Anti-inflammatory and antirheumatic products
Lidocaine	N01BB02	Nervous system	Anesthetics
Meloxicam	M01AC06	Musculo-skeletal system	Anti-inflammatory and antirheumatic products
Morphine	N02AA01	Nervous system	Analgesics
Naproxen	M01AE02	Musculo-skeletal system	Anti-inflammatory and antirheumatic products
Oxycodone	N02AA05	Nervous system	Analgesics
Oxymorphone	N02AA11	Nervous system	Analgesics
Pentazocine	N02AD01	Nervous system	Analgesics
Pethidine	N02AB02	Nervous system	Analgesics
Phenylbutazone	M01AA01	Musculo-skeletal system	Anti-inflammatory and antirheumatic products
Procaine	N01BA02	Nervous system	Anesthetics
Tolfenamic acid	M01AG02	Musculo-skeletal system	Anti-inflammatory and antirheumatic products
Tramadol	N02AX02	Nervous system	Analgesics
Antiarrhythmic agents			
Amiodarone	C01BD01	Cardiovascular system	Cardiac therapy
Digitoxin	C01AA04	Cardiovascular system	Cardiac therapy
Propafenone	C01BC03	Cardiovascular system	Cardiac therapy
Strophanthidin	--	Cardiovascular system	Cardiac therapy
Strophanthin	--	Cardiovascular system	Cardiac therapy
Antibiotics			
Amoxicillin	J01CA04	Antiinfectives for systemic use	Antibacterials for systemic use
Azithromycin	J01FA10	Antiinfectives for systemic use	Antibacterials for systemic use
Cinoxacin	J01MB06	Antiinfectives for systemic use	Antibacterials for systemic use
Ciprofloxacin	J01MA02	Antiinfectives for systemic use	Antibacterials for systemic use
Clarithromycin	J01FA09	Antiinfectives for systemic use	Antibacterials for systemic use
Doxycycline	J01AA02	Antiinfectives for systemic use	Antibacterials for systemic use
Enoxacin	J01MA04	Antiinfectives for systemic use	Antibacterials for systemic use
Erythromycin	J01FA01	Antiinfectives for systemic use	Antibacterials for systemic use
Flumequine	J01MB07	Antiinfectives for systemic use	Antibacterials for systemic use
Furazolidon	G01AX06	Genito-urinary system and sex hormones	Gynecological antiinfectives and antiseptics
Lomefloxacin	J01MA07	Antiinfectives for systemic use	Antibacterials for systemic use
Metronidazole	J01XD01	Antiinfectives for systemic use	Antibacterials for systemic use
Minocycline	J01AA08	Antiinfectives for systemic use	Antibacterials for systemic use
Nalidixic Acid	J01MB02	Antiinfectives for systemic use	Antibacterials for systemic use
Norfloxacin	J01MA06	Antiinfectives for systemic use	Antibacterials for systemic use
Ofloxacin	J01MA01	Antiinfectives for systemic use	Antibacterials for systemic use
Oleandomycin	J01FA05	Antiinfectives for systemic use	Antibacterials for systemic use

Table S1. *(continued)*

Compound	ATC	Anatomical main group	Therapeutic subgroup
Oxolinic Acid	J01MB05	Antiinfectives for systemic use	Antibacterials for systemic use
Oxytetracycline	D06AA03	Dermatologicals	Antibiotics and chemotherapeutics for dermatological use
Penicillin G	J01CE01	Antiinfectives for systemic use	Antibacterials for systemic use
Pipemidic acid	J01MB04	Antiinfectives for systemic use	Antibacterials for systemic use
Roxithromycin	J01FA06	Antiinfectives for systemic use	Antibacterials for systemic use
Silvadene	D06BA01	Dermatologicals	Antibiotics and chemotherapeutics for dermatological use
Spiramycin	J01FA02	Antiinfectives for systemic use	Antibacterials for systemic use
Sulfabenzamide	--	Antiinfectives for systemic use	Antibacterials for systemic use
Sulfadimethoxine	J01ED02	Antiinfectives for systemic use	Antibacterials for systemic use
Sulfadimidine	J01EB03	Antiinfectives for systemic use	Antibacterials for systemic use
Sulfafurazole	J01EB05	Antiinfectives for systemic use	Antibacterials for systemic use
Sulfaguanidine	A07AB03	Alimentary tract and metabolism	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents
Sulfamerazine	D06BA06	Dermatologicals	Antibiotics and chemotherapeutics for dermatological use
Sulfamethizole	D06BA04	Dermatologicals	Antibiotics and chemotherapeutics for dermatological use
Sulfamethoxazole	J01EC01	Antiinfectives for systemic use	Antibacterials for systemic use
Sulfamethoxydiazine	J01ED04	Antiinfectives for systemic use	Antibacterials for systemic use
Sulfamethoxypyridazine	J01ED05	Antiinfectives for systemic use	Antibacterials for systemic use
Sulfanilamide	J01EB06	Antiinfectives for systemic use	Antibacterials for systemic use
Sulfaphenazole	J01ED08	Antiinfectives for systemic use	Antibacterials for systemic use
Sulfapyridine	J01EB04	Antiinfectives for systemic use	Antibacterials for systemic use
Sulfathiazole	D06BA02	Dermatologicals	Antibiotics and chemotherapeutics for dermatological use
Tinidazole	J01XD02	Antiinfectives for systemic use	Antibacterials for systemic use
Trimethoprim	J01EA01	Antiinfectives for systemic use	Antibacterials for systemic use
Antifungals			
Sulfacetamide	D10AF06	Dermatologicals	Anti-acne preparations
Antifungals			
Terbinafine	D01AE15	Dermatologicals	Antifungals for dermatological use
Tiabendazole	D01AC06	Dermatologicals	Antifungals for dermatological use
Antihistamines			
Diphenhydramine	D04AA32	Dermatologicals	Antipruritics, including antihistamines, anesthetics, etc.
Promethazine	D04AA10	Dermatologicals	Antipruritics, including antihistamines, anesthetics, etc.
Antihypertensives			
Clonidine	C02AC01	Cardiovascular system	Antihypertensives
Antiparasitics			
Albendazole	P02CA03	Antiparasitic products, insecticides and repellents	Anthelmintics
Flubendazole	P02CA05	Antiparasitic products, insecticides and repellents	Anthelmintics
Levamisole	P02CE01	Antiparasitic products, insecticides and repellents	Anthelmintics
Mebendazole	P02CA01	Antiparasitic products, insecticides and repellents	Anthelmintics
Praziquantel	P02BA01	Antiparasitic products, insecticides and repellents	Anthelmintics
Triclabendazole	P02BX04	Antiparasitic products, insecticides and repellents	Anthelmintics
Antiseptics			
Nitrofural	D08AF02	Dermatologicals	Antiseptics and disinfectants
Beta-blockers			
Atenolol	C07AB03	Cardiovascular system	Beta blocking agents
Bisoprolol	C07AB07	Cardiovascular system	Beta blocking agents

Table S1. *(continued)*

Compound	ATC	Anatomical main group	Therapeutic subgroup
Metoprolol	C07AB02	Cardiovascular system	Beta blocking agents, selective
Calcium channel blockers			
Verapamil	C08DA01	Cardiovascular system	Calcium channel blockers
Diuretics			
Torasemide	C03CA04	Cardiovascular system	Diuretics
Drug metabolites			
10-Hydroxycarbazepine	--	--	--
2-NP-AOZ	--	--	--
4-Acetylaminoantipyrine	--	--	--
4-FormylAminoAntipyrine	--	--	--
6-Acetylmorphine	--	--	--
7-Aminoclonazepam	--	--	--
7-Aminoflunitrazepam	--	--	--
Acetylcodeine	--	--	--
Benzoylecgonine	--	--	--
Buprenorphine glucuronide	--	--	--
Cocaethylene	--	--	--
Cotinine	--	--	--
Desalkylflurazepam	--	--	--
Ecgonine methyl ester	--	--	--
EDDP	--	--	--
Morphine-6-β-D-glucuronide	--	--	--
N-Desmethylclozapine	--	--	--
Norbuprenorphine	--	--	--
Norfentanyl	--	--	--
Norpethidine	--	--	--
Norpropoxyphene	--	--	--
O-Desmethyltramadol	--	--	--
Ritalinic acid	--	--	--
α-Hydroxyalprazolam	--	--	--
α-Hydroxymidazolam	--	--	--
α-Hydroxytriazolam	--	--	--
Hormones			
Fludrocortisone-Acetate	--	--	--
Flumethasone	D07AB03	Dermatologicals	Corticosteroids, dermatological preparations
Hydrocortisone	--	--	--
Methylprednisolone	D07AA01	Dermatologicals	Corticosteroids, dermatological preparations
Mometasone furoate	D07AC13	Dermatologicals	Corticosteroids, dermatological preparations
Prednicarbate	D07AC18	Dermatologicals	Corticosteroids, dermatological preparations
Prednisolone	A07EA01; C05AA04; D07AA03	Alimentary tract and metabolism; Cardiovascular system; Dermatologicals	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents; Vasoprotectives; Corticosteroids, dermatological preparations
Triamcinolone	D07AB09	Dermatologicals	Corticosteroids, dermatological preparations
Triamcinolone Acetonide	D07AB09	Dermatologicals	Corticosteroids, dermatological preparations
Illicit drugs			
Cocaine	N01BC01	Nervous system	Anesthetics
Ketamine	N01AX03	Nervous system	Anesthetics
MDA	--	--	--
MDEA	--	--	--
MDMA	--	--	--
Phencyclidine	--	--	--
Plastic additives			
Benzotriazole	--	--	--

Table S1. *(continued)*

Compound	ATC	Anatomical main group	Therapeutic subgroup
p-Toluenesulfonamide	--	--	--
Psychiatric drugs			
Alprazolam	N05BA12	Nervous system	Psychoanaleptics
Amisulpride	N05AL05	Nervous system	Psycholeptics
Amitriptyline	N06AA09	Nervous system	Psychoanaleptics
Amoxapine	N06AA17	Nervous system	Psychoanaleptics
Bromazepam	N05BA08	Nervous system	Psycholeptics
Carbamazepine	N03AF01	Nervous system	Antiepileptics
Chlordiazepoxide	N05BA02	Nervous system	Psycholeptics
Chlorprothixene	N05AF03	Nervous system	Psycholeptics
Citalopram	N06AB04	Nervous system	Psychoanaleptics
Clobazam	N05BA09	Nervous system	Psycholeptics
Clomipramine	N06AA04	Nervous system	Psychoanaleptics
Clonazepam	N03AE01	Nervous system	Antiepileptics
Clorazepate	N05BA05	Nervous system	Psycholeptics
Clozapine	N05AH02	Nervous system	Psycholeptics
Desipramine	N06AA01	Nervous system	Psychoanaleptics
Desvenlafaxine	N06AX23	Nervous system	Psychoanaleptics
Dexametasone	N06AA01	Nervous system	Psychoanaleptics
Diazepam	N05BA01	Nervous system	Psycholeptics
Dothiepin	N06AA16	Nervous system	Psychoanaleptics
Doxepin	D04AX01; N06AA12	Dermatologicals; Nervous system	Antipruritics, including antihistamines, anesthetics, etc.; Psychoanaleptics
Felbamate	N03AX10	Nervous system	Antiepileptics
Fluoxetine	N06AB03	Nervous system	Psychoanaleptics
Flupentixol	N05AF01	Nervous system	Psycholeptics
Flurazepam	N05CD01	Nervous system	Psycholeptics
Fluvoxamine	N06AB08	Nervous system	Psychoanaleptics
Gabapentin	N03AX12	Nervous system	Antiepileptics
Haloperidol	N05AD01	Nervous system	Psycholeptics
Imipramine	N06AA02	Nervous system	Psychoanaleptics
Lamotrigine	N03AX09	Nervous system	Antiepileptics
Lorazepam	N05BA06	Nervous system	Psycholeptics
Maprotiline	N06AA21	Nervous system	Psychoanaleptics
Medazepam	N05BA03	Nervous system	Psycholeptics
Memantine	N06DX01	Nervous system	Psychoanaleptics
Mianserin	N06AX03	Nervous system	Psychoanaleptics
Mirtazapine	N06AX11	Nervous system	Psychoanaleptics
Naltrexone	N07BB04	Nervous system	Other nervous system drugs
Nitrazepam	N05CD02	Nervous system	Psycholeptics
Nordiazepam	N05BA16	Nervous system	Psycholeptics
Nortriptyline	N06AA10	Nervous system	Psychoanaleptics
Olanzapine	N05AH03	Nervous system	Psycholeptics
Opipramol	N06AA05	Nervous system	Psychoanaleptics
Oxazepam	N05BA04	Nervous system	Psycholeptics
Oxcarbazepine	N03AF02	Nervous system	Antiepileptics
Paliperidone	N05AX13	Nervous system	Psycholeptics
Paroxetine	N06AB05	Nervous system	Psychoanaleptics
Phenazepam	N05BX	Nervous system	Psycholeptics
Phenytoin	N03AB02	Nervous system	Antiepileptics
Pipamperone	N05AD05	Nervous system	Psycholeptics
Prazepam	N05BA11	Nervous system	Psycholeptics
Promazine	N05AA03	Nervous system	Psycholeptics
Protriptyline	N06AA11	Nervous system	Psychoanaleptics
Quetiapine	N05AH04	Nervous system	Psycholeptics
Risperidone	N05AX08	Nervous system	Psycholeptics
Secobarbital	N05CA06	Nervous system	Psycholeptics
Sertraline	N06AB06	Nervous system	Psychoanaleptics
Temazepam	N05CD07	Nervous system	Psycholeptics

Table S1. *(continued)*

Compound	ATC	Anatomical main group	Therapeutic subgroup
Topiramate	N03AX11	Nervous system	Antiepileptics
Trazodone	N06AX05	Nervous system	Psychoanaleptics
Triazolam	N05CD05	Nervous system	Psycholeptics
Trimipramine	N06AA10	Nervous system	Psychoanaleptics
Venlafaxine	N06AX16	Nervous system	Psychoanaleptics
Zolpidem	N05CF02	Nervous system	Psycholeptics
Zopiclone	N05CF01	Nervous system	Psycholeptics
Receptor antagonists			
Atropine	A03BA01; S01FA01	Alimentary tract and metabolism; Sensory organs	Drugs for functional gastrointestinal disorders; Ophthalmologicals
Flumazenil	V03AB25	Various	All other therapeutic products
Stimulants			
Amphetamine	N06BA01	Nervous system	Psychoanaleptics
Caffeine	N06BC01	Nervous system	Psychoanaleptics
Cannabinol	--	--	--
Methadone	N07BC02	Nervous system	Other nervous system drugs
Methamphetamine	N06BA03	Nervous system	Psychoanaleptics
Methylphenidate	N06BA04	Nervous system	Psychoanaleptics
Phentermine	A08AA01	Alimentary tract and metabolism	Antiobesity preparations, excluding diet products
THC	A04AD10	Alimentary tract and metabolism	Antiemetics and antinauseants
UV filters			
Octyl methoxycinnamate	D02BA02	Dermatologicals	Emollients and protectives
Veterinary drugs			
Carprofen	QM01AE91	Musculo-skeletal system	Anti-inflammatory and antirheumatic products
Diaveridine	QP51AX18	Antiparasitic products, insecticides and repellents	Antiprotozoals
Difloxacin	QJ01MA94	Antiinfectives for systemic use	Antibacterials for systemic use
Dimetridazole	QP51AA07	Antiparasitic products, insecticides and repellents	Antiprotozoals
Enrofloxacin	QJ01MA90	Antiinfectives for systemic use	Antibacterials for systemic use
Flunixin	QM01AG90	Musculo-skeletal system	Anti-inflammatory and antirheumatic products
Furaltadone	QJ01XX93	Antiinfectives for systemic use	Antibacterials for systemic use
Ipronidazole	QP51AA10	Antiparasitic products, insecticides and repellents	Antiprotozoals
Marbofloxacin	QJ01MA93	Antiinfectives for systemic use	Antibacterials for systemic use
Monensin	QA16QA06	Alimentary tract and metabolism	Other alimentary tract and metabolism products
Orbifloxacin	QJ01MA95	Antiinfectives for systemic use	Antibacterials for systemic use
Oxibendazole	QP52AC07	Antiparasitic products, insecticides and repellents	Anthelmintics
Ronidazole	QP51AA08	Antiparasitic products, insecticides and repellents	Antiprotozoals
Salinomycin	QP51AH01	Antiparasitic products, insecticides and repellents	Antiprotozoals
Sarafloxacin	QJ01MA98	Antiinfectives for systemic use	Antibacterials for systemic use
Sulfachlorpyridazine	--	--	--
Sulfaclozine	QP51AG04	Antiparasitic products, insecticides and repellents	Antiprotozoals
Sulfadoxine	QJ01EQ13	Antiinfectives for systemic use	Antibacterials for systemic use
Sulfamonomethoxine	QJ01EQ18	Antiinfectives for systemic use	Antibacterials for systemic use
Sulfanitran	--	--	--
Sulfaquinoxaline	QP51AG03	Antiparasitic products, insecticides and repellents	Antiprotozoals
Tilmicosin	QJ01FA91	Antiinfectives for systemic use	Antibacterials for systemic use
X-Ray contrast media			
Iopromide	V08AB05	Various	Contrast media

Table S2. List of compounds analysed for the non-target analysis in UHPLC-QTOF-MS.

Name	CAS#	Formula
1-Methylimidazole	616-47-7	C4H6N2
1-Naphthylamine	134-32-7	C10 H9 N
1,2-Benzisothiazolinone	2634-33-5	C7H5NOS
2,2'-Oxamido bis-[ethyl-3-(3,5-di-t-butyl-4-hydroxyphenyl) propionate	70331-94-1	C40 H60 N2 O8
2,6-Xylidine (Lidocaine-M) (Dimethylaniline)	87-62-7	C8 H11 N
2-Hydroxyquinoline	59-31-4	C9 H7 N O
3-Hydroxycotinine	34834-67-8	C10 H12 N2 O2
5-Methyl-1H-benzotriazole	136-85-6	C7H7N3
10,11-Dihydro-10-hydroxycarbamazepine	29331-92-8	C15 H14 N2 O2
N4-Acetylsulfamethoxazole	21312-10-7	C12H13N3O4S
Acridine (Carbamazepine-M)	260-94-6	C13 H9 N
AHDI / Phantolide	15323-35-0	C17H24O
Allopurinol	315-30-0	C5 H4 N4 O
Atorvastatin	134523-00-5	C33 H35 F N2 O5
Azelastine	58581-89-8	C22 H24 Cl N3 O
Azithromycin 3'-N-oxide	90503-06-3	C38H72N2O13
Azithromycin N'-(Desmethyl)	172617-84-4	C37H70N2O12
Benzocaine	94-09-7	C9 H11 N O2
Bezafibrate	41859-67-0	C19H20ClNO4
Boldione	897-06-3	C19H24O2
Candesartan	139481-59-7	C24 H20 N6 O3
Carbamazepine 10,11-epoxide	36507-30-9	C15 H12 N2 O2
Cefalexin	15686-71-2	C16H17N3O4S
Cefoxitin	35607-66-0	C16H17N3O7S2
Celestolide	13171-00-1	C17H24O
Chlorhexidine	55-56-1	C22 H30 Cl2 N10
Clarithromycin-N-oxide	118074-07-0	C38 H69 N O14
Clopidogrel	113665-84-2	C16 H16 Cl N O2 S
Dabigatran	211914-51-1	C25 H25 N7 O3
DEET / Diethyltoluamide	134-62-3	C12 H17 N O
Desacetylmetipranolol	57193-14-3	C15H25NO3
Despropionylbezitramide	83898-28-6	C28 H28 N4 O
Diatrizoate (Amidotrizoic acid)	117-96-4	C11 H9 I3 N2 O4
Dimethylaminophenazone	58-15-1	C13 H17 N3 O
Dioxybenzone (Benzophenone-8)	131-53-3	C14 H12 O4
Erythromycin A enol ether	33396-29-1	C37H65NO12
Fenoprofen	31879-05-7	C15 H14 O3
Fexofenadine	83799-24-0	C32 H39 N O4
Flecainide	54143-55-4	C17 H20 F6 N2 O3
Flutamide	13311-84-7	C11H11F3N2O3
Gatifloxacin	112811-59-3	C19 H22 F N3 O4
Hydroxychloroquine	118-42-3	C18 H26 Cl N3 O
Indole	120-72-9	C8 H7 N
Iohexol	66108-95-0	C19 H26 I3 N3 O9
Iopamidol	60166-93-0	C17 H22 I3 N3 O8
Irbesartan	138402-11-6	C25 H28 N6 O
Lansoprazole	103577-45-3	C16H14F3N3O2S
Levetiracetam	102767-28-2	C8H14N2O2
Losartan	114798-26-4	C22 H23 Cl N6 O
Metaxalone	1665-48-1	C12 H15 N O3
Methylsalicylate	119-36-8	C8 H8 O3
Metoclopramide	364-62-5	C14 H22 Cl N3 O2
Metoprolol acid	56392-14-4	C14 H21 N O4
MIT / Methylisothiazolinone	2682-20-4	C4 H5 N O S
Moxifloxacin	354812-41-2	C21H24FN3O4
NDEA / Nitrosodiethylamine	55-18-5	C4 H10 N2 O
Nicopholine	492-85-3	C10 H12 N2 O2
Nicotine	54-11-5	C10 H14 N2
Niflumic acid	4394-00-7	C13H9F3N2O2
Nitrendipin	39562-70-4	C18 H20 N2 O6
Norcitalopram (Desmethylcitalopram)	62498-67-3	C19 H19 F N2 O
Norcocaine	129944-99-6	C16H19NO5
Olmesartan	144689-63-4	C24 H26 N6 O3
Omeprazole	73590-58-6	C17 H19 N3 O3 S

Table S2. *(continued)*

Name	CAS#	Formula
Paramethasone acetate	1597-82-6	C24 H31 F O6
Paraxanthine	611-59-6	C7H8N4O2
Parsalmide	30653-83-9	C14 H18 N2 O2
Pazufloxacin	127045-41-4	C16 H15 F N2 O
Picaridin (Bayrepel) (Icaridin)	119515-38-7	C12 H23 N O3
Pregabalin	148553-50-8	C8 H17 N O2
Propacetamol	66532-85-2	C14 H20 N2 O3
Propyperone	3781-28-0	C23 H33 F N2 O2
Rifaximin	80621-81-4	C43 H51 N3 O11
Sitagliptin	486460-32-6	C16 H15 F6 N5 O
Sotalol	3930-20-9	C12 H20 N2 O3 S
Sulpiride	15676-16-1	C15 H23 N3 O4 S
Tapentadol	175591-23-8	C14 H23 N O
Telmisartan	144701-48-4	C33 H30 N4 O2
Terbutaline	23031-25-6	C12 H19 N O3
Theobromine	83-67-0	C7 H8 N4 O2
Theophylline	58-55-9	C7 H8 N4 O2
Tramadol-N-oxide	147441-56-3	C16H25NO3
Triethyl citrate	77-93-0	C12 H20 O7
Troxipide	30751-05-4	C15 H22 N2 O4
Valsartan	137862-53-4	C24 H29 N5 O3
4-Chloroaniline	106-47-8	C6H6ClN
Cyclophosphamide	50-18-0	C7H15Cl2N2O2P
Cytarabine	147-94-4	C9H13N3O5
Lapatinib	231277-92-2	C29H26ClFN4O4S
Metformin	657-24-9	C4H11N5

Table S3. Calendar of the *0.1PAC* experimental campaign, that is, MBR coupled to PAC (0.1 g/L) added inside the bioreactor. Pink colour indicates OMPs sampling (with the sampling point indicated between brackets), blue colour indicates wastewater sampling in the HWW, INF, and EFF sampling points and brown colour indicates sampling in the mixed liquor. Conventional parameters refer to COD, BOD5, DOC, UV254, NO3-, NO2-, NH4+, Ntot, Ptot.

2021	September					
MONDAY	**TUESDAY**	**WEDNESDAY**	**THRUSDAY**	**FRIDAY**	**SATURDAY**	**SUNDAY**
30	31	01	02	03	04	05
06	07	08	09	10	11	12
	PAC addition (conc. 0.1 g/L)		OMPs sampling (HWW, INF, EFF)	OMPs sampling (MBR perm)		
	Sampling of conventional parameters *Surfactants, D. magna, E. coli*		Sampling of conventional parameters *Surfactants, D. magna, E. coli*			
			Sampling of SST, SVI			
13	14	15	16	17	18	19
	PAC addition (conc. 0.1 g/L)	OMPs sampling (MBR perm)	Sampling of SST, SVI			
	OMPs sampling (HWW, INF, EFF)					
	Sampling of conventional parameters					
	Sampling of DOC, UV_{254},SST, SVI					
20	21	22	23	24	25	26
PAC addition (conc. 0.1 g/L)	OMPs sampling (HWW, INF, EFF)	OMPs sampling (MBR perm)		PAC addition (conc. 0.1 g/L)		
Sampling of DOC, UV_{254}	Sampling of conventional parameters	Sampling of SST, SVI		Sampling of DOC, UV_{254}		
27	28	29	30	01	02	03
Sampling of SST, SVI	OMPs sampling (HWW, INF, EFF)	OMPs sampling (MBR perm)	PAC addition (conc. 0.1 g/L)			
	Sampling of conventional parameters		Sampling of DOC, UV_{254}			
	Sampling of DOC, UV_{254}					

Table S3. *(continued)*

2021	October					
MONDAY	**TUESDAY**	**WEDNESDAY**	**THRUSDAY**	**FRIDAY**	**SATURDAY**	**SUNDAY**
27	28	29	30	01	02	03
04	05	06	07	08	09	10
	OMPs sampling (HWW, INF, EFF) Sampling of conventional parameters *Surfactants, D. magna, E. coli* Sampling of DOC, UV_{254}	PAC addition (conc. 0.1 g/L) OMPs sampling (MBR perm) Sampling of DOC, UV_{254}		Sampling of SST, SVI		
11	12	13	14	15	16	17
	PAC addition (concentration 0.1 g/L) OMPs sampling (HWW, INF, EFF) Sampling of conventional parameters Sampling of DOC, UV_{254}	OMPs sampling (MBR perm)	Sampling of SST, SVI			
17	18	19	20	21	22	23
Sampling of DOC, UV_{254}	PAC addition (conc. 0.1 g/L) OMPs sampling (HWW, INF, EFF) Sampling of conventional parameters Sampling of DOC, UV_{254}	OMPs sampling (MBR perm) Sampling of SST, SVI		PAC addition (conc. 0.1 g/L) Sampling of DOC, UV_{254}		
25	26	27	28	29	30	31
Sampling of SST, SVI	OMPs sampling (HWW, INF, EFF) Sampling of conventional parameters Sampling of DOC, UV_{254}	OMPs sampling (MBR perm)	PAC addition (conc. 0.1 g/L) Sampling of DOC, UV_{254}			

Table S3. *(continued)*

2021	November					
MONDAY	**TUESDAY**	**WEDNESDAY**	**THRUSDAY**	**FRIDAY**	**SATURDAY**	**SUNDAY**
01	02	03	04	05	06	07
		OMPs sampling (HWW, INF, EFF)	PAC addition (conc. 0.1 g/L)	Sampling of SST, SVI		
		Sampling of conventional parameters *Surfactants, D. magna, E. coli*	OMPs sampling (MBR perm)			
		Sampling of DOC, UV_{254}	Sampling of DOC, UV_{254}			
08	09	10	11	12	13	14
	PAC addition (conc. 0.1 g/L)	OMPs sampling (MBR perm)	Sampling of SST, SVI			
	OMPs sampling (HWW, INF, EFF)					
	Sampling of conventional parameters					
	Sampling of DOC, UV_{254}					

Table S4. Compound method in HPLC-QTOF-MS.

Name	CAS#	Formula	Transition	Transition 1	Transition 2	LOD	LOQ	CF R2	RT	Mass Accuracy
2-NP-AOZ	19687-73-1	C10H9N3O4	236.0666	134.0243	236.0688	0.00199	0.00664	0.9970	8.81	5.55
4-Acetylaminoantipyrine	83-15-8	C13H15N3O2	246.1237	205.1155	204.1124	0.00192	0.00641	0.9998	6.56	6.44
4-FormylAminoAntipyrine	1672-58-8	C12H13N3O2	232.1081	214.0975	215.0994	0.00117	0.00390	0.9969	6.39	0.08
6-Acetylmorphine	2784-73-8	C19H21NO4	328.1543	165.0699	181.0648	0.00133	0.00443	0.9997	6.04	2.84
7-Aminoclonazepam	4959-17-5	C15H12ClN3O	284.1194	135.0917	226.0901	0.00081	0.00270	0.9994	9.18	7.82
7-Aminoflunitrazepam	34084-50-9	C16H14FN3O	284.1194	240.0932	256.1240	0.00081	0.00270	0.9996	9.18	7.82
10-Hydroxycarbazepine	29331-92-8	C15H14N2O2	255.1128	194.0964	179.0730	0.00134	0.00448	0.9977	10.31	1.00
Acetaminophen	103-90-2	C8H9NO2	152.0706	65.0386	109.0522	0.00509	0.01698	0.9997	4.54	-0.32
Acetylcodeine	6703-27-1	C20 H23 N O4	342.1700	225.0910	282.1489	0.00190	0.00634	0.9994	8.23	3.17
Albendazole	54965-21-8	C12 H15 N3 O2 S	266.0958	234.0696	191.0148	0.00142	0.00473	0.9977	13.86	1.79
Alfentanil	71195-58-9	C21 H32 N6 O3	417.2609	268.1768	197.1285	0.00080	0.00268	0.9990	11.33	2.49
alpha-Hydroxyalprazolam	37115-43-8	C17H13ClN4O	325.0851	216.0808	243.0917	0.00261	0.00871	0.9978	12.74	-0.31
alpha-Hydroxymidazolam	59468-90-5	C18H13ClFN3O	342.0804	168.0682	203.0366	0.00070	0.00234	0.9998	12.77	1.33
alpha-Hydroxytriazolam	37115-45-0	C17H12Cl2N4O	359.0461	331.0274	250.0418	0.00180	0.00600	0.9992	12.46	0.79
Alprazolam	28981-97-7	C17 H13 Cl N4	309.0902	281.0714	205.0761	0.00156	0.00521	0.9994	13.23	3.84
Aminopyrine	58-15-1	C13 H17 N3 O	232.1444	56.0495	98.0839	0.00381	0.01271	0.9990	6.21	-0.78
Amiodarone	1951-25-3	C25 H29 I2 N O3	646.0310	100.1121	86.0964	0.00272	0.00905	0.9988	17.08	2.57
Amisulpride	71675-85-9	C17 H27 N3 O4 S	370.1795	242.0482	112.1121	0.00149	0.00497	0.9994	6.62	3.16
Amitriptyline	50-48-6	C20H23N	278.1903	233.1325	91.0542	0.00132	0.00439	0.9995	12.98	3.68
Amoxapine	14028-44-5	C17 H16 Cl N3 O	314.1055	271.0633	193.0522	0.00185	0.00618	0.9987	12.63	1.64
Amoxicillin	61336-70-7	C16H19N3O5S	366.1118	114.0008	134.0600	0.00204	0.00679	0.9982	6.04	-4.02
Amphetamine	300-62-9	C9H13N	136.1121	91.0542	65.0386	0.00203	0.00678	0.9979	6.27	-0.75
Acetylsalicylic acid	50-78-2	C9H8O4	181.0495	149.0236	150.0267	0.00339	0.01131	0.9953	8.03	3.54
Atenolol	29122-68-7	C14H22N2O3	267.1703	145.0648	56.0495	0.00120	0.00399	0.9993	4.66	4.16
Atropine	51-55-8	C17H23NO3	290.1751	93.0699	124.1121	0.00204	0.00681	0.9994	7.21	6.06
Azithromycin	83905-01-5	C38H72N2O12	749.5158	158.1176	591.4215	0.00280	0.00933	0.9963	10.82	-0.40
Benzoylecgonine	519-09-5	C16 H19 N O4	290.1387	168.1019	105.0335	0.00193	0.00642	0.9986	7.61	7.50
Betamethasone 17,21-dipropionate	5593-20-4	C28 H37 F O7	505.2596	209.0819	453.2053	0.00252	0.00839	0.9991	16.53	0.71
Bisoprolol	66722-44-9	C18H31NO4	326.2326	74.0600	56.0495	0.00258	0.00859	0.9971	10.53	4.59
Bromazepam	1812-30-2	C14 H10 Br N3 O	318.0061	182.0839	209.0947	0.00189	0.00630	0.9996	11.82	-0.25
BTA / Benzotriazole	95-14-7	C6H5N3	120.0556	65.0386	92.0495	0.00165	0.00550	0.9995	4.85	-2.46
Buprenorphine	52485-79-7	C29 H41 N O4	468.3108	414.2639	396.2169	0.00097	0.00325	0.9995	11.98	2.83
Buprenorphine glucuronide	101224-22-0	C35 H49 N O10	644.3429	468.3108	414.2639	0.00371	0.01238	0.9994	9.82	-0.62
Caffeine	58-08-2	C8 H10 N4 O2	195.0877	138.0662	110.0713	0.00154	0.00514	0.9990	6.83	0.03
Carbamazepine	298-46-4	C15H12N2O	237.1022	193.0886	179.0730	0.00079	0.00264	0.9982	12.25	7.27
Carisoprodol	78-44-4	C12H24N2O4	261.1809	55.0542	62.0237	0.00311	0.01035	0.9975	12.96	-0.48
Carprofen	53716-49-7	C15H12ClNO2	274.0629	228.0586	190.0662	0.00186	0.00620	0.9981	15.82	5.77
CBN / Cannabinol	521-35-7	C21H26O2	311.2006	208.0883	179.0855	0.00455	0.01516	0.9983	18.31	1.29

Table S4. *(continued)*

Name	CAS#	Formula	Transition	Transition 1	Transition 2	LOD	LOQ	CF R2	RT	Mass Accuracy
Chlordiazepoxide	58-25-3	C16 H14 Cl N3 O	300.0898	282.0793	227.0496	0.00216	0.00719	0.9994	12.46	0.90
Chlorprothixene	113-59-7	C18 H18 Cl N S	316.0921	231.0030	271.0343	0.00332	0.01105	0.9985	14.12	3.13
Cinoxacin	28657-80-9	C12 H10 N2 O5	263.0662	245.0557	189.0295	0.00112	0.00372	0.9994	9.46	1.16
Ciprofloxacin	85721-33-1	C17 H18 F N3 O3	332.1405	294.1237	314.1299	0.00319	0.01064	0.9986	7.70	1.31
Citalopram	59729-33-8	C20H21FN2O	325.1711	109.0448	234.0714	0.00236	0.00786	0.9994	11.09	6.82
Clarithromycin	81103-11-9	C38 H69 N O13	748.4842	158.1176	590.3899	0.00227	0.00755	0.9968	14.43	1.87
Clobazam	22316-47-8	C16 H13 Cl N2 O2	301.0738	224.0944	259.0633	0.00135	0.00451	0.9983	12.88	2.43
Clomipramine	303-49-1	C19 H23 Cl N2	315.1623	86.0964	58.0651	0.00167	0.00557	0.9971	14.17	3.16
Clonazepam	1622-61-3	C15 H10 Cl N3 O3	316.0483	270.0554	207.0917	0.00241	0.00804	0.9986	12.34	1.13
Clonidine	4205-90-7	C9H9Cl2N3	230.0246	159.9715	144.9606	0.00026	0.00088	0.9983	5.82	1.68
Diazepam	439-14-5	C16 H13 Cl N2 O	285.0789	193.0886	154.0417	0.00148	0.00494	0.9974	14.44	7.16
Diclofenac	15307-79-6	C14H11Cl2NO2	296.0240	214.0418	180.0808	0.00089	0.00297	0.9963	15.61	1.02
Difloxacin	98106-17-3	C21 H19 F2 N3 O3	400.1467	382.1362	299.0991	0.00400	0.01334	0.9986	8.31	1.36
Digitoxin	71-63-6	C41 H64 O13	787.4239	97.0648	113.0597	0.00615	0.02052	0.9974	16.31	-1.57
Dimetridazole	551-92-8	C5H7N3O2	142.0611	78.0338	96.0682	0.00109	0.00364	0.9984	14.21	6.21
Diphenhydramine	58-73-1	C17H21NO	256.1696	165.0699	152.0621	0.00178	0.00593	0.9985	11.28	0.67
Dothiepin	113-53-1	C19H21NS	296.1467	221.0420	203.0855	0.00240	0.00802	0.9992	12.36	3.56
Doxepin	1668-19-5	C19H21NO	280.1696	115.0542	107.0491	0.00166	0.00552	0.9991	11.57	2.82
Doxycycline	24390-14-5	C22H24N2O8	445.1605	98.0600	267.0652	0.00147	0.00488	0.9981	13.73	8.00
Dextromethorphan	125-71-3	C18H25NO	272.2009	171.0804	147.0804	0.00158	0.00528	0.9957	11.30	3.33
Ecgonine methyl ester	7143-09-1	C10H17NO3	200.1281	91.0542	94.0651	0.00378	0.01261	0.9990	17.19	6.71
EDDP	30223-73-5	C11 H17 O3 P S	278.1913	234.1277	186.1277	0.00079	0.00265	0.9984	11.24	0.41
Enoxacin	74011-58-8	C15H17FN4O3	321.1357	303.1252	234.1038	0.00271	0.00902	0.9989	7.29	2.43
Enrofloxacin	93106-60-6	C19H22FN3O3	360.1718	316.1820	245.1084	0.00214	0.00712	0.9954	7.90	5.33
Erythromycin A	114-07-8	C37H67NO13	734.4685	233.1536	576.3742	0.00275	0.00916	0.9989	13.19	0.31
Etodolac	41340-25-4	C17H21NO3	286.1594	181.0897	212.1418	0.00170	0.00565	0.9996	3.44	-3.20
Felbamate	25451-15-4	C11 H14 N2 O4	261.0846	115.0542	117.0699	0.00179	0.00598	0.9990	8.49	0.89
Phenazepam	51753-57-2	C15 H10 Br Cl N2 O	350.9716	242.0605	183.9756	0.00294	0.00980	0.9992	14.01	1.81
Fentanyl	437-38-7	C22H28N2O	337.2274	105.0699	188.1434	0.00110	0.00367	0.9981	10.72	2.27
Flubendazole	31430-15-6	C16 H12 F N3 O3	314.0935	282.0673	123.0241	0.00326	0.01086	0.9994	13.31	1.73
Fludrocortisone-Acetate	514-36-3	C23H31FO6	423.2177	181.1012	143.0855	0.00381	0.01269	0.9961	13.73	0.40
Flumazenil	78755-81-4	C15 H14 F N3 O3	326.0911	258.0673	217.0396	0.00387	0.01289	0.9997	10.75	0.74
Flumequine	42835-25-6	C14 H12 F N O3	262.0874	244.0768	202.0287	0.00183	0.00609	0.9987	11.86	2.50
Flumethasone	2135-17-3	C22H28F2O5	411.1978	277.1587	275.1430	0.00297	0.00990	0.9989	16.54	6.20
Flunixin	38677-85-9	C14H11F3N2O2	297.0845	264.0505	279.0740	0.00175	0.00583	0.9964	14.62	7.73
Fluoxetine	54910-89-3	C17H18F3NO	310.1413	199.1842	149.0236	0.00177	0.00591	0.9969	13.35	2.20
Flupentixol	2709-56-0	C23 H25 F3 N2 O S	435.1712	305.0606	265.0293	0.00159	0.00530	0.9976	15.23	4.30

Table S4. *(continued)*

Name	CAS#	Formula	Transition	Transition 1	Transition 2	LOD	LOQ	CF R2	RT	Mass Accuracy
Flurazepam	17617-23-1	C21 H23 Cl F N3 O	388.1586	315.0695	317.0851	0.00103	0.00342	0.9985	11.29	2.96
Fluvoxamine	54739-18-3	C15 H21 F3 N2 O2	319.1628	71.0503	200.0682	0.00144	0.00480	0.9972	13.23	2.22
Furaltadone	139-91-3	C13 H16 N4 O6	325.1143	100.0757	128.1070	0.00282	0.00941	0.9962	5.01	0.01
Furazolidon	67-45-8	C8 H7 N3 O5	226.0458	67.0417	122.0111	0.00168	0.00560	0.9995	6.40	1.37
Gabapentin	60142-96-3	C9H17NO2	172.1332	67.0542	91.0542	0.00088	0.00292	0.9988	5.96	-1.18
Haloperidol	52-86-8	C21 H23 Cl F N O2	376.1474	165.0710	123.0241	0.00123	0.00408	0.9984	11.84	3.41
Hydrocodone	125-29-1	C18H21NO3	300.1594	199.0754	171.0804	0.00166	0.00553	0.9957	5.22	3.27
Hydrocortisone	50-23-7	C21H30O5	363.2166	121.0648	97.0648	0.00156	0.00520	0.9987	12.67	0.06
Hydromorphone	466-99-9	C17H19NO3	286.1438	185.0597	157.0648	0.00172	0.00573	0.9998	3.44	1.32
Ibuprofen	15687-27-1	C13H18O2	207.1380	105.0707	162.1352	0.00184	0.00612	0.9974	9.52	8.18
Imipramine	50-49-7	C19H24N2	281.2012	58.0651	86.0964	0.00049	0.00164	0.9971	12.91	3.03
Iopromide	73334-07-3	C18H24I3N3O8	791.8770	558.8850	572.9007	0.00101	0.00335	0.9952	5.12	-0.57
Ipronidazole	14885-29-1	C7 H11 N3 O2	170.0924	124.0995	109.0760	0.00111	0.00371	0.9991	7.08	7.44
Ketamine	6740-88-1	C13H16ClNO	238.0993	125.0153	128.0621	0.00196	0.00654	0.9966	8.02	2.21
Ketoprofen	22071-15-4	C16H14O3	255.1016	77.0386	103.0542	0.00402	0.01340	0.9983	13.64	-0.02
Lamotrigine	84057-84-1	C9 H7 Cl2 N5	256.0151	156.9606	58.0400	0.00114	0.00379	0.9988	8.79	3.82
Levamisole	14769-73-4	C11H12N2S	205.0794	178.0685	91.0542	0.00315	0.01050	0.9994	5.67	0.35
Lidocaine	137-58-6	C14 H22 N2 O	235.1805	86.0964	58.0651	0.00129	0.00430	0.9984	7.34	1.85
Lomefloxacin	98079-51-7	C17 H19 F2 N3 O3	352.1467	265.1147	334.1362	0.00239	0.00796	0.9991	8.04	1.50
Lorazepam	846-49-1	C15H10Cl2N2O2	321.0192	229.0527	275.0137	0.00200	0.00666	0.9962	13.11	1.02
Maprotiline	10262-69-8	C20 H23 N	278.1903	234.1283	186.1277	0.00098	0.00328	0.9984	11.24	3.94
Marbofloxacin	115550-35-1	C17H19FN4O4	363.1463	72.0781	345.1358	0.00359	0.01195	0.9966	6.75	1.25
MDA	4764-17-4	C10H13NO2	180.1019	79.0542	77.0386	0.00356	0.01186	0.9979	6.48	-0.45
MDEA (MDE)	82801-81-8	C12H17NO2	208.1332	105.0699	135.0441	0.00169	0.00563	0.9988	7.22	1.90
MDMA	42542-10-9	C11H15NO2	194.1176	77.0386	79.0542	0.00142	0.00473	0.9969	6.60	0.30
Mebendazole	31431-39-7	C16 H13 N3 O3	296.1030	191.0862	134.0966	0.00126	0.00419	0.9993	12.92	1.98
Medazepam	2898-12-6	C16 H15 Cl N2	271.0997	207.1043	242.0731	0.00295	0.00984	0.9995	11.96	0.76
Meloxicam	71125-38-7	C14 H13 N3 O4 S2	352.0420	115.0324	141.0117	0.00204	0.00679	0.9989	13.31	1.93
Memantine	19982-08-2	C12H21N	180.1747	91.0542	107.0855	0.00191	0.00638	0.9997	11.61	-0.29
Pethidine	57-42-1	C15H21NO2	248.1645	70.0651	91.0542	0.00117	0.00391	0.9985	9.16	4.68
Methadone	76-99-3	C11 H15 N O2	310.2165	105.0335	77.0386	0.00319	0.01062	0.9997	13.09	5.86
Methamphetamine	537-46-2	C10H15N	150.1277	91.0542	65.0386	0.00096	0.00318	0.9989	6.49	0.71
Methylphenidate	113-45-1	C14H19NO2	234.1489	84.0808	56.0495	0.00420	0.01399	0.9972	8.71	0.39
Methylprednisolone	83-43-2	C22H30O5	375.2166	161.0961	135.0804	0.00507	0.01690	0.9975	13.68	-0.38
Metoprolol	37350-58-6	C15 H25 N O3	268.1907	72.0808	56.0495	0.00162	0.00541	0.9970	13.06	-6.04
Metronidazole	443-48-1	C6H9N3O3	172.0717	128.0455	82.0526	0.00146	0.00487	0.9996	4.73	0.18
Mianserin	24219-97-4	C18 H20 N2	265.1699	58.0651	208.1121	0.00150	0.00501	0.9986	11.33	2.47
Minocycline	13614-98-7	C23H27N3O7	458.1922	337.0945	283.0839	0.00347	0.01157	0.9955	13.75	3.35

Table S4. *(continued)*

Name	CAS#	Formula	Transition	Transition 1	Transition 2	LOD	LOQ	CF R2	RT	Mass Accuracy
Mirtazapine	61337-67-5	C17 H19 N3	266.1652	195.0917	72.0808	0.00205	0.00683	0.9974	9.07	2.09
Mometasone furoate	83919-23-7	C27 H30 Cl2 O6	543.1312	278.1665	355.1459	0.00202	0.00673	0.9969	15.90	0.18
Monensin	17090-79-8	C36 H62 O11	693.4184	675.4079	461.2820	0.00244	0.00814	0.9955	19.15	0.99
Morphine-6-β-D-glucuronide	20290-10-2	C23H27NO9	462.1759	286.1438	58.0651	0.00120	0.00398	0.9991	3.15	-0.67
Morphine	57-27-2	C17H19NO3	286.1438	165.0699	153.0699	0.00172	0.00573	0.9998	3.44	1.32
Nalidixic Acid	389-08-2	C12H12N2O3	233.0921	159.0553	104.0495	0.00353	0.01176	0.9977	11.57	2.09
Naltrexone	16590-41-3	C20H23NO4	342.1700	55.0542	267.1254	0.00240	0.00799	0.9998	5.75	2.20
Naproxen	22204-53-1	C14H14O3	231.1016	185.0961	141.0699	0.00119	0.00396	0.9959	4.14	-6.86
N-Desmethylclozapine	6104-71-8	C17 H17 Cl N4	313.1215	253.0523	192.0682	0.00247	0.00823	0.9969	11.58	2.59
Nitrazepam	146-22-5	C15 H11 N3 O3	282.0873	236.0944	207.0917	0.00299	0.00996	0.9987	12.29	0.35
Nitrofural	59-87-0	C6H6N4O4	199.0462	54.0100	69.0447	0.00215	0.00717	0.9997	6.44	-0.52
Norbuprenorphine	78715-23-8	C25H35NO4	414.2639	101.0961	83.0855	0.00491	0.01636	0.9972	10.61	-1.04
Nordiazepam	1088-11-5	C15H11ClN2O	271.0633	140.0257	165.0209	0.00110	0.00366	0.9987	15.82	1.10
Norfentanyl	1609-66-1	C14 H20 N2 O	233.1648	84.0808	55.0542	0.00119	0.00396	0.9972	8.11	4.17
Norfloxacin	70458-96-7	C16 H18 F N3 O3	320.1405	302.1299	276.1504	0.00243	0.00811	0.9962	7.46	0.51
Norpethidine	77-17-8	C14H19NO2	234.1489	56.0495	84.0808	0.00173	0.00577	0.9994	11.25	-8.16
Norpropoxyphene	3376-94-1	C21H27NO2	326.2121	91.0694	128.0842	0.00173	0.00576	0.9998	10.53	6.45
Nortriptyline	72-69-5	C19H21N	264.1747	91.0542	203.0855	0.00147	0.00489	0.9968	12.98	5.44
Octyl methoxycinnamate	5466-77-3	C18H26O3	291.1955	133.0635	79.0542	0.00174	0.00581	0.9997	7.21	-5.90
Desvenlafaxine	93413-62-8	C16H25NO2	264.1958	133.0648	107.0491	0.00096	0.00321	0.9959	8.17	2.05
O-Desmethyltramadol	73986-53-5	C15H23NO2	250.1802	58.0651	232.1696	0.00122	0.00407	0.9996	6.61	3.84
Ofloxacin	82419-36-1	C18 H20 F N3 O4	362.1511	318.1612	261.1033	0.00372	0.01240	0.9990	7.24	1.51
Olanzapine	132539-06-1	C17 H20 N4 S	313.1481	256.0903	198.0246	0.00339	0.01131	0.9954	6.88	1.03
Oleandomycin	3922-90-5	C35 H61 N O12	688.4267	158.1176	544.3453	0.00211	0.00703	0.9992	12.01	1.17
Opipramol	315-72-0	C23H29N3O	364.2383	143.1179	100.0757	0.00129	0.00429	0.9972	12.63	4.35
Orbifloxacin	113617-63-3	C19 H20 F3 N3 O3	396.1530	352.1631	378.1424	0.00231	0.00771	0.9970	8.19	2.08
OTC / Oxytetracycline	2058-46-0	C22H24N2O9	461.1555	283.0561	201.0506	0.00428	0.01427	0.9993	13.71	3.31
Oxazepam	604-75-1	C15H11ClN2O2	287.0582	241.0527	104.0495	0.00106	0.00354	0.9988	14.45	64.57
Oxcarbazepine	28721-07-5	C15H12N2O2	253.0972	236.0706	180.0808	0.00183	0.00609	0.9989	11.78	-69.19
Oxibendazole	20559-55-1	C12 H15 N3 O3	250.1186	176.0455	218.0924	0.00096	0.00321	0.9998	11.89	6.11
Oxolinic Acid	14698-29-4	C13H11NO5	262.0710	160.0393	216.0291	0.00150	0.00500	0.9992	10.08	2.30
Oxycodone	76-42-6	C18 H21 N O4	316.1543	80.0498	298.1438	0.00159	0.00529	0.9989	5.59	1.97
Oxymorphone	76-41-5	C17H19NO4	302.1387	227.0941	198.0913	0.00195	0.00652	0.9992	3.72	0.62
Paliperidone	144598-75-4	C23 H27 F N4 O3	427.2140	207.1128	110.0598	0.00140	0.00467	0.9955	9.51	3.16
Paroxetine	61869-08-7	C19 H20 F N O3	330.1500	192.1183	151.0390	0.00302	0.01007	0.9952	12.49	2.61
Phencyclidine	77-10-1	C17 H25 N	244.2060	91.0542	86.0964	0.00380	0.01267	0.9989	10.40	0.09
Penicillin G	113-98-4	C16H18N2O4S	335.1060	176.0706	160.0427	0.00897	0.02992	0.9958	15.13	27.92
Pentazocine	359-83-1	C19 H27 N O	286.2165	69.0699	218.1539	0.00126	0.00420	0.9984	10.01	8.68

Table S4. *(continued)*

Name	CAS#	Formula	Transition	Transition 1	Transition 2	LOD	LOQ	CF R2	RT	Mass Accuracy
Phenazepam	51753-57-2	C15H10BrClN2O	348.9738	206.0839	183.9756	0.00250	0.00833	0.9994	14.02	0.74
Phentermine	122-09-8	C10H15N	150.1277	91.0542	65.0386	0.00255	0.00851	0.9989	6.49	0.71
Phenylbutazone	50-33-9	C19H20N2O2	309.1598	92.0495	77.0386	0.00172	0.00572	0.9984	9.48	2.55
Phenytoin	57-41-0	C15 H12 N2 O2	253.0972	180.0808	208.0757	0.00489	0.01629	0.9990	11.00	0.29
Pipamperone	1893-33-0	C21 H30 F N3 O2	376.2395	165.0710	98.0600	0.00208	0.00695	0.9976	9.10	2.47
Pipemidic acid	51940-44-4	C14 H17 N5 O3	304.1404	286.1299	217.1085	0.00322	0.01074	0.9978	6.48	1.50
Prazepam	2955-38-6	C19 H17 Cl N2 O	325.1102	271.0633	140.0261	0.00119	0.00396	0.9991	15.81	7.39
Praziquantel	55268-74-1	C19H24N2O2	313.1911	55.0542	83.0855	0.00264	0.00881	0.9974	14.43	1.50
Prednicarbate	73771-04-7	C27 H36 O8	511.2302	289.1587	307.1693	0.00378	0.01260	0.9996	16.09	-0.98
Prednisolone	50-24-8	C21H28O5	395.1631	147.0804	67.0542	0.00651	0.02169	0.9950	10.92	0.26
Procaine (Novocaine)	59-46-1	C13H20N2O2	237.1598	100.1121	120.0444	0.00128	0.00428	0.9988	4.86	2.17
Promazine	58-40-2	C17H20N2S	285.1420	86.0964	58.0651	0.00392	0.01307	0.9984	12.62	2.49
Promethazine	60-87-7	C17H20N2S	285.1420	198.0372	86.0964	0.00297	0.00991	0.9972	12.34	1.84
Propafenone	53-16-7	C18 H22 O2	342.2064	72.0808	116.1070	0.00095	0.00318	0.9967	12.85	6.91
Dextropropoxyphene	469-62-5	C22H29NO2	340.2271	58.0651	91.0542	0.00515	0.01716	0.9993	12.74	0.48
Protriptyline	438-60-8	C19 H21 N	264.1747	191.0855	91.0545	0.00123	0.00411	0.9989	13.00	5.58
p-Toluenesulfonamide	70-55-3	C7H9NO2S	172.0427	91.0542	119.0604	0.00249	0.00829	0.9988	10.07	3.96
Quetiapine	111974-69-7	C21H25N3O2S	384.1740	221.1073	253.0794	0.00145	0.00485	0.9993	11.78	5.03
Risperidone	106266-06-2	C23 H27 F N4 O2	411.2191	191.1179	192.1236	0.00148	0.00493	0.9956	10.25	4.09
Ritalinic acid	19395-41-6	C13H17NO2	220.1332	84.0808	56.0495	0.00229	0.00762	0.9989	7.67	1.19
Ronidazole	7681-76-7	C6 H8 N4 O4	223.0438	55.0417	140.0455	0.00265	0.00885	0.9972	4.58	-0.35
Roxithromycin	80214-83-1	C41H76N2O15	837.5319	679.4382	158.1176	0.00419	0.01397	0.9977	14.60	1.95
Salinomycin	53003-10-4	C42 H70 O11	768.5256	733.4888	531.3260	0.00814	0.02712	0.9960	12.73	-5.16
Sarafloxacin	98105-99-8	C20 H17 F2 N3 O3	386.1311	368.1205	342.1439	0.00387	0.01290	0.9986	8.49	0.84
Secobarbital	76-73-3	C12 H18 N2 O3	256.1656	91.0552	176.1442	0.00173	0.00575	0.9964	11.28	1.28
Sertraline	79617-96-2	C17 H17 Cl2 N	306.0811	158.9763	129.0699	0.00279	0.00932	0.9985	13.95	0.84
Spiramycin	8025-81-8	C43H74N2O14	843.5213	174.1125	101.0597	0.00786	0.02620	0.9966	10.29	0.06
Strophanthidin	66-28-4	C23H32O6	405.2310	145.0997	125.0589	0.00396	0.01320	0.9954	10.97	-9.97
Strophanthin	11005-63-3	C36H54O14	549.3065	405.2273	387.2164	0.00444	0.01481	0.9991	16.54	-1.82
Sulfabenzamide	127-71-9	C13H12N2O3S	277.0641	92.0495	65.0386	0.00322	0.01075	0.9986	8.49	-1.13
Sulfacetamide	144-80-9	C8 H10 N2 O3 S	237.0304	94.9895	65.0386	0.00174	0.00581	0.9977	3.92	0.64
Sulfachlorpyridazine	80-32-0	C10H9ClN4O2S	285.0208	157.0150	156.0118	0.00110	0.00365	0.9975	7.29	0.54
Sulfaclozine	102-65-8	C10H9ClN4O2S	285.0208	156.0118	108.0457	0.00126	0.00420	0.9976	7.29	0.54
Sulfadiazine	68-35-9	C10H10N4O2S	251.0597	92.0495	65.0386	0.00229	0.00763	0.9990	4.74	1.35
Sulfadimethoxine	122-11-2	C12 H14 N4 O4 S	311.0809	92.0495	108.0444	0.00210	0.00701	0.9971	7.92	3.98
Sulfadimidine	57-68-1	C12 H14 N4 O2 S	279.0910	124.0869	186.0332	0.00197	0.00656	0.9986	6.83	2.07
Sulfadoxine	2447-57-6	C12H14N4O4S	311.0809	140.0455	154.0611	0.00274	0.00912	0.9999	7.93	4.03
Sulfafurazole	127-69-5	C11 H13 N3 O3 S	268.0750	65.0386	113.0709	0.00380	0.01268	0.9996	7.87	2.44

Table S4. *(continued)*

Name	CAS#	Formula	Transition	Transition 1	Transition 2	LOD	LOQ	CF R2	RT	Mass Accuracy
Sulfaguanidine	57-67-0	C7H10N4O2S	215.0597	65.0386	92.0495	0.00142	0.00475	0.9959	6.47	-3.22
Sulfamerazine	127-79-7	C11 H12 N4 O2 S	265.0754	92.0495	108.0430	0.00205	0.00682	0.9996	5.83	0.88
Sulfamethoxydiazine	651-06-9	C11H12N4O3S	281.0703	215.0930	156.0122	0.00381	0.01270	0.9998	6.44	0.47
Sulfamethizole	144-82-1	C9H10N4O2S2	271.0318	108.0444	92.0495	0.00375	0.01250	0.9978	6.56	0.86
Sulfamethoxazole	723-46-6	C10H11N3O3S	254.0594	65.0386	92.0468	0.00181	0.00604	0.9997	7.40	1.70
Sulfamethoxypyridazine	80-35-3	C11H12N4O3S	281.0703	108.0444	92.0495	0.00112	0.00373	0.9998	6.44	0.47
Sulfamonomethoxine	1220-83-3	C11H12N4O3S	281.0703	126.0662	156.0100	0.00167	0.00557	0.9989	6.97	1.72
Sulfanilamide	63-74-1	C6H8N2O2S	173.0379	93.0573	65.0386	0.00331	0.01104	0.9976	10.07	1.31
Sulfanitran	122-16-7	C14H13N3O5S	336.0649	93.0335	65.0386	0.00219	0.00732	0.9959	13.32	3.41
Sulfaphenazole	526-08-9	C15H14N4O2S	315.0910	158.0713	92.0495	0.00265	0.00882	0.9993	8.95	1.02
Sulfapyridine	144-83-2	C11H11N3O2S	250.0645	156.0114	108.0444	0.00168	0.00559	0.9997	5.50	1.19
Sulfaquinoxaline	59-40-5	C14 H12 N4 O2 S	301.0754	108.0444	156.0114	0.00149	0.00497	0.9963	9.80	-0.31
Sulfathiazole	72-14-0	C9 H9 N3 O2 S2	256.0209	92.0495	108.0444	0.00171	0.00571	0.9984	8.79	-1.74
Tiabendazole	148-79-8	C10H7N3S	202.0433	131.0604	175.0325	0.00068	0.00226	0.9959	8.28	4.24
Temazepam	846-50-4	C16H13ClN2O2	301.0738	255.0684	177.0209	0.00189	0.00630	0.9990	13.51	1.78
Terbinafine	91161-71-6	C21H25N	292.2060	141.0699	115.0542	0.00150	0.00501	0.9970	14.21	4.02
THC	1972-08-3	C13 H19 N O2 S	315.2319	123.0441	193.1223	0.00291	0.00971	0.9976	17.51	1.13
Tilmicosin	108050-54-0	C46 H80 N2 O13	869.5733	174.1125	870.5847	0.00383	0.01276	0.9974	11.77	0.76
Tinidazole	19387-91-8	C8 H13 N3 O4 S	248.0700	82.0526	121.0318	0.00212	0.00708	0.9997	5.76	0.70
Tolfenamic acid	13710-19-5	C14H12ClNO2	262.0629	244.0524	229.0289	0.00129	0.00431	0.9966	10.08	3.13
Topiramate	97240-79-4	C12H21NO8S	340.1061	59.0491	55.0178	0.00231	0.00770	0.9972	5.20	2.71
Torasemide	56211-40-6	C16H20N4O3S	349.1329	183.0910	264.0798	0.00241	0.00803	0.9975	11.16	0.86
Tramadol	27203-92-5	C16 H25 N O2	264.1958	58.0651	58.0654	0.00102	0.00340	0.9969	8.55	4.57
Trazodone	19794-93-5	C19 H22 Cl N5 O	372.1586	176.0818	148.0524	0.00187	0.00624	0.9993	10.04	2.32
Triamcinolone	124-94-7	C21H27FO6	395.1864	147.0816	121.0648	0.00099	0.00330	0.9988	10.92	1.24
Triamcinolone Acetonide	76-25-5	C24H31FO6	435.2177	147.0804	213.1274	0.00192	0.00642	0.9989	13.75	0.51
Triazolam	28911-01-5	C17 H12 Cl2 N4	343.0512	308.0823	239.0389	0.00123	0.00411	0.9985	13.18	3.38
Triclabendazole	68786-66-3	C14 H9 Cl3 N2 O S	360.9545	273.9962	343.9339	0.00100	0.00332	0.9985	16.80	2.93
Trimethoprim	738-70-5	C14H18N4O3	291.1452	110.0587	81.0447	0.00113	0.00378	0.9988	6.64	6.84
Trimipramine	739-71-9	C20H26N2	295.2169	58.0651	100.1121	0.00295	0.00985	0.9961	13.37	3.95
Venlafaxine	93413-69-5	C17 H27 N O2	278.2115	58.0652	165.0714	0.00076	0.00254	0.9997	11.24	-1.88
Verapamil	52-53-9	C27 H38 N2 O4	455.2904	165.0910	150.0675	0.00117	0.00390	0.9967	12.17	4.40
Zolpidem	82626-48-0	C19 H21 N3 O	308.1757	235.1230	236.1308	0.00115	0.00382	0.9988	9.48	4.86
Zopiclone	43200-80-2	C17 H17 Cl N6 O3	411.0943	245.0220	217.0271	0.00377	0.01258	0.9996	8.25	-0.43

Table S5. Minimum, maximum and average load (mg/day) of the 232 OMPs analysed in hospital wastewater (HWW) and WWTP influent (INF), classified by their class. Limit of detection (LOD) and frequency of detection (%) are also listed for each compound.

		HWW				INF			
Compound	**LOD (µg/L)**	**Freq (%)**	**Min load (mg/d)**	**Max load (mg/d)**	**Av. load (mg/d)**	**Freq (%)**	**Min load (mg/d)**	**Max load (mg/d)**	**Av. load (mg/d)**
Analgesics/anti-inflammatories									
Acetaminophen	0.0051	100	66.80	6810.49	3326.54 ± 1606.33	100	63.46	11499.75	4398.88 ± 2488.62
Acetylsalicylic acid	0.0034	100	74.44	745.36	327.56 ± 187.08	100	35.28	1410.01	454.08 ± 323.9
Alfentanil	0.0008	35	0.16	25.48	4.88 ± 8	28	0.22	62.07	6.16 ± 15.25
Aminopyrine	0.0038	53	0.75	820.01	172.15 ± 218.03	56	1.03	902.08	239.44 ± 277.44
Betamethasone dipropionate	0.0025	59	0.49	14.81	5.78 ± 4.76	56	0.68	22.95	8.27 ± 7.69
Buprenorphine	0.0010	82	0.24	116.55	56.43 ± 35.15	67	0.26	353.01	76.22 ± 84.14
Carisoprodol	0.0031	6	0.61	220.19	13.83 ± 53.18	6	0.84	123.13	8.06 ± 28.72
Codeine	0.0017	100	30.97	308.89	160.3 ± 64.71	100	50.24	454.53	206.83 ± 96.57
Dextromethorphan	0.0016	0	0.31	0.90	0.5 ± 0.15	6	0.43	11.20	1.24 ± 2.5
Dextropropoxyphene	0.0051	0	1.01	2.91	1.63 ± 0.48	0	1.39	5.05	2.21 ± 0.87
Diclofenac	0.0009	100	13.49	141.08	53.95 ± 36.71	100	32.84	14905.20	984.52 ± 3475.57
Etodolac	0.0017	0	0.33	0.96	0.54 ± 0.16	0	0.46	1.66	0.73 ± 0.29
Fentanyl	0.0011	0	0.22	0.62	0.35 ± 0.1	0	0.30	1.08	0.47 ± 0.19
Hydrocodone	0.0017	88	0.49	282.54	131.35 ± 76.86	94	0.89	415.85	181.21 ± 99.14
Hydromorphone	0.0017	100	23.59	209.35	93.03 ± 53.11	100	27.25	252.14	112.47 ± 66.08
Ibuprofen	0.0018	94	0.54	856.49	377.41 ± 254.59	100	44.25	1616.24	525.68 ± 414.44
Ketoprofen	0.0040	100	306.15	1553.69	968.12 ± 365.92	100	478.02	3228.39	1411.08 ± 687.89
Lidocaine	0.0013	100	41.45	222.44	139.61 ± 57.4	100	46.17	292.41	171.5 ± 71.16
Meloxicam	0.0020	6	0.40	1.15	0.68 ± 0.22	0	0.55	2.00	0.88 ± 0.34
Morphine	0.0017	100	23.59	209.35	94.51 ± 52.31	100	27.25	252.14	113.46 ± 65.06
Naproxen	0.0012	18	0.23	26311.02	1884.9 ± 6445.27	17	0.32	26624.70	2174.5 ± 6774.57
Oxycodone	0.0016	82	0.41	32.56	16.63 ± 10.77	83	0.52	31.15	17.49 ± 10.54
Oxymorphone	0.0020	94	0.74	45.84	21.42 ± 12.34	94	0.64	84.97	32.54 ± 22.09
Pentazocine	0.0013	0	0.25	0.71	0.4 ± 0.12	0	0.34	1.24	0.54 ± 0.21
Pethidine	0.0012	18	0.23	7.42	1.15 ± 1.93	22	0.32	18.90	2.17 ± 4.44
Phenylbutazone	0.0017	18	0.34	19.53	3.26 ± 6.38	11	0.46	39.13	4.4 ± 11.03
Procaine	0.0013	94	0.73	116.96	20.87 ± 29.78	89	0.42	89.71	28.93 ± 31.58
Tolfenamic acid	0.0013	6	0.25	4.01	0.62 ± 0.88	6	0.35	4.99	0.81 ± 1.07
Tramadol	0.0010	100	27.95	350.96	182.47 ± 76.4	100	136.44	501.51	252.85 ± 99.92
Antiarrhythmic agents									
Amiodarone	0.0027	0	0.53	1.54	0.86 ± 0.25	0	0.73	2.66	1.17 ± 0.46
Digitoxin	0.0062	0	1.21	3.48	1.95 ± 0.57	0	1.66	6.04	2.64 ± 1.04
Propafenone	0.0010	100	11.07	62.97	33.45 ± 18.26	94	0.35	128.25	33.41 ± 28.58
Strophanthidin	0.0040	0	0.78	2.24	1.25 ± 0.37	6	1.06	67.35	5.33 ± 15.49
Strophanthin	0.0044	0	0.87	2.51	1.4 ± 0.41	6	1.20	147.25	10 ± 34.26
Antibiotics									
Amoxicillin	0.0020	94	0.40	252.54	63.74 ± 57.45	89	0.55	189.42	70.53 ± 50.76
Azithromycin	0.0028	100	899.37	5922.75	2458.51 ± 1279.39	100	783.14	6303.23	2430.62 ± 1305.86
Cinoxacin	0.0011	18	0.22	5.76	0.89 ± 1.49	17	0.30	10.76	1.64 ± 2.91
Ciprofloxacin	0.0032	100	203.77	1939.78	1029.04 ± 535.53	100	170.82	2656.02	1060.48 ± 672.76
Clarithromycin	0.0023	100	7.48	355.70	152.34 ± 97.8	100	18.06	481.30	152.48 ± 116.1
Doxycycline	0.0015	59	0.29	1583.22	412.69 ± 538.73	61	0.39	2278.73	450.58 ± 609.12
Enoxacin	0.0027	24	0.53	357.19	41.07 ± 95.78	17	0.73	471.72	66.49 ± 155.08

Table S5. *(continued)*

		HWW				INF			
Compound	**LOD (µg/L)**	**Freq (%)**	**Min load (mg/d)**	**Max load (mg/d)**	**Av. load (mg/d)**	**Freq (%)**	**Min load (mg/d)**	**Max load (mg/d)**	**Av. load (mg/d)**
Antibiotics									
Erythromycin	0.0027	100	38.69	1141.20	347.87 ± 261.71	89	0.74	942.53	321.52 ± 257.91
Flumequine	0.0018	0	0.36	1.03	0.58 ± 0.17	0	0.49	1.79	0.79 ± 0.31
Furazolidon	0.0017	0	0.33	0.95	0.53 ± 0.16	6	0.45	6.29	1.04 ± 1.34
Lomefloxacin	0.0024	76	0.47	165.93	58.03 ± 47.07	72	0.64	305.36	76.44 ± 74.59
Metronidazole	0.0015	94	0.42	506.84	182.55 ± 157.31	100	5.92	385.94	124.68 ± 111.25
Minocycline	0.0035	76	0.68	236.12	129.51 ± 82.47	56	0.93	502.47	167.58 ± 170.29
Nalidixic Acid	0.0035	6	0.69	15.60	1.97 ± 3.53	6	0.95	24.80	2.83 ± 5.52
Norfloxacin	0.0024	76	0.48	173.58	49.04 ± 48.97	61	0.65	252.90	57.27 ± 73.38
Ofloxacin	0.0037	100	247.65	2019.64	827.88 ± 447.98	100	334.98	2147.71	1031.62 ± 543.55
Oleandomycin	0.0021	76	0.41	898.84	354.77 ± 314.81	78	0.57	1724.05	414.56 ± 436.04
Oxolinic Acid	0.0015	0	0.29	0.85	0.47 ± 0.14	0	0.40	1.47	0.64 ± 0.25
Oxytetracycline	0.0043	65	0.84	299.11	69.38 ± 81.53	50	1.15	288.46	73.49 ± 91.08
Penicillin G	0.0090	6	1.76	57.50	6.07 ± 13.28	6	2.41	104.29	9.49 ± 23.71
Pipemidic acid	0.0032	0	0.63	1.82	1.02 ± 0.3	0	0.87	3.16	1.38 ± 0.54
Roxithromycin	0.0042	94	0.82	806.85	320.44 ± 248.41	89	1.13	843.75	385.96 ± 222.2
Silvadene	0.0023	35	0.45	669.03	92.79 ± 217.47	44	0.62	1034.61	86.04 ± 247.58
Spiramycin	0.0079	47	1.54	2669.77	795.95 ± 968.96	39	2.11	2013.54	605 ± 827.46
Sulfabenzamide	0.0032	47	0.63	816.07	269.67 ± 318.05	39	0.87	1336.74	377.15 ± 507.23
Sulfadimethoxine	0.0021	0	0.41	1.19	0.66 ± 0.2	0	0.57	2.06	0.9 ± 0.35
Sulfadimidine	0.0020	18	0.39	61.06	7 ± 16.17	17	0.53	143.41	14.25 ± 36.21
Sulfafurazole	0.0038	0	0.75	2.15	1.2 ± 0.35	0	1.02	3.73	1.63 ± 0.64
Sulfaguanidine	0.0014	24	0.28	256.13	29.98 ± 67.18	22	0.38	192.67	31.55 ± 63.25
Sulfamerazine	0.0020	35	0.40	945.36	113.2 ± 312.12	28	0.55	949.51	90.54 ± 262.72
Sulfamethizole	0.0037	12	0.74	65.64	6.11 ± 16.01	17	1.01	57.53	8.59 ± 16.62
Sulfamethoxazole	0.0018	100	85.23	1487.55	348.5 ± 336.12	100	76.50	1669.02	377.75 ± 354.58
Sulfamethoxydiazine	0.0038	0	0.75	2.16	1.2 ± 0.36	0	1.03	3.74	1.64 ± 0.64
Sulfamethoxypyridazine	0.0011	6	0.22	31.71	2.2 ± 7.61	6	0.30	4.57	0.71 ± 0.98
Sulfanilamide	0.0033	0	0.65	1.87	1.05 ± 0.31	0	0.89	3.25	1.42 ± 0.56
Sulfaphenazole	0.0026	0	0.52	1.50	0.84 ± 0.25	0	0.71	2.60	1.14 ± 0.45
Sulfapyridine	0.0017	94	0.50	160.07	40.21 ± 40.92	83	0.54	153.16	44.42 ± 41.14
Sulfathiazole	0.0017	65	0.43	300.56	87.94 ± 93.6	50	0.56	577.31	135.32 ± 166.87
Tinidazole	0.0021	6	0.42	680.10	40.64 ± 164.78	6	0.57	1105.70	62.3 ± 260.4
Trimethoprim	0.0011	100	41.53	612.25	145.6 ± 137.88	100	47.47	527.03	155.44 ± 117.26
Antifungals									
Sulfacetamide	0.0017	0	0.34	0.99	0.55 ± 0.16	0	0.47	1.71	0.75 ± 0.29
Terbinafine	0.0015	0	0.30	0.85	0.47 ± 0.14	0	0.40	1.47	0.65 ± 0.25
Tiabendazole	0.0007	12	0.13	1.57	0.3 ± 0.34	6	0.18	2.14	0.39 ± 0.45
Antihistamines									
Diphenhydramine	0.0018	0	0.35	1.01	0.56 ± 0.17	0	0.48	1.75	0.76 ± 0.3
Promethazine	0.0030	0	0.58	1.68	0.94 ± 0.28	0	0.80	2.92	1.28 ± 0.5
Antihypertensives									
Clonidine	0.0003	29	0.05	1.22	0.36 ± 0.45	22	0.07	1.86	0.37 ± 0.53
Antiparasitics									
Albendazole	0.0014	41	0.28	1109.86	75.81 ± 267.84	17	0.38	61.31	4.69 ± 14.3
Flubendazole	0.0033	0	0.64	1.84	1.03 ± 0.3	0	0.88	3.20	1.4 ± 0.55
Levamisole	0.0032	24	0.62	83.79	12.19 ± 26.94	17	0.85	107.42	17.13 ± 36.7
Mebendazole	0.0013	24	0.25	838.15	52.66 ± 202.67	11	0.34	61.42	4.09 ± 14.33
Praziquantel	0.0026	59	0.52	155.50	36.25 ± 43.42	61	0.71	128.58	51.52 ± 46.01
Triclabendazole	0.0010	0	0.20	0.56	0.32 ± 0.09	0	0.27	0.98	0.43 ± 0.17

Table S5. *(continued)*

		HWW				INF			
Compound	**LOD (µg/L)**	**Freq (%)**	**Min load (mg/d)**	**Max load (mg/d)**	**Av. load (mg/d)**	**Freq (%)**	**Min load (mg/d)**	**Max load (mg/d)**	**Av. load (mg/d)**
Antiseptics									
Nitrofural	0.0021	12	0.42	919.38	60.17 ± 222.54	11	0.58	1272.27	77.93 ± 299.28
Beta-blockers									
Atenolol	0.0012	100	102.27	599.46	279.25 ± 121.49	100	112.09	1344.44	456.07 ± 264.14
Bisoprolol	0.0026	100	27.51	102.57	60.88 ± 21.94	100	27.95	174.84	85.19 ± 34.6
Metoprolol	0.0016	100	4.49	128.78	50.85 ± 37.38	94	0.64	186.10	69.29 ± 56.49
Calcium channel blockers									
Verapamil	0.0012	71	0.23	89.13	29.76 ± 28.12	89	0.43	108.81	41.31 ± 32.98
Diuretics									
Torasemide	0.0024	0	0.47	1.36	0.76 ± 0.22	0	0.65	2.36	1.03 ± 0.41
Drug metabolites									
10-Hydroxycarbazepine	0.0013	82	0.35	1132.10	394.45 ± 353.72	78	0.36	2040.32	551.62 ± 541.26
2-NP-AOZ	0.0020	0	0.39	1.13	0.63 ± 0.19	0	0.54	1.96	0.86 ± 0.34
4-Acetylaminoantipyrine	0.0019	82	0.50	76.02	30.25 ± 26.77	94	0.64	117.11	42.61 ± 32.84
4-FormylAminoAntipyrine	0.0012	88	0.31	73.07	28.07 ± 25.04	94	0.39	173.77	44.9 ± 44.35
6-Acetylmorphine	0.0013	88	0.35	450.19	61.44 ± 136.88	72	0.44	592.78	56.04 ± 147.33
7-Aminoclonazepam	0.0008	0	0.16	0.46	0.26 ± 0.08	0	0.22	0.79	0.35 ± 0.14
7-Aminoflunitrazepam	0.0008	0	0.16	0.46	0.26 ± 0.08	0	0.22	0.79	0.35 ± 0.14
Acetylcodeine	0.0019	41	0.37	10.27	3.28 ± 3.66	33	0.51	13.93	4.09 ± 5.22
Benzoylecgonine	0.0019	100	35.65	382.75	158.31 ± 98.39	100	75.80	543.16	232.9 ± 123.23
Buprenorphine glucuronide	0.0037	47	0.93	273.84	79.25 ± 100.6	33	1.00	415.22	89.85 ± 141.27
Cocaethylene	0.0005	53	0.10	94.86	24.46 ± 29.91	44	0.14	97.05	27.15 ± 33.53
Cotinine	0.0022	100	168.27	654.97	353.54 ± 129.76	100	233.45	1342.62	539.87 ± 239.72
Desalkylflurazepam	0.0009	12	0.17	2.96	0.53 ± 0.74	6	0.23	3.95	0.57 ± 0.86
Ecgonine methyl ester	0.0038	100	0.95	373.03	69.82 ± 114.26	100	1.21	332.97	47.65 ± 90.28
EDDP	0.0008	94	0.23	48.26	19.45 ± 13.47	89	0.21	64.68	19.79 ± 15.65
Morphine-6-β-D-glucuronide	0.0012	35	0.23	82.00	22.05 ± 33.18	22	0.32	211.87	23.15 ± 57.65
N-Desmethylclozapine	0.0025	12	0.49	7.49	1.45 ± 1.91	6	0.66	6.47	1.38 ± 1.34
Norbuprenorphine	0.0049	59	0.96	324.10	35.38 ± 76.71	50	1.32	803.80	69.8 ± 188.63
Norfentanyl	0.0012	94	0.31	52.43	18.08 ± 14.05	89	0.32	59.99	21.82 ± 17.25
Norpethidine	0.0017	88	0.45	45.78	19.61 ± 13.78	78	0.57	47.40	20.02 ± 15.93
Norpropoxyphene	0.0017	6	0.34	14.49	1.37 ± 3.39	0	0.46	1.70	0.74 ± 0.29
O-Desmethyltramadol	0.0012	100	34.15	240.07	115.19 ± 73.69	100	72.01	495.17	224.05 ± 121.08
Ritalinic acid	0.0023	29	0.45	128.54	19.85 ± 40.19	44	0.61	74.76	14.96 ± 23.29
α-Hydroxyalprazolam	0.0026	6	0.51	11.58	1.46 ± 2.62	6	0.70	17.92	2.06 ± 3.98
α-Hydroxymidazolam	0.0007	100	2.22	32.91	9.06 ± 7.96	100	3.07	32.20	11.48 ± 7.88
α-Hydroxytriazolam	0.0018	12	0.35	61.84	5.32 ± 15.3	11	0.48	28.97	3.7 ± 8.7
Hormones									
Fludrocortisone-Acetate	0.0038	0	0.75	2.15	1.2 ± 0.36	0	1.02	3.74	1.64 ± 0.64
Flumethasone	0.0030	0	0.58	1.68	0.94 ± 0.28	0	0.80	2.92	1.28 ± 0.5
Hydrocortisone	0.0016	88	0.39	297.33	84.5 ± 91.96	83	0.52	425.81	87.5 ± 121.75
Methylprednisolone	0.0051	0	1.00	2.87	1.6 ± 0.47	0	1.36	4.98	2.18 ± 0.86
Mometasone furoate	0.0020	0	0.40	1.14	0.64 ± 0.19	0	0.54	1.98	0.87 ± 0.34
Prednicarbate	0.0038	0	0.74	2.14	1.19 ± 0.35	0	1.02	3.71	1.62 ± 0.64
Prednisolone	0.0065	12	1.62	73.34	9.24 ± 20.45	0	1.75	6.39	2.79 ± 1.1
Triamcinolone	0.0010	0	0.19	0.56	0.31 ± 0.09	0	0.27	0.97	0.43 ± 0.17
Triamcinolone Acetonide	0.0019	24	0.38	105.78	16.89 ± 32.69	22	0.52	148.73	24.34 ± 48.47
Illicit drugs									
Cocaine	0.0030	29	0.59	33.71	7.04 ± 11.52	44	0.81	57.07	13.53 ± 18.74
Ketamine	0.0020	18	0.39	12.08	2.11 ± 3.6	17	0.53	16.10	2.66 ± 4.49
MDA	0.0036	100	13.65	1609.36	508.87 ± 535.9	78	1.29	1463.78	729.65 ± 595.46
MDEA	0.0017	59	0.33	66.18	10.4 ± 15.86	44	0.45	64.22	8.39 ± 15.58
MDMA	0.0014	76	0.38	111.81	16.54 ± 27.91	50	0.38	184.55	27.17 ± 49.02

Table S5. *(continued)*

		HWW				INF			
Compound	**LOD (µg/L)**	**Freq (%)**	**Min load (mg/d)**	**Max load (mg/d)**	**Av. load (mg/d)**	**Freq (%)**	**Min load (mg/d)**	**Max load (mg/d)**	**Av. load (mg/d)**
Phencyclidine	0.0038	0	0.75	2.15	1.2 ± 0.35	0	1.02	3.73	1.63 ± 0.64
Plastic additives									
Benzotriazole	0.0017	100	476.35	8555.43	3220.95 ± 2005.16	100	479.61	9866.55	4169.01 ± 2972.93
p-Toluenesulfonamide	0.0025	59	0.49	206.83	39.88 ± 51.39	39	0.67	173.26	33.44 ± 55.18
Psychiatric drugs									
Alprazolam	0.0016	0	0.31	0.88	0.49 ± 0.15	0	0.42	1.53	0.67 ± 0.26
Amisulpride	0.0015	53	0.39	47.49	9.11 ± 14.24	83	0.50	736.78	87.67 ± 215.27
Amitriptyline	0.0013	47	0.26	107.16	13.09 ± 28.23	39	0.35	95.14	8 ± 22.05
Amoxapine	0.0019	0	0.36	1.05	0.59 ± 0.17	0	0.50	1.82	0.8 ± 0.31
Bromazepam	0.0019	0	0.37	1.07	0.6 ± 0.18	11	0.51	471.93	27.3 ± 110.97
Carbamazepine	0.0008	100	22.50	161.27	81.49 ± 42.48	100	57.15	364.78	163.13 ± 78.25
Chlordiazepoxide	0.0022	0	0.42	1.22	0.68 ± 0.2	0	0.58	2.12	0.93 ± 0.36
Chlorprothixene	0.0033	0	0.65	1.88	1.05 ± 0.31	0	0.89	3.25	1.42 ± 0.56
Citalopram	0.0024	100	10.98	59.00	19.68 ± 11.7	89	0.85	43.82	19.26 ± 11.48
Clobazam	0.0014	12	0.27	3.31	0.65 ± 0.73	0	0.36	1.33	0.58 ± 0.23
Clomipramine	0.0017	18	0.33	21.53	2.88 ± 5.77	11	0.45	94.72	6.87 ± 22.26
Clonazepam	0.0024	0	0.47	1.36	0.76 ± 0.22	6	0.65	14.33	1.78 ± 3.16
Clorazepate	0.0032	0	0.62	1.79	1 ± 0.29	0	0.85	3.11	1.36 ± 0.53
Clozapine	0.0012	41	0.23	35.44	7.02 ± 10.68	33	0.31	35.03	6.04 ± 11.1
Desipramine	0.0040	6	0.79	95.62	6.83 ± 22.88	0	1.08	3.94	1.72 ± 0.68
Desvenlafaxine	0.0010	100	5.63	39.41	21.69 ± 11.08	100	15.36	106.44	46.43 ± 22.33
Dexametasone	0.0032	18	0.63	364.42	37.57 ± 97.81	6	0.86	202.30	12.56 ± 47.36
Diazepam	0.0015	6	0.29	3.37	0.64 ± 0.72	0	0.40	1.45	0.64 ± 0.25
Dothiepin	0.0024	24	0.47	73.16	14.96 ± 27	17	0.65	155.52	16.71 ± 40.38
Doxepin	0.0017	0	0.33	0.94	0.52 ± 0.15	0	0.45	1.63	0.71 ± 0.28
Felbamate	0.0018	6	0.35	97.58	6.28 ± 23.53	6	0.48	130.53	7.99 ± 30.58
Fluoxetine	0.0018	76	0.46	21.49	10.37 ± 6.87	78	0.57	43.39	14.1 ± 11.09
Flupentixol	0.0016	0	0.31	0.90	0.5 ± 0.15	0	0.43	1.56	0.68 ± 0.27
Flurazepam	0.0010	0	0.20	0.58	0.32 ± 0.1	6	0.28	17.65	1.37 ± 4.07
Fluvoxamine	0.0014	65	0.28	70.41	23.13 ± 25.42	56	0.39	120.66	30.72 ± 39.75
Gabapentin	0.0009	100	249.93	3370.42	1629.96 ± 877.8	100	835.89	8557.77	2958.29 ± 1734.24
Haloperidol	0.0012	0	0.24	0.69	0.39 ± 0.11	0	0.33	1.20	0.53 ± 0.21
Imipramine	0.0005	0	0.10	0.28	0.16 ± 0.05	0	0.13	0.48	0.21 ± 0.08
Lamotrigine	0.0011	100	29.44	269.51	121.18 ± 73.57	100	76.44	517.24	227.04 ± 117.37
Lorazepam	0.0020	82	0.57	125.55	52.56 ± 32.7	72	0.54	115.75	58.69 ± 40.04
Maprotiline	0.0010	88	0.29	46.36	17.51 ± 13.26	89	0.36	56.53	16.59 ± 14.14
Medazepam	0.0030	0	0.58	1.67	0.93 ± 0.28	0	0.79	2.90	1.27 ± 0.5
Memantine	0.0019	88	0.50	42.77	10.12 ± 9.74	94	0.69	74.55	19.6 ± 18.86
Mianserin	0.0015	0	0.30	0.85	0.47 ± 0.14	0	0.40	1.47	0.65 ± 0.25
Mirtazapine	0.0021	59	0.54	12.18	4.67 ± 3.96	50	0.55	18.35	6.43 ± 6.5
Naltrexone	0.0024	18	0.47	13.76	2.59 ± 4.19	17	0.64	17.92	3.73 ± 6.2
Nitrazepam	0.0030	47	0.59	54.51	16.77 ± 18.27	39	0.80	68.34	20.25 ± 25.89
Nordiazepam	0.0011	6	0.22	2.18	0.46 ± 0.46	11	0.30	2.58	0.65 ± 0.56
Nortriptyline	0.0015	0	0.29	0.83	0.46 ± 0.14	0	0.39	1.44	0.63 ± 0.25
Olanzapine	0.0034	35	0.67	81.37	17.08 ± 26.76	33	0.91	72.69	15.72 ± 23.76
Opipramol	0.0013	12	0.25	11.21	1.65 ± 3.48	11	0.35	15.66	2.01 ± 4.29
Oxazepam	0.0011	0	0.21	0.60	0.34 ± 0.1	0	0.29	1.04	0.46 ± 0.18
Oxcarbazepine	0.0018	71	0.36	70.72	14.46 ± 18.2	56	0.49	51.04	13.8 ± 16.02
Paliperidone	0.0014	6	0.28	95.13	6.01 ± 22.97	6	0.38	79.44	4.99 ± 18.58
Paroxetine	0.0030	0	0.59	1.71	0.96 ± 0.28	0	0.81	2.97	1.3 ± 0.51
Phenazepam	0.0025	24	0.49	243.91	30.43 ± 66.56	11	0.67	428.39	28.66 ± 101.08
Phenytoin	0.0049	65	0.96	120.38	39.18 ± 38.1	67	1.31	296.71	68.91 ± 75.37
Pipamperone	0.0021	6	0.41	9.93	1.17 ± 2.26	6	0.56	12.76	1.53 ± 2.82
Prazepam	0.0012	0	0.23	0.67	0.38 ± 0.11	0	0.32	1.17	0.51 ± 0.2
Promazine	0.0039	0	0.77	2.22	1.24 ± 0.37	0	1.05	3.85	1.68 ± 0.66
Protriptyline	0.0012	0	0.24	0.70	0.39 ± 0.12	0	0.33	1.21	0.53 ± 0.21
Quetiapine	0.0015	94	0.38	29.12	14.61 ± 7.5	100	4.09	38.02	16.74 ± 9.24
Risperidone	0.0015	47	0.29	84.54	16.51 ± 27.64	33	0.40	154.10	22.32 ± 43.78
Secobarbital	0.0017	0	0.34	0.98	0.55 ± 0.16	0	0.46	1.69	0.74 ± 0.29
Sertraline	0.0028	6	0.55	6.95	1.2 ± 1.49	0	0.75	2.74	1.2 ± 0.47

Table S5. *(continued)*

		HWW				INF			
Compound	**LOD (µg/L)**	**Freq (%)**	**Min load (mg/d)**	**Max load (mg/d)**	**Av. load (mg/d)**	**Freq (%)**	**Min load (mg/d)**	**Max load (mg/d)**	**Av. load (mg/d)**
Temazepam	0.0019	35	0.37	17.96	3.61 ± 4.88	39	0.51	51.63	7.96 ± 13.71
Topiramate	0.0023	6	0.45	30.48	2.48 ± 7.22	11	0.62	20.30	2.52 ± 4.84
Trazodone	0.0019	94	0.49	47.85	20.41 ± 11.66	94	0.68	81.22	25.75 ± 18.26
Triazolam	0.0012	0	0.24	0.70	0.39 ± 0.11	0	0.33	1.21	0.53 ± 0.21
Trimipramine	0.0030	6	0.58	149.90	9.7 ± 36.13	6	0.79	40.31	3.45 ± 9.21
Venlafaxine	0.0008	100	5.99	54.23	28.98 ± 15.97	100	14.05	95.01	46.85 ± 22.37
Zolpidem	0.0011	0	0.23	0.65	0.36 ± 0.11	0	0.31	1.12	0.49 ± 0.19
Zopiclone	0.0038	6	0.74	19.15	2.25 ± 4.37	0	1.02	3.70	1.62 ± 0.64
Receptor antagonists									
Atropine	0.0020	6	0.40	5.44	0.93 ± 1.18	0	0.55	2.00	0.88 ± 0.34
Flumazenil	0.0039	6	0.76	10.19	1.75 ± 2.21	6	1.04	10.82	2.18 ± 2.25
Stimulants									
Amphetamine	0.0020	94	0.51	9523.80	1027.01 ± 2724.12	100	16.91	2216.82	282.09 ± 510.8
Caffeine	0.0015	100	726.41	2518.02	1457.93 ± 547.18	100	916.46	5744.64	2274.34 ± 1351.03
Cannabinol	0.0045	35	0.89	35.85	8.34 ± 11.55	28	1.22	32.76	4.92 ± 7.46
Methadone	0.0032	47	0.63	48.20	8.98 ± 12.49	33	0.86	35.99	8.73 ± 12.34
Methamphetamine	0.0010	6	0.19	8.01	0.76 ± 1.87	11	0.26	11.34	1.51 ± 3.23
Methylphenidate	0.0042	47	0.82	18.10	6.19 ± 5.83	44	1.13	24.27	7.23 ± 7.01
Phentermine	0.0026	0	0.50	1.44	0.81 ± 0.24	0	0.69	2.50	1.1 ± 0.43
THC	0.0029	76	0.57	66.27	19.2 ± 15.83	50	0.78	171.45	27.93 ± 42.38
UV filters									
Octyl methoxycinnamate	0.0017	88	0.45	78.80	39.23 ± 23.37	94	0.58	210.26	83.47 ± 52.02
Veterinary drugs									
Carprofen	0.0019	18	0.37	76.47	7.67 ± 19.24	17	0.50	91.53	11.25 ± 25.58
Diaveridine	0.0016	94	0.32	570.05	244.49 ± 131.11	94	0.44	1183.93	363.62 ± 246.79
Difloxacin	0.0040	12	0.79	22.71	2.62 ± 5.21	17	1.08	28.42	4.19 ± 7.37
Dimetridazole	0.0011	0	0.21	0.62	0.34 ± 0.1	0	0.29	1.07	0.47 ± 0.18
Enrofloxacin	0.0021	18	0.42	10.90	1.86 ± 2.9	6	0.57	4.64	1.09 ± 0.95
Flunixin	0.0018	59	0.34	16.01	6.17 ± 5.47	50	0.47	36.15	9.27 ± 10.97
Furaltadone	0.0028	71	0.55	93.26	36.82 ± 29.92	61	0.76	110.08	40.1 ± 35.9
Ipronidazole	0.0011	6	0.22	7.14	0.74 ± 1.65	6	0.30	2.26	0.56 ± 0.46
Marbofloxacin	0.0036	59	0.70	729.28	189.34 ± 239.76	50	0.96	635.36	169.62 ± 220.36
Monensin	0.0024	0	0.48	1.38	0.77 ± 0.23	0	0.66	2.40	1.05 ± 0.41
Orbifloxacin	0.0023	0	0.45	1.31	0.73 ± 0.22	6	0.62	7.86	1.37 ± 1.67
Oxibendazole	0.0010	6	0.19	2.37	0.43 ± 0.51	6	0.26	3.30	0.58 ± 0.7
Ronidazole	0.0027	6	0.52	21.81	2.07 ± 5.09	6	0.71	28.14	2.63 ± 6.38
Salinomycin	0.0081	6	1.60	312.12	20.8 ± 75.08	6	2.19	319.23	21.08 ± 74.42
Sarafloxacin	0.0039	0	0.76	2.19	1.22 ± 0.36	0	1.04	3.80	1.66 ± 0.65
Sulfachlorpyridazine	0.0011	24	0.22	34.87	5.93 ± 11.2	22	0.29	34.15	5.79 ± 10.6
Sulfaclozine	0.0013	6	0.25	22.83	1.72 ± 5.44	11	0.34	52.61	5.09 ± 13.75
Sulfadoxine	0.0027	100	0.54	1.55	0.86 ± 0.26	100	0.74	2.68	1.17 ± 0.46
Sulfamonomethoxine	0.0017	0	0.33	0.95	0.53 ± 0.16	0	0.45	1.64	0.72 ± 0.28
Sulfanitran	0.0022	0	0.43	1.24	0.69 ± 0.2	0	0.59	2.15	0.94 ± 0.37
Sulfaquinoxaline	0.0015	18	0.29	40.85	6.08 ± 12.78	6	0.40	147.73	8.81 ± 34.67
Tilmicosin	0.0038	6	0.75	201.20	12.98 ± 48.5	6	1.03	123.62	8.44 ± 28.75
X-Ray contrast media									
Iopromide	0.0010	100	166.06	28549.92	7025.35 ± 9056.67	100	140.95	31828.88	6406.16 ± 9447.46

Table S6. Minimum, maximum and average concentration (µg/L) of the 232 OMPs analysed in hospital wastewater (HWW) (n=3), WWTP influent (INF) (n=3), MBR permeate (MBRperm) (n=2) and WWTP effluent (EFF) (n=3) during the *noPAC* treatment, that is, just the MBR. Compounds are divided according to their class and the limit of detection (LOD) for each compound is reported.

		HWW			INF			MBRperm			EFF		
Compound	**LOD (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Analgesics/anti-inflammatories													
Acetaminophen	0.005	0.952	6.020	4.163 ± 2.792	0.507	7.256	4.177 ± 3.413	0.043	0.055	0.049 ± 0.008	0.030	0.037	0.033 ± 0.003
Acetylsalicylic acid	0.003	0.427	0.631	0.544 ± 0.105	0.500	0.776	0.631 ± 0.138	0.474	0.807	0.641 ± 0.235	0.056	0.680	0.452 ± 0.345
Alfentanil	0.001	<LOD	0.035	0.015 ± 0.018	<LOD	0.007	0.004 ± 0.004	<LOD	0.002	0.001 ± 0.001	<LOD	0.005	0.002 ± 0.003
Aminopyrine	0.004	0.373	0.725	0.502 ± 0.194	<LOD	1.299	0.6 ± 0.654	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Betamethasone dipropionate	0.003	<LOD	0.026	0.012 ± 0.013	0.011	0.033	0.023 ± 0.011	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Buprenorphine	0.001	0.079	0.185	0.132 ± 0.053	0.063	0.143	0.103 ± 0.04	0.015	0.016	0.016 ± 0.001	<LOD	0.023	0.009 ± 0.013
Carisoprodol	0.003	<LOD	0.195	0.066 ± 0.111	<LOD	0.091	0.031 ± 0.051	<LOD	0.133	0.067 ± 0.093	<LOD	0.257	0.133 ± 0.128
Codeine	0.002	0.166	0.417	0.313 ± 0.131	0.135	0.393	0.295 ± 0.139	0.024	0.034	0.029 ± 0.007	<LOD	0.037	0.021 ± 0.019
Dextromethorphan	0.002	<LOD	<LOD	<LOD	<LOD	0.008	0.003 ± 0.004	<LOD	0.006	0.003 ± 0.004	<LOD	<LOD	<LOD
Dextropropoxyphene	0.005	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Diclofenac	0.001	0.055	0.102	0.075 ± 0.024	0.187	0.326	0.264 ± 0.071	0.157	0.241	0.199 ± 0.059	0.051	0.200	0.101 ± 0.086
Etodolac	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Fentanyl	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Hydrocodone	0.002	0.146	0.390	0.285 ± 0.125	0.118	0.365	0.27 ± 0.133	<LOD	0.012	0.006 ± 0.008	<LOD	0.030	0.012 ± 0.016
Hydromorphone	0.002	0.105	0.371	0.259 ± 0.138	0.067	0.277	0.198 ± 0.114	<LOD	0.002	<LOD ± 0.001	<LOD	0.004	0.002 ± 0.002
Ibuprofen	0.002	0.747	1.004	0.836 ± 0.145	0.635	1.449	1.062 ± 0.409	0.032	0.051	0.042 ± 0.014	0.039	0.092	0.072 ± 0.029
Ketoprofen	0.004	1.264	2.179	1.766 ± 0.464	1.219	3.828	2.504 ± 1.305	0.027	0.033	0.03 ± 0.005	<LOD	0.019	0.008 ± 0.01
Lidocaine	0.001	0.151	0.394	0.272 ± 0.121	0.131	0.376	0.268 ± 0.125	0.173	0.353	0.263 ± 0.127	0.074	0.269	0.193 ± 0.104
Meloxicam	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Morphine	0.002	0.105	0.371	0.259 ± 0.138	0.067	0.277	0.198 ± 0.114	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Naproxen	0.001	0.001	23.256	10.926 ± 11.691	0.001	19.621	12.544 ± 10.892	0.593	0.726	0.66 ± 0.094	0.001	0.233	0.135 ± 0.12
Oxycodone	0.002	0.021	0.058	0.035 ± 0.019	0.018	0.035	0.025 ± 0.009	0.010	0.014	0.012 ± 0.003	<LOD	0.010	0.004 ± 0.005
Oxymorphone	0.002	0.041	0.041	0.041 ± 0	0.041	0.081	0.061 ± 0.02	0.010	0.010	0.01 ± 0	<LOD	<LOD	<LOD
Pentazocine	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Pethidine	0.001	<LOD	0.006	0.002 ± 0.003	<LOD	0.008	0.003 ± 0.004	<LOD	0.008	0.004 ± 0.005	<LOD	0.012	0.004 ± 0.007
Phenylbutazone	0.002	<LOD	0.017	0.006 ± 0.009	<LOD	0.029	0.01 ± 0.016	<LOD	0.030	0.015 ± 0.02	<LOD	0.029	0.019 ± 0.016
Procaine	0.001	<LOD	0.005	0.004 ± 0.003	<LOD	0.009	0.005 ± 0.004	<LOD	0.013	0.007 ± 0.009	<LOD	0.013	0.008 ± 0.007
Tolfenamic acid	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Tramadol	0.001	0.310	0.367	0.341 ± 0.029	0.284	0.482	0.354 ± 0.111	0.275	0.459	0.367 ± 0.13	0.141	0.489	0.33 ± 0.176

Table S6. *(continued)*

Compound	LOD (µg/L)	HWW			INF			MBRperm			EFF		
		Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)
Antiarrhythmic agents													
Amiodarone	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Digitoxin	0.006	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Propafenone	0.001	0.048	0.111	0.071 ± 0.035	0.018	0.201	0.088 ± 0.099	0.006	0.015	0.011 ± 0.007	<LOD	0.026	0.015 ± 0.013
Strophanthidin	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Strophanthin	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Antibiotics													
Amoxicillin	0.002	0.106	0.447	0.228 ± 0.19	0.081	0.204	0.146 ± 0.062	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Azithromycin	0.003	2.998	10.483	5.703 ± 4.152	1.483	9.873	4.623 ± 4.576	0.075	0.110	0.092 ± 0.025	0.013	0.058	0.035 ± 0.022
Cinoxacin	0.001	<LOD	0.006	0.004 ± 0.003	<LOD	0.008	0.005 ± 0.004	<LOD	0.010	0.005 ± 0.006	<LOD	0.017	0.008 ± 0.008
Ciprofloxacin	0.003	1.466	2.010	1.652 ± 0.31	0.729	1.715	1.253 ± 0.496	0.288	0.488	0.388 ± 0.142	0.093	0.580	0.366 ± 0.249
Clarithromycin	0.002	0.065	0.504	0.238 ± 0.233	0.072	0.330	0.185 ± 0.131	<LOD	0.004	0.003 ± 0.002	0.008	0.036	0.023 ± 0.014
Doxycycline	0.001	<LOD	0.341	0.13 ± 0.184	<LOD	0.416	0.174 ± 0.216	0.111	0.142	0.126 ± 0.022	0.022	0.230	0.1 ± 0.113
Enoxacin	0.003	<LOD	0.191	0.065 ± 0.11	<LOD	0.388	0.13 ± 0.223	<LOD	0.016	0.009 ± 0.011	<LOD	0.073	0.043 ± 0.037
Erythromycin	0.003	0.068	1.897	0.767 ± 0.988	0.114	0.362	0.241 ± 0.124	<LOD	0.121	0.061 ± 0.085	<LOD	0.174	0.072 ± 0.091
Flumequine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Furazolidon	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Lomefloxacin	0.002	0.087	0.160	0.123 ± 0.037	0.096	0.169	0.13 ± 0.037	0.137	0.194	0.165 ± 0.04	0.050	0.202	0.143 ± 0.082
Metronidazole	0.001	0.375	0.843	0.563 ± 0.247	0.170	0.556	0.31 ± 0.213	0.073	0.082	0.078 ± 0.006	0.016	0.053	0.04 ± 0.021
Minocycline	0.003	0.141	0.379	0.23 ± 0.13	0.131	0.787	0.421 ± 0.334	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Nalidixic Acid	0.004	<LOD	0.026	0.01 ± 0.014	<LOD	0.036	0.013 ± 0.02	<LOD	0.053	0.027 ± 0.036	<LOD	0.043	0.016 ± 0.024
Norfloxacin	0.002	<LOD	0.142	0.087 ± 0.075	<LOD	0.150	0.091 ± 0.079	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Ofloxacin	0.004	1.380	1.897	1.687 ± 0.272	1.331	1.635	1.516 ± 0.163	1.689	1.783	1.736 ± 0.067	0.522	2.600	1.58 ± 1.039
Oleandomycin	0.002	0.602	1.481	0.982 ± 0.451	0.300	1.176	0.671 ± 0.453	0.052	0.069	0.06 ± 0.012	<LOD	0.172	0.074 ± 0.088
Oxolinic Acid	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Oxytetracycline	0.004	0.138	0.216	0.179 ± 0.039	0.129	0.277	0.206 ± 0.074	0.062	0.075	0.068 ± 0.009	<LOD	0.084	0.03 ± 0.047
Penicillin G	0.009	<LOD	0.102	0.037 ± 0.056	<LOD	0.163	0.057 ± 0.092	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Pipemidic acid	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Roxithromycin	0.004	0.690	0.991	0.85 ± 0.151	0.122	1.236	0.606 ± 0.571	0.043	0.096	0.07 ± 0.037	<LOD	0.127	0.046 ± 0.07
Silvadene	0.002	<LOD	0.052	0.018 ± 0.029	<LOD	0.047	0.031 ± 0.026	<LOD	0.010	0.005 ± 0.006	<LOD	<LOD	<LOD
Spiramycin	0.008	1.653	4.439	2.735 ± 1.493	1.178	2.513	1.722 ± 0.701	<LOD	0.262	0.133 ± 0.182	<LOD	0.100	0.036 ± 0.055
Sulfabenzamide	0.003	<LOD	0.467	0.157 ± 0.269	<LOD	1.677	0.56 ± 0.967	<LOD	<LOD	<LOD	<LOD	0.975	0.326 ± 0.562
Sulfadimethoxine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfadimidine	0.002	<LOD	0.054	0.018 ± 0.03	<LOD	0.097	0.033 ± 0.055	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

Table S6. *(continued)*

		HWW			INF			MBRperm			EFF		
Compound	**LOD (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Sulfafurazole	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfaguanidine	0.001	<LOD	0.226	0.076 ± 0.13	<LOD	0.142	0.048 ± 0.082	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfamerazine	0.002	<LOD	1.663	0.555 ± 0.959	<LOD	1.014	0.339 ± 0.585	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfamethizole	0.004	<LOD	0.036	0.013 ± 0.019	<LOD	0.059	0.029 ± 0.029	<LOD	0.042	0.022 ± 0.028	<LOD	<LOD	<LOD
Sulfamethoxazole	0.002	0.198	1.315	0.7 ± 0.567	0.235	1.230	0.614 ± 0.538	0.104	1.371	0.737 ± 0.896	0.023	0.834	0.451 ± 0.407
Sulfamethoxydiazine	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfamethoxypyridazine	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfanilamide	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfaphenazole	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfapyridine	0.002	<LOD	0.018	0.01 ± 0.009	<LOD	0.009	0.004 ± 0.005	<LOD	0.011	0.006 ± 0.007	<LOD	0.025	0.011 ± 0.012
Sulfathiazole	0.002	<LOD	0.209	0.124 ± 0.109	<LOD	0.404	0.211 ± 0.202	<LOD	0.492	0.247 ± 0.347	<LOD	0.216	0.072 ± 0.124
Tinidazole	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Trimethoprim	0.001	0.087	0.541	0.32 ± 0.227	0.093	0.388	0.231 ± 0.149	0.008	0.056	0.032 ± 0.033	0.014	0.074	0.038 ± 0.032
Antifungals													
Sulfacetamide	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Terbinafine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Tiabendazole	0.001	<LOD	0.003	0.001 ± 0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Antihistamines													
Diphenhydramine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.019	0.007 ± 0.01
Promethazine	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Antihypertensives													
Clonidine	0.000	<LOD	0.002	0.001 ± 0.001	<LOD	0.002	0.001 ± 0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Antiparasitics													
Albendazole	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Flubendazole	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Levamisole	0.003	<LOD	0.020	0.008 ± 0.011	<LOD	0.079	0.027 ± 0.045	<LOD	<LOD	<LOD	<LOD	0.011	0.005 ± 0.005
Mebendazole	0.001	<LOD	0.012	0.004 ± 0.007	<LOD	0.006	0.003 ± 0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Praziquantel	0.003	0.028	0.120	0.073 ± 0.046	0.067	0.157	0.098 ± 0.051	0.017	0.030	0.023 ± 0.009	<LOD	0.044	0.026 ± 0.022
Triclabendazole	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Antiseptics													
Nitrofural	0.002	<LOD	0.165	0.056 ± 0.095	<LOD	0.181	0.061 ± 0.104	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Beta-blockers													
Atenolol	0.001	0.330	0.600	0.444 ± 0.14	0.461	0.841	0.653 ± 0.19	0.009	0.011	0.01 ± 0.001	0.005	0.025	0.017 ± 0.011
Bisoprolol	0.003	0.091	0.152	0.12 ± 0.031	0.082	0.165	0.122 ± 0.042	<LOD	<LOD	<LOD	<LOD	0.014	0.008 ± 0.006

Table S6. *(continued)*

		HWW			INF			MBRperm			EFF		
Compound	**LOD (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Metoprolol	0.002	0.007	0.074	0.039 ± 0.033	0.011	0.064	0.038 ± 0.027	0.006	0.063	0.035 ± 0.04	0.037	0.083	0.053 ± 0.026
Calcium channel blockers													
Verapamil	0.001	0.043	0.113	0.078 ± 0.035	0.023	0.039	0.033 ± 0.009	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Diuretics													
Torasemide	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Drug metabolites													
10-Hydroxycarbazepine	0.001	0.329	0.500	0.417 ± 0.085	0.618	0.845	0.708 ± 0.121	0.075	0.078	0.077 ± 0.002	<LOD	<LOD	<LOD
2-NP-AOZ	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
4-Acetylaminoantipyrine	0.002	<LOD	0.083	0.045 ± 0.041	0.021	0.113	0.058 ± 0.048	0.046	0.065	0.055 ± 0.013	0.008	0.062	0.035 ± 0.027
4-FormylAminoAntipyrine	0.001	0.007	0.099	0.057 ± 0.046	0.036	0.134	0.082 ± 0.049	0.050	0.059	0.054 ± 0.006	0.012	0.070	0.035 ± 0.031
6-Acetylmorphine	0.001	0.008	0.009	0.009 ± 0.001	0.011	0.013	0.012 ± 0.001	0.007	0.009	0.008 ± 0.001	0.007	0.013	0.009 ± 0.003
7-Aminoclonazepam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
7-Aminoflunitrazepam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Acetylcodeine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Benzoylecgonine	0.002	0.082	0.338	0.181 ± 0.138	0.268	0.348	0.303 ± 0.041	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Buprenorphine glucuronide	0.004	0.094	0.414	0.244 ± 0.161	0.125	0.500	0.268 ± 0.203	<LOD	<LOD	<LOD	<LOD	0.150	0.051 ± 0.085
Cocaethylene	0.001	<LOD	0.084	0.029 ± 0.048	<LOD	0.040	0.014 ± 0.023	<LOD	<LOD	<LOD	<LOD	0.002	0.001 ± 0.001
Cotinine	0.002	0.445	0.631	0.538 ± 0.093	0.573	0.838	0.684 ± 0.138	0.013	0.015	0.014 ± 0.002	<LOD	0.023	0.012 ± 0.011
Desalkylflurazepam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Ecgonine methyl ester	0.004	<LOD	0.258	0.087 ± 0.148	<LOD	0.029	0.011 ± 0.016	<LOD	0.006	0.004 ± 0.003	<LOD	0.025	0.009 ± 0.013
EDDP	0.001	0.038	0.085	0.054 ± 0.027	0.024	0.067	0.04 ± 0.024	0.009	0.018	0.014 ± 0.006	<LOD	0.017	0.009 ± 0.008
Morphine-6-β-D-glucuronide	0.001	<LOD	0.070	0.039 ± 0.035	<LOD	0.156	0.062 ± 0.083	0.095	0.537	0.316 ± 0.313	<LOD	0.106	0.065 ± 0.056
N-Desmethylclozapine	0.002	<LOD	0.013	0.008 ± 0.006	<LOD	0.010	0.004 ± 0.005	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Norbuprenorphine	0.005	<LOD	0.063	0.032 ± 0.031	0.035	0.059	0.044 ± 0.013	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Norfentanyl	0.001	0.027	0.071	0.043 ± 0.025	0.028	0.085	0.048 ± 0.032	0.035	0.076	0.055 ± 0.029	0.046	0.065	0.056 ± 0.01
Norpethidine	0.002	0.040	0.076	0.058 ± 0.018	0.033	0.074	0.05 ± 0.022	0.021	0.036	0.028 ± 0.011	0.008	0.027	0.02 ± 0.01
Norpropoxyphene	0.002	<LOD	0.024	0.009 ± 0.013	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
O-Desmethyltramadol	0.001	0.083	0.425	0.295 ± 0.185	0.299	0.479	0.413 ± 0.099	0.015	0.436	0.225 ± 0.298	0.020	0.451	0.172 ± 0.242
Ritalinic acid	0.002	0.016	0.228	0.139 ± 0.11	0.019	0.102	0.051 ± 0.044	0.194	0.312	0.253 ± 0.084	<LOD	0.062	0.021 ± 0.035
α-Hydroxyalprazolam	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
α-Hydroxymidazolam	0.001	0.012	0.013	0.013 ± 0.001	0.016	0.017	0.017 ± 0	0.009	0.010	0.01 ± 0.001	0.007	0.009	0.008 ± 0.001
α-Hydroxytriazolam	0.002	<LOD	0.109	0.048 ± 0.056	<LOD	0.042	0.015 ± 0.024	<LOD	0.073	0.037 ± 0.051	<LOD	0.105	0.036 ± 0.06
Hormones													
Fludrocortisone-Acetate	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

Table S6. *(continued)*

		HWW			INF			MBRperm			EFF		
Compound	**LOD (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Flumethasone	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Hydrocortisone	0.002	0.263	0.357	0.304 ± 0.048	0.169	0.263	0.206 ± 0.05	0.074	0.127	0.101 ± 0.038	<LOD	0.063	0.027 ± 0.032
Methylprednisolone	0.005	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Mometasone furoate	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Prednicarbate	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Prednisolone	0.007	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Triamcinolone	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Triamcinolone Acetonide	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.804	0.345 ± 0.413
Illicit drugs													
Cocaine	0.003	<LOD	0.017	0.007 ± 0.009	<LOD	0.040	0.018 ± 0.02	<LOD	0.009	0.005 ± 0.005	<LOD	0.009	0.004 ± 0.004
Ketamine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
MDA	0.004	1.210	1.656	1.43 ± 0.223	1.055	2.293	1.772 ± 0.641	0.514	0.624	0.569 ± 0.078	0.345	0.596	0.464 ± 0.126
MDEA	0.002	0.007	0.117	0.051 ± 0.059	0.003	0.022	0.012 ± 0.009	<LOD	0.033	0.017 ± 0.023	<LOD	0.031	0.013 ± 0.016
MDMA	0.001	0.010	0.198	0.075 ± 0.106	0.018	0.289	0.115 ± 0.151	0.002	0.010	0.006 ± 0.005	<LOD	0.004	0.002 ± 0.002
Phencyclidine	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Plastic additives													
Benzotriazole	0.002	5.254	9.191	7.336 ± 1.978	5.126	10.500	7.632 ± 2.705	0.825	1.528	1.177 ± 0.497	0.678	1.924	1.22 ± 0.639
p-Toluenesulfonamide	0.002	0.054	0.138	0.089 ± 0.044	<LOD	0.133	0.056 ± 0.069	0.012	0.025	0.018 ± 0.009	<LOD	0.084	0.033 ± 0.044
Psychiatric drugs													
Alprazolam	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Amisulpride	0.001	<LOD	0.017	0.006 ± 0.009	0.015	0.037	0.027 ± 0.011	0.018	0.040	0.029 ± 0.015	<LOD	0.049	0.024 ± 0.024
Amitriptyline	0.001	0.012	0.190	0.072 ± 0.102	0.004	0.149	0.054 ± 0.082	<LOD	0.002	0.002 ± 0.001	<LOD	0.033	0.012 ± 0.019
Amoxapine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Bromazepam	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Carbamazepine	0.001	0.091	0.143	0.121 ± 0.027	0.216	0.290	0.258 ± 0.038	0.333	0.456	0.395 ± 0.087	0.307	0.455	0.395 ± 0.078
Chlordiazepoxide	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Chlorprothixene	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Citalopram	0.002	0.027	0.098	0.056 ± 0.038	0.014	0.030	0.024 ± 0.009	0.015	0.023	0.019 ± 0.005	<LOD	0.016	0.01 ± 0.008
Clobazam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Clomipramine	0.002	<LOD	0.036	0.012 ± 0.02	<LOD	0.136	0.046 ± 0.078	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Clonazepam	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Clorazepate	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Clozapine	0.001	<LOD	0.059	0.036 ± 0.031	<LOD	0.019	0.01 ± 0.009	<LOD	0.007	0.004 ± 0.004	0.003	0.014	0.008 ± 0.006
Desipramine	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

Table S6. *(continued)*

		HWW			INF			MBRperm			EFF		
Compound	**LOD (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Desvenlafaxine	0.001	0.019	0.070	0.038 ± 0.028	0.049	0.103	0.07 ± 0.029	0.050	0.073	0.061 ± 0.016	0.011	0.081	0.051 ± 0.036
Dexametasone	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.180	0.061 ± 0.103
Diazepam	0.001	<LOD	0.006	0.002 ± 0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Dothiepin	0.002	<LOD	0.130	0.044 ± 0.074	<LOD	0.104	0.035 ± 0.059	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Doxepin	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Felbamate	0.002	<LOD	0.173	0.058 ± 0.099	<LOD	0.204	0.069 ± 0.118	<LOD	0.049	0.025 ± 0.034	0.010	0.060	0.034 ± 0.025
Fluoxetine	0.002	<LOD	0.017	0.006 ± 0.01	<LOD	0.025	0.014 ± 0.012	<LOD	0.003	<LOD ± 0.001	<LOD	0.012	0.007 ± 0.006
Flupentixol	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Flurazepam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.014	0.005 ± 0.008
Fluvoxamine	0.001	0.020	0.081	0.055 ± 0.031	0.021	0.102	0.067 ± 0.041	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Gabapentin	0.001	1.033	4.981	2.491 ± 2.167	1.991	5.332	3.163 ± 1.88	0.249	0.563	0.406 ± 0.222	0.054	0.262	0.188 ± 0.116
Haloperidol	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Imipramine	0.000	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Lamotrigine	0.001	0.145	0.188	0.171 ± 0.023	0.204	0.362	0.276 ± 0.08	0.355	0.440	0.397 ± 0.06	0.195	0.441	0.332 ± 0.126
Lorazepam	0.002	0.054	0.120	0.086 ± 0.033	0.085	0.112	0.096 ± 0.014	0.089	0.091	0.09 ± 0.001	0.063	0.161	0.118 ± 0.05
Maprotiline	0.001	0.034	0.082	0.051 ± 0.027	0.020	0.062	0.037 ± 0.023	0.011	0.013	0.012 ± 0.002	<LOD	<LOD	<LOD
Medazepam	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Memantine	0.002	0.010	0.018	0.012 ± 0.004	0.010	0.043	0.024 ± 0.017	0.024	0.052	0.038 ± 0.02	0.021	0.180	0.086 ± 0.084
Mianserin	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Mirtazapine	0.002	0.011	0.018	0.014 ± 0.004	0.010	0.019	0.014 ± 0.004	0.008	0.013	0.011 ± 0.003	<LOD	<LOD	<LOD
Naltrexone	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Nitrazepam	0.003	<LOD	0.048	0.031 ± 0.025	<LOD	0.060	0.035 ± 0.03	<LOD	0.026	0.014 ± 0.018	<LOD	0.014	0.006 ± 0.007
Nordiazepam	0.001	<LOD	<LOD	<LOD	<LOD	0.004	0.002 ± 0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Nortriptyline	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Olanzapine	0.003	<LOD	0.072	0.037 ± 0.035	<LOD	0.054	0.029 ± 0.026	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Opipramol	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Oxazepam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Oxcarbazepine	0.002	<LOD	0.019	0.01 ± 0.009	<LOD	0.028	0.019 ± 0.015	0.040	0.085	0.063 ± 0.032	0.032	0.095	0.073 ± 0.035
Paliperidone	0.001	<LOD	0.158	0.053 ± 0.091	<LOD	0.114	0.039 ± 0.066	<LOD	0.005	0.003 ± 0.003	<LOD	<LOD	<LOD
Paroxetine	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Phenazepam	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Phenytoin	0.005	0.034	0.062	0.045 ± 0.015	0.034	0.107	0.081 ± 0.041	0.062	0.105	0.083 ± 0.03	0.018	0.407	0.175 ± 0.205
Pipamperone	0.002	<LOD	0.009	0.004 ± 0.004	<LOD	0.009	0.004 ± 0.005	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Prazepam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Promazine	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

Table S6. *(continued)*

		HWW			INF			MBRperm			EFF		
Compound	**LOD (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Protriptyline	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Quetiapine	0.001	0.020	0.048	0.029 ± 0.016	0.010	0.040	0.022 ± 0.016	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Risperidone	0.001	<LOD	0.098	0.035 ± 0.055	<LOD	0.127	0.043 ± 0.073	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Secobarbital	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sertraline	0.003	<LOD	0.006	0.003 ± 0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Temazepam	0.002	<LOD	0.032	0.011 ± 0.018	<LOD	0.048	0.022 ± 0.024	0.012	0.017	0.014 ± 0.004	0.017	0.020	0.019 ± 0
Topiramate	0.002	<LOD	0.054	0.019 ± 0.03	<LOD	0.032	0.011 ± 0.018	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Trazodone	0.002	0.022	0.041	0.033 ± 0.01	0.025	0.039	0.03 ± 0.008	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Triazolam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Trimipramine	0.003	<LOD	0.249	0.084 ± 0.143	<LOD	0.058	0.02 ± 0.033	<LOD	0.035	0.018 ± 0.024	<LOD	0.054	0.019 ± 0.03
Venlafaxine	0.001	0.018	0.080	0.042 ± 0.033	0.031	0.119	0.069 ± 0.046	0.041	0.099	0.07 ± 0.041	0.032	0.106	0.066 ± 0.037
Zolpidem	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Zopiclone	0.004	<LOD	0.032	0.012 ± 0.017	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Receptor antagonists													
Atropine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Flumazenil	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Stimulants													
Amphetamine	0.002	0.246	11.258	6.641 ± 5.717	0.301	1.634	0.991 ± 0.667	0.206	0.547	0.377 ± 0.241	0.045	0.365	0.225 ± 0.164
Caffeine	0.002	2.037	2.619	2.291 ± 0.298	2.312	3.125	2.641 ± 0.428	0.793	1.133	0.963 ± 0.24	0.268	2.065	1.021 ± 0.933
Cannabinol	0.005	<LOD	<LOD	<LOD	0.008	0.024	0.015 ± 0.008	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Methadone	0.003	<LOD	0.085	0.03 ± 0.048	<LOD	0.056	0.02 ± 0.032	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Methamphetamine	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Methylphenidate	0.004	0.016	0.018	0.017 ± 0.001	<LOD	0.023	0.013 ± 0.011	<LOD	0.015	0.009 ± 0.009	<LOD	0.050	0.026 ± 0.024
Phentermine	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
THC	0.003	0.017	0.110	0.052 ± 0.051	0.037	0.247	0.118 ± 0.113	<LOD	<LOD	<LOD	<LOD	0.026	0.016 ± 0.013
UV filters													
Octyl methoxycinnamate	0.002	0.058	0.109	0.079 ± 0.027	0.108	0.220	0.154 ± 0.059	<LOD	0.009	0.005 ± 0.006	<LOD	0.040	0.014 ± 0.023
Veterinary drugs													
Carprofen	0.002	<LOD	0.135	0.046 ± 0.078	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Diaveridine	0.002	0.357	0.526	0.415 ± 0.096	0.303	0.582	0.449 ± 0.14	0.036	0.040	0.038 ± 0.003	0.041	0.061	0.048 ± 0.011
Difloxacin	0.004	<LOD	0.006	<LOD ± 0.002	<LOD	0.014	0.008 ± 0.006	<LOD	<LOD	<LOD	<LOD	0.255	0.086 ± 0.146
Dimetridazole	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Enrofloxacin	0.002	<LOD	0.010	0.006 ± 0.005	<LOD	0.003	<LOD ± 0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Flunixin	0.002	<LOD	0.017	0.01 ± 0.008	<LOD	0.022	0.013 ± 0.011	<LOD	0.029	0.015 ± 0.02	<LOD	0.066	0.039 ± 0.034

Table S6. *(continued)*

		HWW			INF			MBRperm			EFF		
Compound	**LOD (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Furaltadone	0.003	0.038	0.105	0.075 ± 0.034	0.039	0.111	0.085 ± 0.04	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Ipronidazole	0.001	<LOD	0.006	0.002 ± 0.003	<LOD	0.002	<LOD ± 0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Marbofloxacin	0.004	0.390	0.861	0.549 ± 0.27	0.327	0.531	0.442 ± 0.105	0.011	0.536	0.273 ± 0.371	<LOD	0.418	0.175 ± 0.217
Monensin	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Orbifloxacin	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Oxibendazole	0.001	<LOD	0.004	0.002 ± 0.002	<LOD	0.005	0.002 ± 0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Ronidazole	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Salinomycin	0.008	<LOD	0.552	0.187 ± 0.317	<LOD	0.500	0.169 ± 0.286	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sarafloxacin	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfachlorpyridazine	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfaclozine	0.001	<LOD	<LOD	<LOD	<LOD	0.076	0.026 ± 0.043	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfadoxine	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfamonomethoxine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfanitran	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfaquinoxaline	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Tilmicosin	0.004	<LOD	0.335	0.113 ± 0.192	<LOD	0.178	0.061 ± 0.102	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
X-Ray contrast media													
Iopromide	0.001	0.294	3.300	1.632 ± 1.53	0.221	3.644	2.418 ± 1.907	<LOD	0.079	0.04 ± 0.056	<LOD	<LOD	<LOD

Table S7. Minimum, maximum and average concentration (µg/L) of the 232 OMPs analysed in hospital wastewater (HWW) (n=8), WWTP influent (INF) (n=9), MBR permeate (MBRperm) (n=9) and WWTP effluent (EFF) (n=9) during the *0.1PAC* treatment, that is, MBR coupled to 0.1 g/L of PAC added inside the bioreactor. Compounds are divided according to their class and the limit of detection (LOD) for each compound is reported.

		HWW			INF			MBRperm			EFF		
Compound	**LOD (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Analgesics/anti-inflammatories													
Acetaminophen	0.005	0.134	6.261	5.122 ± 2.031	0.095	6.759	5.442 ± 2.035	0.021	0.060	0.038 ± 0.014	<LOD	0.065	0.038 ± 0.019
Acetylsalicylic acid	0.003	0.476	1.212	0.703 ± 0.23	0.431	0.772	0.662 ± 0.107	0.061	0.443	0.287 ± 0.128	0.126	0.547	0.245 ± 0.144
Alfentanil	0.001	<LOD	0.040	0.009 ± 0.014	<LOD	0.065	0.01 ± 0.021	<LOD	0.052	0.006 ± 0.017	<LOD	<LOD	<LOD ± 0
Aminopyrine	0.004	<LOD	0.650	0.326 ± 0.233	<LOD	1.139	0.422 ± 0.317	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Betamethasone dipropionate	0.003	0.010	0.019	0.014 ± 0.003	<LOD	0.018	0.011 ± 0.006	<LOD	<LOD	<LOD	<LOD	0.028	0.004 ± 0.009
Buprenorphine	0.001	<LOD	0.114	0.064 ± 0.044	<LOD	0.180	0.097 ± 0.066	<LOD	0.019	0.01 ± 0.008	<LOD	0.046	0.02 ± 0.017
Carisoprodol	0.003	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Codeine	0.002	0.186	0.382	0.285 ± 0.066	0.211	0.407	0.304 ± 0.067	<LOD	0.023	0.006 ± 0.007	<LOD	0.023	0.006 ± 0.008
Dextromethorphan	0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Dextropropoxyphene	0.005	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Diclofenac	0.001	0.054	0.207	0.11 ± 0.054	0.050	15.491	1.89 ± 5.101	0.058	0.258	0.17 ± 0.071	0.036	0.188	0.11 ± 0.046
Etodolac	0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Fentanyl	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Hydrocodone	0.002	0.165	0.356	0.261 ± 0.063	0.190	0.380	0.278 ± 0.063	<LOD	0.013	0.007 ± 0.005	<LOD	0.009	0.004 ± 0.003
Hydromorphone	0.002	0.088	0.350	0.157 ± 0.081	0.087	0.327	0.163 ± 0.078	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Ibuprofen	0.002	0.621	1.092	0.769 ± 0.163	0.102	0.928	0.678 ± 0.331	0.052	0.081	0.067 ± 0.011	0.021	0.121	0.087 ± 0.029
Ketoprofen	0.004	1.136	2.340	1.74 ± 0.4	1.226	2.296	1.781 ± 0.335	<LOD	0.414	0.235 ± 0.129	<LOD	0.054	0.03 ± 0.021
Lidocaine	0.001	0.133	0.403	0.24 ± 0.094	0.144	0.384	0.253 ± 0.087	0.029	0.273	0.159 ± 0.085	<LOD	0.263	0.149 ± 0.082
Meloxicam	0.002	<LOD	0.002	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Morphine	0.002	0.088	0.350	0.157 ± 0.081	0.087	0.327	0.163 ± 0.078	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Naproxen	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Oxycodone	0.002	0.010	0.050	0.032 ± 0.012	<LOD	0.044	0.023 ± 0.016	<LOD	0.019	0.007 ± 0.007	<LOD	0.020	0.008 ± 0.007
Oxymorphone	0.002	0.025	0.066	0.042 ± 0.012	<LOD	0.078	0.04 ± 0.024	<LOD	0.028	0.01 ± 0.009	<LOD	0.012	0.005 ± 0.005
Pentazocine	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Pethidine	0.001	<LOD	0.008	0.002 ± 0.003	<LOD	0.010	0.003 ± 0.004	<LOD	0.009	0.002 ± 0.003	<LOD	0.021	0.004 ± 0.007
Phenylbutazone	0.002	<LOD	0.019	0.005 ± 0.008	<LOD	0.015	0.002 ± 0.005	<LOD	0.016	0.003 ± 0.005	<LOD	0.017	0.004 ± 0.007
Procaine	0.001	0.005	0.235	0.063 ± 0.079	<LOD	0.135	0.049 ± 0.053	<LOD	0.009	0.005 ± 0.004	<LOD	0.010	0.004 ± 0.004
Tolfenamic acid	0.001	<LOD	0.007	0.001 ± 0.002	<LOD	0.007	0.001 ± 0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Tramadol	0.001	0.242	0.421	0.303 ± 0.061	0.230	0.478	0.314 ± 0.075	0.043	0.353	0.208 ± 0.098	0.040	0.367	0.251 ± 0.097

Table S7. *(continued)*

		HWW			INF			MBRperm			EFF		
Compound	**LOD (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Antiarrhythmic agents													
Amiodarone	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.005	<LOD ± 0.001	<LOD	0.005	<LOD ± 0.001
Digitoxin	0.006	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Propafenone	0.001	0.018	0.096	0.046 ± 0.03	0.019	0.069	0.037 ± 0.016	<LOD	0.009	0.002 ± 0.003	<LOD	0.021	0.006 ± 0.007
Strophanthidin	0.004	<LOD	<LOD	<LOD	<LOD	0.069	0.009 ± 0.022	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Strophanthin	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.038	0.006 ± 0.012	<LOD	<LOD	<LOD
Antibiotics													
Amoxicillin	0.002	0.067	0.166	0.1 ± 0.032	<LOD	0.219	0.089 ± 0.056	<LOD	0.057	0.036 ± 0.017	<LOD	0.055	0.026 ± 0.02
Azithromycin	0.003	1.379	6.820	4.31 ± 1.653	2.061	4.961	3.424 ± 0.971	0.026	0.235	0.093 ± 0.067	0.030	0.321	0.125 ± 0.092
Cinoxacin	0.001	<LOD	0.002	<LOD ± 0.001	<LOD	0.007	0.001 ± 0.002	<LOD	0.008	0.002 ± 0.003	<LOD	0.007	0.002 ± 0.003
Ciprofloxacin	0.003	1.040	2.884	2.237 ± 0.606	1.186	2.834	1.79 ± 0.54	0.140	0.699	0.423 ± 0.202	0.146	0.653	0.397 ± 0.164
Clarithromycin	0.002	0.013	0.562	0.248 ± 0.162	0.026	0.498	0.185 ± 0.141	<LOD	0.022	0.012 ± 0.006	<LOD	0.075	0.028 ± 0.028
Doxycycline	0.001	0.353	2.533	1.308 ± 0.753	<LOD	1.947	0.899 ± 0.531	<LOD	0.568	0.316 ± 0.204	0.055	0.680	0.4 ± 0.2
Enoxacin	0.003	<LOD	0.179	0.024 ± 0.063	<LOD	0.224	0.026 ± 0.074	<LOD	0.013	<LOD ± 0.004	<LOD	<LOD	<LOD
Erythromycin	0.003	0.106	0.849	0.39 ± 0.246	<LOD	1.441	0.366 ± 0.423	<LOD	0.108	0.035 ± 0.042	<LOD	0.216	0.07 ± 0.069
Flumequine	0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Furazolidon	0.002	<LOD	<LOD	<LOD ± 0	<LOD	0.010	0.002 ± 0.003	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Lomefloxacin	0.002	<LOD	0.185	0.114 ± 0.06	<LOD	0.156	0.105 ± 0.061	<LOD	0.103	0.052 ± 0.038	<LOD	0.098	0.061 ± 0.035
Metronidazole	0.001	<LOD	0.883	0.255 ± 0.304	0.022	0.387	0.15 ± 0.111	0.041	0.098	0.079 ± 0.016	0.048	0.144	0.077 ± 0.031
Minocycline	0.003	0.174	0.473	0.283 ± 0.101	<LOD	0.458	0.26 ± 0.163	<LOD	0.057	0.018 ± 0.025	<LOD	0.041	0.01 ± 0.017
Nalidixic Acid	0.004	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.012	<LOD ± 0.003
Norfloxacin	0.002	0.023	0.122	0.065 ± 0.034	<LOD	0.141	0.048 ± 0.044	<LOD	0.021	0.007 ± 0.008	<LOD	0.013	0.003 ± 0.004
Ofloxacin	0.004	0.700	2.485	1.527 ± 0.53	0.745	1.922	1.479 ± 0.381	0.347	1.425	0.962 ± 0.406	0.428	1.504	1.063 ± 0.34
Oleandomycin	0.002	0.031	1.057	0.716 ± 0.329	<LOD	0.962	0.659 ± 0.375	<LOD	0.101	0.039 ± 0.035	<LOD	0.179	0.067 ± 0.059
Oxolinic Acid	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Oxytetracycline	0.004	<LOD	0.600	0.155 ± 0.189	<LOD	0.315	0.105 ± 0.114	<LOD	0.225	0.068 ± 0.076	<LOD	0.157	0.056 ± 0.057
Penicillin G	0.009	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Pipemidic acid	0.003	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Roxithromycin	0.004	0.108	0.836	0.527 ± 0.287	0.430	0.715	0.576 ± 0.094	<LOD	0.127	0.041 ± 0.041	<LOD	0.231	0.062 ± 0.089
Silvadene	0.002	<LOD	1.167	0.309 ± 0.496	<LOD	1.075	0.18 ± 0.368	<LOD	0.243	0.032 ± 0.079	<LOD	0.456	0.052 ± 0.152
Spiramycin	0.008	<LOD	3.275	1.607 ± 1.456	<LOD	2.668	0.927 ± 1.161	<LOD	0.249	0.048 ± 0.083	<LOD	0.123	0.027 ± 0.046
Sulfabenzamide	0.003	<LOD	1.524	0.926 ± 0.461	<LOD	1.569	0.814 ± 0.662	<LOD	1.338	0.773 ± 0.585	<LOD	1.697	0.878 ± 0.583
Sulfadimethoxine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfadimidine	0.002	<LOD	0.060	0.013 ± 0.023	<LOD	0.073	0.015 ± 0.029	<LOD	0.044	0.009 ± 0.015	<LOD	0.020	0.003 ± 0.006

Table S7. *(continued)*

		HWW			INF			MBRperm			EFF		
Compound	**LOD (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Sulfafurazole	0.004	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfaguanidine	0.001	<LOD	0.116	0.042 ± 0.057	<LOD	0.132	0.037 ± 0.055	<LOD	0.009	0.002 ± 0.003	<LOD	<LOD	<LOD ± 0
Sulfamerazine	0.002	<LOD	1.766	0.228 ± 0.621	<LOD	1.370	0.156 ± 0.455	<LOD	0.051	0.007 ± 0.017	<LOD	<LOD	<LOD
Sulfamethizole	0.004	<LOD	0.132	0.018 ± 0.046	<LOD	0.087	0.011 ± 0.028	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfamethoxazole	0.002	0.151	0.920	0.459 ± 0.24	0.108	0.725	0.412 ± 0.187	0.047	0.564	0.25 ± 0.185	0.043	0.536	0.139 ± 0.153
Sulfamethoxydiazine	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.028	0.007 ± 0.011	<LOD	<LOD	<LOD
Sulfamethoxypyridazine	0.001	<LOD	0.055	0.007 ± 0.019	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfanilamide	0.003	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Sulfaphenazole	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfapyridine	0.002	0.007	0.119	0.057 ± 0.043	0.017	0.127	0.057 ± 0.034	<LOD	0.013	0.005 ± 0.006	<LOD	0.014	0.004 ± 0.005
Sulfathiazole	0.002	<LOD	0.361	0.194 ± 0.169	<LOD	0.441	0.207 ± 0.202	<LOD	0.571	0.195 ± 0.211	<LOD	0.499	0.182 ± 0.191
Tinidazole	0.002	<LOD	1.208	0.152 ± 0.427	<LOD	1.567	0.175 ± 0.522	<LOD	0.081	0.01 ± 0.027	<LOD	<LOD	<LOD
Trimethoprim	0.001	0.080	0.305	0.188 ± 0.075	0.081	0.324	0.19 ± 0.071	0.007	0.069	0.033 ± 0.023	0.008	0.388	0.068 ± 0.121
Antifungals													
Sulfacetamide	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Terbinafine	0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Tiabendazole	0.001	<LOD	<LOD	<LOD ± 0	<LOD	0.003	<LOD ± 0.001	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Antihistamines													
Diphenhydramine	0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Promethazine	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Antihypertensives													
Clonidine	0.000	<LOD	0.002	0.001 ± 0.001	<LOD	0.002	0.001 ± 0.001	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Antiparasitics													
Albendazole	0.001	<LOD	1.972	0.28 ± 0.687	<LOD	0.031	0.006 ± 0.01	<LOD	0.005	<LOD ± 0.002	<LOD	<LOD	<LOD ± 0
Flubendazole	0.003	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Levamisole	0.003	<LOD	0.146	0.037 ± 0.062	<LOD	0.101	0.022 ± 0.041	<LOD	0.011	<LOD ± 0.003	<LOD	0.043	0.007 ± 0.014
Mebendazole	0.001	<LOD	1.489	0.192 ± 0.524	<LOD	0.031	0.004 ± 0.01	<LOD	0.006	0.001 ± 0.002	<LOD	0.014	0.002 ± 0.005
Praziquantel	0.003	<LOD	0.152	0.034 ± 0.054	<LOD	0.172	0.06 ± 0.063	<LOD	0.017	0.005 ± 0.006	<LOD	0.023	0.006 ± 0.009
Triclabendazole	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Nitrofural	0.002	<LOD	1.453	0.183 ± 0.513	<LOD	1.686	0.188 ± 0.562	<LOD	2.235	0.249 ± 0.745	<LOD	2.415	0.269 ± 0.805
Beta-blockers													
Atenolol	0.001	0.397	0.595	0.525 ± 0.07	0.414	0.721	0.61 ± 0.102	0.010	0.023	0.016 ± 0.004	<LOD	0.059	0.02 ± 0.018
Bisoprolol	0.003	0.071	0.132	0.107 ± 0.019	0.089	0.150	0.119 ± 0.021	<LOD	0.024	0.009 ± 0.008	<LOD	0.061	0.015 ± 0.019
Metoprolol	0.002	0.034	0.066	0.045 ± 0.011	<LOD	0.077	0.036 ± 0.022	0.022	0.089	0.053 ± 0.02	0.011	0.102	0.058 ± 0.034

Table S7. *(continued)*

Compound	LOD (µg/L)	HWW			INF			MBRperm			EFF		
		Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)
Calcium channel blockers													
Verapamil	0.001	<LOD	0.107	0.055 ± 0.048	<LOD	0.112	0.07 ± 0.036	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Diuretics													
Torasemide	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Drug metabolites													
10-Hydroxycarbazepine	0.001	0.329	1.663	1.024 ± 0.482	<LOD	1.503	0.825 ± 0.504	<LOD	0.345	0.166 ± 0.091	<LOD	0.394	0.136 ± 0.14
2-NP-AOZ	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
4-Acetylaminoantipyrine	0.002	<LOD	0.143	0.054 ± 0.051	0.014	0.176	0.057 ± 0.053	0.022	0.187	0.061 ± 0.053	0.013	0.103	0.043 ± 0.033
4-FormylAminoAntipyrine	0.001	<LOD	0.147	0.052 ± 0.046	0.019	0.127	0.058 ± 0.041	0.022	0.135	0.047 ± 0.038	<LOD	0.079	0.035 ± 0.027
6-Acetylmorphine	0.001	0.007	0.019	0.011 ± 0.004	<LOD	0.015	0.009 ± 0.006	<LOD	0.006	0.002 ± 0.002	<LOD	<LOD	<LOD
7-Aminoclonazepam	0.001	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
7-Aminoflunitrazepam	0.001	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Acetylcodeine	0.002	<LOD	0.017	0.01 ± 0.005	<LOD	0.019	0.009 ± 0.007	<LOD	0.010	0.005 ± 0.004	<LOD	0.012	0.004 ± 0.005
Benzoylecgonine	0.002	0.071	0.375	0.236 ± 0.12	0.104	0.379	0.257 ± 0.095	<LOD	0.010	0.004 ± 0.004	<LOD	0.017	0.005 ± 0.007
Buprenorphine glucuronide	0.004	<LOD	0.216	0.029 ± 0.076	<LOD	0.528	0.093 ± 0.19	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Cocaethylene	0.001	<LOD	0.083	0.035 ± 0.038	<LOD	0.111	0.035 ± 0.04	<LOD	0.006	0.001 ± 0.002	<LOD	<LOD	<LOD
Cotinine	0.002	0.538	0.701	0.63 ± 0.045	0.576	0.750	0.691 ± 0.055	0.007	0.043	0.018 ± 0.011	<LOD	0.033	0.016 ± 0.01
Desalkylflurazepam	0.001	<LOD	0.006	0.001 ± 0.002	<LOD	0.006	0.001 ± 0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Ecgonine methyl ester	0.004	<LOD	0.365	0.065 ± 0.122	<LOD	0.170	0.049 ± 0.063	<LOD	0.025	0.006 ± 0.009	<LOD	0.078	0.01 ± 0.026
EDDP	0.001	0.013	0.047	0.03 ± 0.011	0.013	0.037	0.026 ± 0.008	<LOD	0.010	0.007 ± 0.004	<LOD	0.018	0.009 ± 0.006
Morphine-6-ß-D-glucuronide	0.001	<LOD	0.153	0.053 ± 0.066	<LOD	0.143	0.023 ± 0.049	<LOD	0.073	0.009 ± 0.024	<LOD	0.201	0.023 ± 0.067
N-Desmethylclozapine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Norbuprenorphine	0.005	<LOD	0.576	0.102 ± 0.194	<LOD	1.139	0.162 ± 0.371	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Norfentanyl	0.001	0.014	0.105	0.033 ± 0.03	0.009	0.036	0.027 ± 0.01	<LOD	0.049	0.022 ± 0.013	<LOD	0.068	0.032 ± 0.022
Norpethidine	0.002	0.016	0.041	0.029 ± 0.01	<LOD	0.040	0.025 ± 0.012	<LOD	0.014	0.008 ± 0.005	<LOD	0.024	0.012 ± 0.009
Norpropoxyphene	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
O-Desmethyltramadol	0.001	0.075	0.355	0.145 ± 0.095	0.108	0.414	0.259 ± 0.101	0.017	0.393	0.094 ± 0.123	0.011	0.389	0.102 ± 0.143
Ritalinic acid	0.002	<LOD	0.123	0.018 ± 0.043	<LOD	0.108	0.021 ± 0.036	<LOD	0.297	0.042 ± 0.096	<LOD	0.153	0.038 ± 0.054
α-Hydroxyalprazolam	0.003	<LOD	0.018	0.003 ± 0.006	<LOD	0.024	0.004 ± 0.007	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
α-Hydroxymidazolam	0.001	0.008	0.052	0.02 ± 0.016	0.008	0.043	0.017 ± 0.011	0.003	0.018	0.008 ± 0.005	<LOD	0.015	0.007 ± 0.004
α-Hydroxytriazolam	0.002	<LOD	<LOD	<LOD ± 0	<LOD	0.013	0.002 ± 0.004	<LOD	0.013	0.002 ± 0.004	<LOD	<LOD	<LOD
Hormones													
Fludrocortisone-Acetate	0.004	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Flumethasone	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

Table S7. *(continued)*

		HWW			INF			MBRperm			EFF		
Compound	**LOD (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Hydrocortisone	0.002	<LOD	0.295	0.135 ± 0.11	<LOD	0.438	0.133 ± 0.165	<LOD	0.104	0.036 ± 0.041	<LOD	0.122	0.035 ± 0.049
Methylprednisolone	0.005	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Mometasone furoate	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Prednicarbate	0.004	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Prednisolone	0.007	<LOD	0.090	0.014 ± 0.031	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Triamcinolone	0.001	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Triamcinolone Acetonide	0.002	<LOD	0.155	0.06 ± 0.07	<LOD	0.215	0.062 ± 0.08	<LOD	0.331	0.103 ± 0.128	<LOD	1.297	0.216 ± 0.429
Illicit drugs													
Cocaine	0.003	<LOD	0.053	0.021 ± 0.024	<LOD	0.073	0.027 ± 0.028	<LOD	0.006	<LOD ± 0.002	<LOD	0.019	0.003 ± 0.006
Ketamine	0.002	<LOD	0.021	0.006 ± 0.008	<LOD	0.018	0.005 ± 0.007	<LOD	0.014	0.003 ± 0.005	<LOD	0.013	0.003 ± 0.005
MDA	0.004	0.054	2.234	1.013 ± 0.872	0.075	1.725	1.171 ± 0.581	<LOD	0.557	0.235 ± 0.194	<LOD	0.482	0.164 ± 0.187
MDEA	0.002	<LOD	0.026	0.016 ± 0.009	<LOD	0.033	0.012 ± 0.014	<LOD	0.033	0.009 ± 0.011	<LOD	0.036	0.014 ± 0.014
MDMA	0.001	<LOD	0.031	0.007 ± 0.01	<LOD	0.134	0.035 ± 0.051	<LOD	0.023	0.005 ± 0.008	<LOD	0.017	0.004 ± 0.005
Phencyclidine	0.004	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Plastic additives													
Benzotriazole	0.002	2.581	8.235	4.103 ± 1.839	1.678	9.794	3.844 ± 2.479	0.543	2.797	1.623 ± 0.738	0.477	2.745	1.704 ± 0.753
p-Toluenesulfonamide	0.002	<LOD	0.386	0.094 ± 0.126	<LOD	0.233	0.053 ± 0.075	<LOD	0.295	0.071 ± 0.124	<LOD	0.373	0.081 ± 0.13
Psychiatric drugs													
Alprazolam	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Amisulpride	0.001	<LOD	0.080	0.022 ± 0.028	<LOD	0.937	0.219 ± 0.407	<LOD	0.106	0.015 ± 0.034	<LOD	0.111	0.015 ± 0.036
Amitriptyline	0.001	<LOD	0.106	0.018 ± 0.036	<LOD	0.016	0.004 ± 0.005	<LOD	0.018	0.003 ± 0.006	<LOD	0.030	0.006 ± 0.011
Amoxapine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Bromazepam	0.002	<LOD	<LOD	<LOD	<LOD	0.490	0.055 ± 0.163	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Carbamazepine	0.001	0.120	0.264	0.166 ± 0.054	0.116	0.273	0.205 ± 0.054	0.028	0.299	0.185 ± 0.101	0.018	0.302	0.188 ± 0.088
Chlordiazepoxide	0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Chlorprothixene	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Citalopram	0.002	0.020	0.032	0.026 ± 0.005	0.016	0.054	0.028 ± 0.012	<LOD	0.014	0.006 ± 0.005	<LOD	0.022	0.008 ± 0.008
Clobazam	0.001	<LOD	0.005	0.001 ± 0.001	<LOD	<LOD	<LOD ± 0	<LOD	0.012	0.002 ± 0.004	<LOD	0.011	0.002 ± 0.003
Clomipramine	0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Clonazepam	0.002	<LOD	<LOD	<LOD ± 0	<LOD	0.020	0.003 ± 0.006	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Clorazepate	0.003	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Clozapine	0.001	<LOD	0.019	0.009 ± 0.008	<LOD	0.036	0.008 ± 0.012	<LOD	<LOD	<LOD	<LOD	0.009	0.003 ± 0.003
Desipramine	0.004	<LOD	0.170	0.023 ± 0.059	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Desvenlafaxine	0.001	0.027	0.062	0.04 ± 0.014	0.032	0.086	0.06 ± 0.015	0.017	0.081	0.053 ± 0.02	0.012	0.080	0.058 ± 0.02

Table S7. *(continued)*

		HWW			INF			MBRperm			EFF		
Compound	**LOD (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Dexametasone	0.003	<LOD	0.405	0.11 ± 0.172	<LOD	0.304	0.035 ± 0.101	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Diazepam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Dothiepin	0.002	<LOD	0.101	0.032 ± 0.044	<LOD	0.093	0.02 ± 0.038	<LOD	0.025	0.007 ± 0.01	<LOD	0.010	<LOD ± 0.003
Doxepin	0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Felbamate	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Fluoxetine	0.002	<LOD	0.038	0.02 ± 0.01	<LOD	0.029	0.019 ± 0.011	<LOD	0.004	<LOD ± 0.001	<LOD	0.011	0.004 ± 0.004
Flupentixol	0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Flurazepam	0.001	<LOD	<LOD	<LOD	<LOD	0.009	0.001 ± 0.003	<LOD	<LOD	<LOD	<LOD	0.005	<LOD ± 0.001
Fluvoxamine	0.001	0.014	0.103	0.049 ± 0.032	<LOD	0.086	0.039 ± 0.031	<LOD	0.009	0.004 ± 0.004	<LOD	0.029	0.004 ± 0.009
Gabapentin	0.001	0.501	3.608	2.511 ± 0.969	2.905	4.908	3.819 ± 0.658	0.175	0.670	0.361 ± 0.148	0.161	0.654	0.309 ± 0.17
Haloperidol	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Imipramine	0.000	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Lamotrigine	0.001	0.176	0.324	0.267 ± 0.058	0.131	0.435	0.317 ± 0.092	0.060	0.513	0.273 ± 0.157	0.046	0.448	0.274 ± 0.125
Lorazepam	0.002	<LOD	0.119	0.067 ± 0.044	<LOD	0.132	0.083 ± 0.05	<LOD	0.087	0.041 ± 0.039	<LOD	0.087	0.037 ± 0.043
Maprotiline	0.001	0.018	0.043	0.028 ± 0.009	0.010	0.030	0.021 ± 0.007	<LOD	0.009	0.006 ± 0.003	<LOD	0.012	0.007 ± 0.005
Medazepam	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Memantine	0.002	0.003	0.068	0.02 ± 0.021	0.010	0.057	0.028 ± 0.016	0.006	0.062	0.027 ± 0.02	0.009	0.102	0.037 ± 0.034
Mianserin	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Mirtazapine	0.002	<LOD	0.014	0.007 ± 0.005	<LOD	0.019	0.008 ± 0.007	<LOD	0.008	<LOD ± 0.002	<LOD	<LOD	<LOD
Naltrexone	0.002	<LOD	0.024	0.008 ± 0.01	<LOD	0.026	0.008 ± 0.011	<LOD	0.016	0.005 ± 0.006	<LOD	0.018	0.003 ± 0.006
Nitrazepam	0.003	<LOD	0.097	0.049 ± 0.033	<LOD	0.097	0.042 ± 0.04	<LOD	0.077	0.039 ± 0.03	<LOD	0.092	0.032 ± 0.033
Nordiazepam	0.001	<LOD	0.004	<LOD ± 0.001	<LOD	0.002	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Nortriptyline	0.001	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Olanzapine	0.003	<LOD	0.148	0.031 ± 0.052	<LOD	0.069	0.018 ± 0.026	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Opipramol	0.001	<LOD	0.022	0.005 ± 0.009	<LOD	0.017	0.004 ± 0.007	<LOD	0.014	0.003 ± 0.005	<LOD	0.024	0.005 ± 0.008
Oxazepam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Oxcarbazepine	0.002	0.007	0.055	0.028 ± 0.019	<LOD	0.055	0.024 ± 0.02	<LOD	0.063	0.017 ± 0.022	<LOD	0.072	0.032 ± 0.026
Paliperidone	0.001	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Paroxetine	0.003	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Phenazepam	0.003	<LOD	0.426	0.102 ± 0.158	<LOD	0.441	0.061 ± 0.146	<LOD	0.120	0.038 ± 0.056	<LOD	0.111	0.036 ± 0.052
Phenytoin	0.005	0.073	0.210	0.11 ± 0.047	<LOD	0.165	0.113 ± 0.049	<LOD	0.271	0.15 ± 0.079	<LOD	0.259	0.1 ± 0.074
Pipamperone	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Prazepam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Promazine	0.004	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Protriptyline	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

Table S7. *(continued)*

		HWW			INF			MBRperm			EFF		
Compound	**LOD (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Quetiapine	0.001	0.019	0.035	0.026 ± 0.005	0.017	0.034	0.026 ± 0.005	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Risperidone	0.001	<LOD	0.107	0.027 ± 0.042	<LOD	0.115	0.035 ± 0.049	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Secobarbital	0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Sertraline	0.003	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	0.014	<LOD ± 0.004	<LOD	<LOD	<LOD ± 0
Temazepam	0.002	<LOD	0.014	0.008 ± 0.006	<LOD	0.026	0.008 ± 0.009	<LOD	0.012	0.006 ± 0.004	<LOD	0.014	0.005 ± 0.006
Topiramate	0.002	<LOD	<LOD	<LOD	<LOD	0.009	<LOD ± 0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Trazodone	0.002	0.020	0.076	0.037 ± 0.02	0.018	0.084	0.036 ± 0.02	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Triazolam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Trimipramine	0.003	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Venlafaxine	0.001	0.034	0.086	0.059 ± 0.02	0.048	0.102	0.064 ± 0.019	0.010	0.089	0.051 ± 0.028	0.004	0.095	0.052 ± 0.035
Zolpidem	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Zopiclone	0.004	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Receptor antagonists													
Atropine	0.002	<LOD	0.009	<LOD ± 0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Flumazenil	0.004	<LOD	0.016	<LOD ± 0.005	<LOD	0.014	<LOD ± 0.004	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Stimulants													
Amphetamine	0.002	<LOD	0.181	0.12 ± 0.054	0.075	0.275	0.181 ± 0.054	<LOD	0.037	0.019 ± 0.017	<LOD	0.028	0.008 ± 0.011
Caffeine	0.002	2.185	3.976	2.655 ± 0.661	2.177	5.971	3.221 ± 1.468	0.077	1.709	0.797 ± 0.496	0.092	1.753	0.867 ± 0.708
Cannabinol	0.005	<LOD	0.057	0.018 ± 0.018	<LOD	0.016	<LOD ± 0.005	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Methadone	0.003	<LOD	0.041	0.019 ± 0.013	<LOD	0.035	0.016 ± 0.016	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Methamphetamine	0.001	<LOD	0.014	0.002 ± 0.005	<LOD	0.013	0.002 ± 0.004	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Methylphenidate	0.004	<LOD	0.020	0.011 ± 0.008	<LOD	0.018	0.011 ± 0.007	<LOD	<LOD	<LOD	<LOD	0.035	0.007 ± 0.011
Phentermine	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
THC	0.003	<LOD	0.047	0.026 ± 0.018	<LOD	0.109	0.034 ± 0.035	<LOD	<LOD	<LOD ± 0	<LOD	0.018	0.003 ± 0.006
UV filters													
Octyl methoxycinnamate	0.002	0.051	0.110	0.076 ± 0.018	0.079	0.141	0.118 ± 0.022	<LOD	0.008	<LOD ± 0.002	<LOD	0.006	<LOD ± 0.002
Veterinary drugs													
Carprofen	0.002	<LOD	0.042	0.01 ± 0.018	<LOD	0.132	0.03 ± 0.048	<LOD	0.100	0.012 ± 0.033	<LOD	<LOD	<LOD
Diaveridine	0.002	0.344	0.557	0.407 ± 0.07	0.342	0.621	0.463 ± 0.092	<LOD	0.072	0.031 ± 0.021	<LOD	0.067	0.033 ± 0.022
Difloxacin	0.004	<LOD	0.022	0.005 ± 0.007	<LOD	0.014	<LOD ± 0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Dimetridazole	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Enrofloxacin	0.002	<LOD	0.013	0.003 ± 0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Flunixin	0.002	0.011	0.017	0.015 ± 0.002	<LOD	0.021	0.014 ± 0.008	<LOD	0.028	0.024 ± 0.009	<LOD	0.098	0.038 ± 0.033
Furaltadone	0.003	0.063	0.115	0.082 ± 0.017	<LOD	0.097	0.064 ± 0.026	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

Table S7. *(continued)*

		HWW			INF			MBRperm			EFF		
Compound	**LOD (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Ipronidazole	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Marbofloxacin	0.004	<LOD	1.462	0.424 ± 0.518	<LOD	0.777	0.234 ± 0.28	<LOD	0.377	0.12 ± 0.147	<LOD	0.314	0.124 ± 0.133
Monensin	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Orbifloxacin	0.002	<LOD	<LOD	<LOD	<LOD	0.008	<LOD ± 0.002	<LOD	<LOD	<LOD	<LOD	0.008	<LOD ± 0.002
Oxibendazole	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Ronidazole	0.003	<LOD	0.034	0.005 ± 0.012	<LOD	0.029	0.004 ± 0.009	<LOD	0.109	0.013 ± 0.036	<LOD	<LOD	<LOD
Salinomycin	0.008	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Sarafloxacin	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Sulfachlorpyridazine	0.001	<LOD	0.065	0.02 ± 0.027	<LOD	0.049	0.016 ± 0.019	<LOD	0.029	0.006 ± 0.011	<LOD	0.012	0.002 ± 0.004
Sulfaclozine	0.001	<LOD	0.046	0.006 ± 0.016	<LOD	0.045	0.006 ± 0.015	<LOD	0.023	0.003 ± 0.008	<LOD	<LOD	<LOD
Sulfadoxine	0.003	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Sulfamonomethoxine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.006	<LOD ± 0.002	<LOD	<LOD	<LOD
Sulfanitran	0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Sulfaquinoxaline	0.001	<LOD	0.060	0.008 ± 0.021	<LOD	0.152	0.018 ± 0.05	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD ± 0
Tilmicosin	0.004	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
X-Ray contrast media													
Iopromide	0.001	1.104	50.728	15.862 ± 19.349	0.410	44.481	8.855 ± 14.184	<LOD	0.778	0.282 ± 0.246	<LOD	0.826	0.269 ± 0.268

Table S8. Minimum, maximum and average concentration (µg/L) of the 232 OMPs analysed in hospital wastewater (HWW) (n=6), WWTP influent (INF) (n=6) and MBR permeate (MBRperm) (n=6) during the *0.2PAC* treatment, that is, MBR coupled to 0.2 g/L of PAC added inside the bioreactor. Compounds are divided according to their class and the limit of detection (LOD) for each compound is reported.

		HWW			INF			MBRperm		
Compound	**LOD (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**	**Min conc. (µg/L)**	**Max conc. (µg/L)**	**Average conc. (µg/L)**
Analgesics/anti-inflammatories										
Acetaminophen	0.005	4.585	6.504	5.696 ± 0.772	3.895	5.258	4.704 ± 0.509	<LOD	0.054	0.021 ± 0.019
Acetylsalicylic acid	0.003	0.136	0.476	0.252 ± 0.135	0.053	0.369	0.21 ± 0.103	0.044	0.202	0.116 ± 0.058
Alfentanil	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Aminopyrine	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Betamethasone 17,21-dipropionate	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Buprenorphine	0.001	<LOD	0.141	0.099 ± 0.053	<LOD	0.112	0.037 ± 0.056	<LOD	<LOD	<LOD
Carisoprodol	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Codeine	0.002	0.059	0.263	0.195 ± 0.085	0.076	0.191	0.141 ± 0.04	<LOD	0.009	0.003 ± 0.003
Dextromethorphan	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Dextropropoxyphene	0.005	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Diclofenac	0.001	0.026	0.082	0.048 ± 0.022	0.104	0.220	0.154 ± 0.041	0.048	0.114	0.07 ± 0.024
Etodolac	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Fentanyl	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Hydrocodone	0.002	<LOD	0.241	0.111 ± 0.106	<LOD	0.177	0.107 ± 0.065	<LOD	<LOD	<LOD
Hydromorphone	0.002	0.045	0.160	0.096 ± 0.045	0.041	0.143	0.071 ± 0.037	<LOD	<LOD	<LOD
Ibuprofen	0.002	<LOD	0.830	0.197 ± 0.313	0.067	0.518	0.242 ± 0.158	<LOD	0.050	0.034 ± 0.017
Ketoprofen	0.004	0.520	1.895	1.187 ± 0.554	0.659	1.740	1.125 ± 0.387	<LOD	<LOD	<LOD
Lidocaine	0.001	0.105	0.251	0.177 ± 0.058	0.084	0.149	0.121 ± 0.03	<LOD	0.099	0.045 ± 0.036
Meloxicam	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Morphine	0.002	0.045	0.160	0.102 ± 0.043	0.041	0.143	0.074 ± 0.035	<LOD	<LOD	<LOD
Naproxen	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Oxycodone	0.002	<LOD	0.049	0.016 ± 0.021	<LOD	0.029	0.017 ± 0.011	<LOD	0.006	0.003 ± 0.003
Oxymorphone	0.002	<LOD	0.041	0.02 ± 0.015	0.014	0.044	0.022 ± 0.011	<LOD	<LOD	<LOD
Pentazocine	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Pethidine	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Phenylbutazone	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Procaine	0.001	0.006	0.044	0.024 ± 0.018	0.007	0.108	0.038 ± 0.038	<LOD	0.011	0.007 ± 0.004
Tolfenamic acid	0.001	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Tramadol	0.001	0.047	0.452	0.253 ± 0.161	0.210	0.336	0.249 ± 0.048	0.090	0.194	0.139 ± 0.042

Table S8. *(continued)*

Compound	LOD (µg/L)	HWW			INF			MBRperm		
		Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)
Antiarrhythmic agents										
Amiodarone	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Digitoxin	0.006	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Propafenone	0.001	0.019	0.108	0.062 ± 0.04	<LOD	0.062	0.029 ± 0.025	<LOD	0.010	0.002 ± 0.004
Strophanthidin	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Strophanthin	0.004	<LOD	<LOD	<LOD	<LOD	0.203	0.036 ± 0.082	<LOD	<LOD	<LOD
Antibiotics										
Amoxicillin	0.002	<LOD	0.100	0.04 ± 0.035	<LOD	0.057	0.039 ± 0.02	<LOD	<LOD	<LOD
Azithromycin	0.003	1.526	4.235	2.749 ± 1.088	1.064	3.172	1.799 ± 0.837	0.025	0.096	0.056 ± 0.024
Cinoxacin	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Ciprofloxacin	0.003	0.345	1.394	0.836 ± 0.397	0.236	0.775	0.487 ± 0.193	0.029	0.176	0.079 ± 0.052
Clarithromycin	0.002	0.101	0.377	0.244 ± 0.108	0.114	0.291	0.165 ± 0.064	0.010	0.030	0.019 ± 0.008
Doxycycline	0.001	<LOD	<LOD	<LOD	<LOD	0.090	0.016 ± 0.037	<LOD	<LOD	<LOD
Enoxacin	0.003	<LOD	0.653	0.117 ± 0.263	<LOD	0.529	0.089 ± 0.216	<LOD	<LOD	<LOD
Erythromycin	0.003	0.590	0.855	0.698 ± 0.103	<LOD	0.791	0.52 ± 0.31	<LOD	0.152	0.033 ± 0.06
Flumequine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Furazolidon	0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Lomefloxacin	0.002	<LOD	0.077	0.031 ± 0.035	<LOD	0.083	0.032 ± 0.035	<LOD	0.063	0.012 ± 0.025
Metronidazole	0.001	0.059	0.508	0.239 ± 0.17	0.008	0.288	0.075 ± 0.105	0.007	0.030	0.012 ± 0.009
Minocycline	0.003	<LOD	0.261	0.085 ± 0.13	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Nalidixic Acid	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Norfloxacin	0.002	<LOD	0.317	0.081 ± 0.124	<LOD	0.284	0.066 ± 0.115	<LOD	<LOD	<LOD
Ofloxacin	0.004	0.494	1.390	0.816 ± 0.362	0.504	0.849	0.662 ± 0.162	0.037	0.694	0.374 ± 0.225
Oleandomycin	0.002	<LOD	0.338	0.08 ± 0.138	<LOD	0.424	0.091 ± 0.167	<LOD	<LOD	<LOD
Oxolinic Acid	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Oxytetracycline	0.004	<LOD	0.117	0.021 ± 0.047	<LOD	0.033	0.007 ± 0.013	<LOD	<LOD	<LOD
Penicillin G	0.009	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Pipemidic acid	0.003	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Roxithromycin	0.004	<LOD	0.462	0.225 ± 0.155	<LOD	0.427	0.239 ± 0.194	<LOD	0.145	0.036 ± 0.059
Silvadene	0.002	<LOD	<LOD	<LOD ± 0	<LOD	0.012	0.003 ± 0.005	<LOD	<LOD	<LOD
Spiramycin	0.008	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfabenzamide	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfadimethoxine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfadimidine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfafurazole	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

Table S8. *(continued)*

Compound	LOD (µg/L)	HWW			INF			MBRperm		
		Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)
Sulfaguanidine	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfamerazine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfamethizole	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfamethoxazole	0.002	0.267	0.902	0.469 ± 0.233	0.159	0.609	0.326 ± 0.151	0.056	0.241	0.114 ± 0.068
Sulfamethoxydiazine	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfamethoxypyridazine	0.001	<LOD	<LOD	<LOD	<LOD	0.006	0.002 ± 0.002	<LOD	<LOD	<LOD
Sulfanilamide	0.003	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfaphenazole	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfapyridine	0.002	0.035	0.320	0.117 ± 0.111	<LOD	0.211	0.083 ± 0.083	<LOD	0.107	0.03 ± 0.041
Sulfathiazole	0.002	<LOD	0.167	0.078 ± 0.066	<LOD	0.244	0.068 ± 0.107	<LOD	0.184	0.064 ± 0.076
Tinidazole	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Trimethoprim	0.001	0.070	0.388	0.188 ± 0.114	0.065	0.192	0.117 ± 0.049	0.008	0.034	0.016 ± 0.011
Antifungals										
Sulfacetamide	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Terbinafine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Tiabendazole	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Antihistamines										
Diphenhydramine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Promethazine	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Antihypertensives										
Clonidine	0.000	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Antiparasitics										
Albendazole	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Flubendazole	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Levamisole	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Mebendazole	0.001	<LOD	0.006	0.001 ± 0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Praziquantel	0.003	<LOD	0.206	0.076 ± 0.078	<LOD	0.120	0.057 ± 0.061	<LOD	<LOD	<LOD
Triclabendazole	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Antiseptics										
Nitrofural	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Beta-blockers										
Atenolol	0.001	0.196	0.433	0.318 ± 0.098	0.155	0.496	0.331 ± 0.126	<LOD	0.012	0.008 ± 0.004
Bisoprolol	0.003	0.057	0.092	0.071 ± 0.014	0.051	0.079	0.064 ± 0.012	<LOD	0.026	0.005 ± 0.01
Metoprolol	0.002	0.095	0.214	0.164 ± 0.042	0.163	0.221	0.179 ± 0.021	0.056	0.621	0.231 ± 0.197
Calcium channel blockers										

Table S8. *(continued)*

Compound	LOD (µg/L)	HWW			INF			MBRperm		
		Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)
Verapamil	0.001	<LOD	0.030	0.019 ± 0.014	<LOD	0.033	0.02 ± 0.012	<LOD	<LOD	<LOD
Diuretics										
Torasemide	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Drug metabolites										
10-Hydroxycarbazepine	0.001	<LOD	0.374	0.179 ± 0.196	<LOD	0.550	0.213 ± 0.244	<LOD	<LOD	<LOD
2-NP-AOZ	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
4-Acetylaminoantipyrine	0.002	<LOD	0.193	0.052 ± 0.072	<LOD	0.133	0.048 ± 0.049	<LOD	0.086	0.027 ± 0.031
4-FormylAminoAntipyrine	0.001	<LOD	0.073	0.027 ± 0.025	<LOD	0.042	0.021 ± 0.015	<LOD	0.042	0.017 ± 0.015
6-Acetylmorphine	0.001	<LOD	0.686	0.262 ± 0.314	<LOD	0.665	0.186 ± 0.274	<LOD	<LOD	<LOD
7-Aminoclonazepam	0.001	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
7-Aminoflunitrazepam	0.001	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Acetylcodeine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Benzoylecgonine	0.002	0.120	0.421	0.281 ± 0.098	0.137	0.403	0.265 ± 0.086	<LOD	<LOD	<LOD
Buprenorphine glucuronide	0.004	<LOD	0.362	0.185 ± 0.152	<LOD	0.277	0.048 ± 0.112	<LOD	<LOD	<LOD
Cocaethylene	0.001	<LOD	0.099	0.038 ± 0.045	<LOD	0.091	0.028 ± 0.043	<LOD	<LOD	<LOD
Cotinine	0.002	0.424	0.514	0.457 ± 0.041	0.434	0.583	0.501 ± 0.057	<LOD	0.011	0.007 ± 0.004
Desalkylflurazepam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Ecgonine methyl ester	0.004	<LOD	0.485	0.143 ± 0.19	<LOD	0.253	0.064 ± 0.105	<LOD	<LOD	<LOD
EDDP	0.001	<LOD	0.041	0.018 ± 0.015	<LOD	0.022	0.009 ± 0.009	<LOD	<LOD	<LOD ± 0
Morphine-6-β-D-glucuronide	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
N-Desmethylclozapine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Norbuprenorphine	0.005	<LOD	0.071	0.014 ± 0.028	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Norfentanyl	0.001	<LOD	0.055	0.018 ± 0.019	<LOD	0.041	0.013 ± 0.015	<LOD	0.007	0.003 ± 0.003
Norpethidine	0.002	<LOD	0.037	0.017 ± 0.014	<LOD	0.022	0.007 ± 0.008	<LOD	<LOD	<LOD
Norpropoxyphene	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
O-Desmethyltramadol	0.001	0.058	0.436	0.22 ± 0.172	0.108	0.347	0.199 ± 0.102	0.018	0.206	0.099 ± 0.082
Ritalinic acid	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
α-Hydroxyalprazolam	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
α-Hydroxymidazolam	0.001	0.005	0.011	0.007 ± 0.002	0.004	0.011	0.007 ± 0.002	<LOD	0.006	0.002 ± 0
α-Hydroxytriazolam	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Hormones										
Fludrocortisone-Acetate	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Flumethasone	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Hydrocortisone	0.002	<LOD	0.146	0.026 ± 0.059	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD ± 0
Methylprednisolone	0.005	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

Table S8. *(continued)*

Compound	LOD (µg/L)	HWW			INF			MBRperm		
		Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)
Mometasone furoate	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Prednicarbate	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Prednisolone	0.007	<LOD	0.187	0.034 ± 0.075	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Triamcinolone	0.001	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Triamcinolone Acetonide	0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Illicit drugs										
Cocaine	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Ketamine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
MDA	0.004	0.022	0.872	0.173 ± 0.343	<LOD	0.514	0.091 ± 0.207	<LOD	0.195	0.064 ± 0.097
MDEA	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
MDMA	0.001	0.008	0.079	0.031 ± 0.029	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Phencyclidine	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Plastic additives										
Benzotriazole	0.002	1.212	6.654	4.594 ± 2.06	0.891	7.585	4.346 ± 2.417	0.277	4.506	2.486 ± 1.435
p-Toluenesulfonamide	0.002	<LOD	0.126	0.022 ± 0.051	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Psychiatric drugs										
Alprazolam	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Amisulpride	0.001	<LOD	0.012	0.005 ± 0.005	<LOD	0.014	0.009 ± 0.005	<LOD	0.013	0.004 ± 0.005
Amitriptyline	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Amoxapine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Bromazepam	0.002	<LOD	<LOD	<LOD	<LOD	0.006	<LOD ± 0.002	<LOD	<LOD	<LOD
Carbamazepine	0.001	0.043	0.133	0.083 ± 0.039	0.106	0.210	0.139 ± 0.04	0.043	0.142	0.077 ± 0.048
Chlordiazepoxide	0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD ± 0
Chlorprothixene	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Citalopram	0.002	0.023	0.036	0.027 ± 0.005	<LOD	0.036	0.016 ± 0.014	<LOD	<LOD	<LOD
Clobazam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Clomipramine	0.002	<LOD	0.023	0.007 ± 0.009	<LOD	0.024	0.005 ± 0.009	<LOD	<LOD	<LOD
Clonazepam	0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Clorazepate	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Clozapine	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Desipramine	0.004	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Desvenlafaxine	0.001	0.014	0.043	0.025 ± 0.01	0.029	0.057	0.038 ± 0.011	<LOD	0.035	0.019 ± 0.012
Dexametasone	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Diazepam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Dothiepin	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

Table S8. *(continued)*

Compound	LOD (µg/L)	HWW			INF			MBRperm		
		Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)
Doxepin	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Felbamate	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Fluoxetine	0.002	<LOD	0.026	0.016 ± 0.008	<LOD	0.018	0.011 ± 0.006	<LOD	<LOD	<LOD
Flupentixol	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Flurazepam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Fluvoxamine	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Gabapentin	0.001	0.690	5.065	2.803 ± 1.67	1.259	4.793	2.817 ± 1.5	0.075	0.439	0.181 ± 0.137
Haloperidol	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Imipramine	0.000	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD ± 0
Lamotrigine	0.001	0.051	0.147	0.087 ± 0.036	0.136	0.217	0.173 ± 0.032	0.084	0.262	0.149 ± 0.066
Lorazepam	0.002	<LOD	0.166	0.117 ± 0.063	<LOD	0.108	0.045 ± 0.049	<LOD	<LOD	<LOD
Maprotiline	0.001	<LOD	0.039	0.014 ± 0.015	<LOD	0.020	0.007 ± 0.007	<LOD	<LOD	<LOD
Medazepam	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Memantine	0.002	<LOD	0.025	0.013 ± 0.01	<LOD	0.022	0.011 ± 0.007	<LOD	0.014	0.005 ± 0.006
Mianserin	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Mirtazapine	0.002	<LOD	0.014	0.005 ± 0.006	<LOD	0.012	0.003 ± 0.004	<LOD	<LOD	<LOD
Naltrexone	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Nitrazepam	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Nordiazepam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Nortriptyline	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Olanzapine	0.003	<LOD	0.089	0.016 ± 0.036	<LOD	0.064	0.012 ± 0.025	<LOD	<LOD	<LOD
Opipramol	0.001	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Oxazepam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Oxcarbazepine	0.002	<LOD	0.141	0.027 ± 0.056	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Paliperidone	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Paroxetine	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Phenazepam	0.003	<LOD	0.072	0.013 ± 0.029	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Phenytoin	0.005	<LOD	<LOD	<LOD	<LOD	0.036	0.008 ± 0.014	<LOD	<LOD	<LOD
Pipamperone	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Prazepam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Promazine	0.004	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Protriptyline	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Quetiapine	0.001	<LOD	0.023	0.015 ± 0.008	0.007	0.017	0.01 ± 0	<LOD	<LOD	<LOD
Risperidone	0.001	<LOD	0.103	0.018 ± 0.042	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Secobarbital	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sertraline	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

Table S8. *(continued)*

Compound	LOD (µg/L)	HWW			INF			MBRperm		
		Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)
Temazepam	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Topiramate	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Trazodone	0.002	<LOD	0.064	0.027 ± 0.021	<LOD	0.053	0.021 ± 0.018	<LOD	0.012	0.003 ± 0
Triazolam	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Trimipramine	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Venlafaxine	0.001	0.015	0.070	0.031 ± 0.021	0.026	0.070	0.039 ± 0.017	0.014	0.039	0.022 ± 0.01
Zolpidem	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Zopiclone	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Receptor antagonists										
Atropine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Flumazenil	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Stimulants										
Amphetamine	0.002	0.040	0.229	0.118 ± 0.069	0.025	0.202	0.093 ± 0.067	<LOD	0.027	0.005 ± 0.01
Caffeine	0.002	1.652	1.998	1.835 ± 0.139	1.648	1.892	1.759 ± 0.087	0.032	0.056	0.047 ± 0.009
Cannabinol	0.005	<LOD	0.056	0.011 ± 0.022	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Methadone	0.003	<LOD	0.012	0.003 ± 0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Methamphetamine	0.001	<LOD	<LOD	<LOD	<LOD	0.011	0.002 ± 0.004	<LOD	<LOD	<LOD
Methylphenidate	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Phentermine	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
THC	0.003	<LOD	0.041	0.023 ± 0.018	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
UV filters										
Octyl methoxycinnamate	0.002	<LOD	0.064	0.031 ± 0.025	<LOD	0.091	0.039 ± 0.029	<LOD	0.016	0.005 ± 0.006
Veterinary drugs										
Carprofen	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Diaveridine	0.002	<LOD	0.773	0.32 ± 0.262	<LOD	0.657	0.294 ± 0.211	<LOD	0.042	0.025 ± 0.019
Difloxacin	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Dimetridazole	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Enrofloxacin	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Flunixin	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Furaltadone	0.003	<LOD	0.053	0.01 ± 0.021	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Ipronidazole	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Marbofloxacin	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Monensin	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Orbifloxacin	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Oxibendazole	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

Table S8. *(continued)*

Compound	LOD (µg/L)	HWW			INF			MBRperm		
		Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)	Min conc. (µg/L)	Max conc. (µg/L)	Average conc. (µg/L)
Ronidazole	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Salinomycin	0.008	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sarafloxacin	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfachlorpyridazine	0.001	<LOD	0.022	0.004 ± 0.009	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfaclozine	0.001	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfadoxine	0.003	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfamonomethoxine	0.002	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfanitran	0.002	<LOD	<LOD	<LOD ± 0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Sulfaquinoxaline	0.001	<LOD	0.051	0.016 ± 0.023	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Tilmicosin	0.004	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
X-Ray contrast media										
Iopromide	0.001	0.937	35.468	11.742 ± 12.173	0.556	11.893	6.938 ± 3.983	<LOD	0.640	0.17 ± 0.25

Table S9. logK_{ow}, PNEC in freshwater (µg/L) and OPBT scores obtained for all the OMPs during each treatment (noPAC, 0.1PAC and 0.2PAC).

Compound	log K_{ow}	PNEC freshwater (µg/L)	OPBT score		
			noPAC	*0.1PAC*	*0.2PAC*
Analgesics/anti-inflammatories					
Acetaminophen	0.91	134	5	5	5
Acetylsalicylic acid	1.24	18.5	13	10	11
Alfentanil	2.81	0.18	9	10	11
Aminopyrine	1.15	17.6	6	6	8
Betamethasone dipropionate	3.96	2.89	9	9	11
Buprenorphine	3.55	0.23	11	10	10
Carisoprodol	1.92	12.5	11	8	8
Codeine	1.34	7.19	8	7	7
Dextromethorphan	3.49	3.20	12	11	11
Dextropropoxyphene	4.90	0.45	13	13	13
Diclofenac	4.26	0.05	17	17	14
Etodolac	3.44	1.43	11	11	11
Fentanyl	3.82	0.17	12	12	12
Hydrocodone	1.96	3.46	7	7	7
Hydromorphone	1.47	3.64	7	7	7
Ibuprofen	3.84	0.01	12	12	13
Ketoprofen	3.61	2.1	10	11	9
Lidocaine	2.84	4.67	14	13	10
Meloxicam	1.92	0.7	10	10	10
Morphine	0.90	5.38	6	6	6
Naproxen	2.99	1.82	11	10	10
Oxycodone	1.03	8.04	10	8	7
Oxymorphone	0.64	4.58	7	6	6
Pentazocine	3.89	0.51	12	12	12
Pethidine	2.46	19.7	11	10	9
Phenylbutazone	4.14	1.09	14	13	11
Procaine	1.88	3.87	11	11	8
Tolfenamic acid	5.49	0.19	13	11	13
Tramadol	2.45	8.65	14	13	12
Antiarrhythmic agents					
Amiodarone	7.64	0.0011	14	16	14
Digitoxin	3.60	0.88	12	12	12
Propafenone	4.31	0.0036	13	11	12
Strophanthidin	0.87	57.7	7	5	7
Strophanthin	0.55	14.3	7	9	5
Antibiotics					
Amoxicillin	-2.31	0.078	8	10	8
Azithromycin	2.44	0.019	11	11	11
Cinoxacin	1.72	3.69	11	11	9
Ciprofloxacin	-0.86	0.089	11	11	9
Clarithromycin	3.24	0.12	10	11	11
Doxycycline	-2.38	0.46	13	11	7
Enoxacin	-1.02	2.51	6	6	6
Erythromycin	2.60	0.2	11	10	14
Flumequine	2.42	1.5	10	10	10
Furazolidon	0.87	2.5	8	6	8
Lomefloxacin	-0.43	0.83	13	10	10
Metronidazole	-0.46	33.1	7	10	7
Minocycline	-2.06	0.041	8	9	10
Nalidixic Acid	0.79	4.66	11	8	8
Norfloxacin	-0.97	0.78	7	7	7

Table S9. *(continued)*

Compound	log K_{ow}	PNEC freshwater (µg/L)	OPBT score		
			noPAC	*0.1PAC*	*0.2PAC*
Ofloxacin	0.09	0.14	15	13	11
Oleandomycin	2.98	0.87	10	10	9
Oxolinic Acid	1.35	15.0	8	8	6
Oxytetracycline	-3.59	0.32	10	10	7
Penicillin G	1.08	--	11	11	11
Pipemidic acid	-1.80	0.95	9	9	9
Roxithromycin	3.00	0.083	12	11	11
Silvadene	0.39	4.6	7	11	6
Spiramycin	2.50	0.12	11	10	11
Sulfabenzamide	1.59	3.05	9	14	9
Sulfadimethoxine	1.26	1.21	9	9	9
Sulfadimidine	0.65	1.12	8	10	8
Sulfafurazole	0.73	4.63	8	8	8
Sulfaguanidine	-0.92	10.6	5	5	7
Sulfamerazine	0.52	1.12	8	6	8
Sulfamethizole	0.21	1.5	11	6	8
Sulfamethoxazole	0.79	0.6	13	12	10
Sulfamethoxydiazine	0.23	1.03	8	10	8
Sulfamethoxypyridazine	0.47	1.38	8	8	6
Sulfanilamide	-0.25	17.5	7	7	7
Sulfaphenazole	1.81	0.12	10	10	10
Sulfapyridine	1.01	1.83	11	7	9
Sulfathiazole	0.98	1.92	12	12	11
Tinidazole	-0.58	14.6	7	5	7
Trimethoprim	1.28	100	7	7	7
Antifungals					
Sulfacetamide	-0.26	14.3	7	7	7
Terbinafine	5.53	0.011	14	14	14
Tiabendazole	2.33	3.3	10	10	10
Antihistamines					
Diphenhydramine	3.27	0.99	12	12	12
Promethazine	4.29	0.13	12	12	12
Antihypertensives					
Clonidine	2.49	2.83	10	8	10
Antiparasitics					
Albendazole	3.20	0.26	12	10	12
Flubendazole	3.40	0.24	12	12	12
Levamisole	2.36	1.81	8	8	10
Mebendazole	3.26	0.16	12	11	12
Praziquantel	2.30	2.22	10	8	8
Triclabendazole	5.88	0.0071	14	14	14
Antiseptics					
Nitrofural	-0.14	5.29	8	12	8
Beta-blockers					
Atenolol	0.43	150	5	5	4
Bisoprolol	2.20	3.18	8	8	8
Metoprolol	1.76	8.6	11	12	13
Calcium channel blockers					
Verapamil	5.04	2.53	10	10	10
Diuretics					
Torasemide	1.86	0.49	10	10	10
Drug metabolites					

Table S9. *(continued)*

Compound	log K_{ow}	PNEC freshwater (µg/L)	OPBT score		
			noPAC	*0.1PAC*	*0.2PAC*
10-Hydroxycarbazepine	1.73	4.03	8	10	7
2-NP-AOZ	1.72	3.2	9	9	9
4-Acetylaminoantipyrine	0.15	100	10	10	8
4-FormylAminoAntipyrine	0.11	1000	9	9	9
6-Acetylmorphine	1.31	5.19	10	8	7
7-Aminoclonazepam	2.38	0.38	11	11	11
7-Aminoflunitrazepam	1.79	0.98	10	10	10
Acetylcodeine	1.78	1.1	9	9	9
Benzoylecgonine	-0.59	--	8	8	8
Buprenorphine glucuronide	-0.65	0.14	7	7	7
Cocaethylene	2.64	1.55	8	8	8
Cotinine	0.21	10	7	7	6
Desalkylflurazepam	3.35	0.78	12	10	12
Ecgonine methyl ester	-0.21	88.8	6	5	5
EDDP	4.63	0.14	14	12	11
Morphine-6-β-D-glucuronide	-2.98	2.16	12	6	8
N-Desmethylclozapine	3.13	0.054	13	13	13
Norbuprenorphine	2.30	1.06	8	8	10
Norfentanyl	1.42	73	11	11	10
Norpethidine	2.07	29.2	11	8	7
Norpropoxyphene	4.52	4.35	12	12	12
O-Desmethyltramadol	1.72	10.1	10	8	9
Ritalinic acid	-0.36	14.2	11	10	7
α-Hydroxyalprazolam	2.21	0.31	11	9	11
α-Hydroxymidazolam	3.16	0.15	12	12	12
α-Hydroxytriazolam	2.81	0.087	15	14	12
Hormones					
Fludrocortisone-Acetate	1.76	21.4	8	8	8
Flumethasone	1.34	19.4	8	8	8
Hydrocortisone	1.28	28.8	10	9	8
Methylprednisolone	1.56	17.4	8	8	8
Mometasone furoate	5.06	1.26	12	12	12
Prednicarbate	3.83	4.59	11	11	11
Prednisolone	1.27	24.4	8	8	8
Triamcinolone	0.24	25.2	7	7	7
Triamcinolone Acetonide	1.94	14.9	8	12	8
Illicit drugs					
Cocaine	2.30	2.46	9	8	10
Ketamine	3.35	5.71	11	11	11
MDA	1.43	50.3	11	9	11
MDEA	2.22	26	12	11	9
MDMA	1.86	47.6	6	6	8
Phencyclidine	4.49	0.17	12	12	12
Plastic additives					
Benzotriazole	1.26	7.77	11	13	13
p-Toluenesulfonamide	1.09	150	10	10	7
Psychiatric drugs					
Alprazolam	3.02	0.077	13	13	13
Amisulpride	0.25	1.43	11	8	7
Amitriptyline	4.81	0.14	12	11	13
Amoxapine	3.08	0.42	12	12	12
Bromazepam	2.54	0.59	11	9	9
Carbamazepine	2.77	0.05	16	16	13

Table S9. *(continued)*

Compound	log K_{ow}	PNEC freshwater (µg/L)	OPBT score		
			noPAC	*0.1PAC*	*0.2PAC*
Chlordiazepoxide	1.63	0.57	10	10	10
Chlorprothixene	5.07	0.075	14	14	14
Citalopram	3.76	16.0	13	9	8
Clobazam	2.55	1.17	10	12	10
Clomipramine	4.88	0.11	11	13	11
Clonazepam	3.15	0.3	12	10	12
Clorazepate	3.21	0.11	12	12	12
Clozapine	3.40	0.18	13	10	12
Desipramine	3.90	0.29	12	12	12
Desvenlafaxine	2.29	7.11	13	13	11
Dexametasone	2.35	24.6	9	7	9
Diazepam	3.08	0.29	12	12	12
Dothiepin	4.52	0.12	13	12	13
Doxepin	3.84	0.36	12	12	12
Felbamate	0.68	11.1	10	7	7
Fluoxetine	4.17	0.1	11	11	11
Flupentixol	4.50	0.082	13	13	13
Flurazepam	3.95	0.092	13	11	13
Fluvoxamine	2.80	2.49	8	8	10
Gabapentin	-1.27	10.0	8	8	8
Haloperidol	3.66	0.76	12	12	12
Imipramine	4.28	0.19	12	12	12
Lamotrigine	1.93	10.0	13	13	13
Lorazepam	3.53	0.096	16	14	11
Maprotiline	4.37	0.3	13	11	10
Medazepam	4.21	0.21	12	12	12
Memantine	2.07	1.84	13	13	9
Mianserin	3.83	0.32	12	12	12
Mirtazapine	3.21	1.0	15	10	10
Naltrexone	1.27	1.92	9	10	9
Nitrazepam	2.55	0.49	12	14	11
Nordiazepam	3.21	0.43	12	12	12
Nortriptyline	4.43	0.19	12	12	12
Olanzapine	2.74	0.054	10	10	10
Opipramol	3.24	0.5	12	13	12
Oxazepam	2.92	0.37	11	11	11
Oxcarbazepine	1.82	2.95	12	11	9
Paliperidone	1.76	0.61	8	10	10
Paroxetine	3.15	1.41	11	11	11
Phenazepam	3.98	0.32	12	14	12
Phenytoin	2.15	0.87	14	15	9
Pipamperone	1.87	1.66	7	9	9
Prazepam	3.86	0.21	12	12	12
Promazine	3.93	0.12	12	12	12
Protriptyline	4.50	0.37	12	12	12
Quetiapine	2.81	0.14	9	9	9
Risperidone	2.63	0.38	11	9	11
Secobarbital	2.03	4.24	10	10	10
Sertraline	5.15	0.091	14	16	14
Temazepam	2.79	0.071	15	14	12
Topiramate	0.13	15.3	7	5	7
Trazodone	3.13	0.016	11	11	11
Triazolam	3.63	0.029	13	13	13

Table S9. *(continued)*

Compound	log K_{ow}	PNEC freshwater (µg/L)	OPBT score		
			noPAC	*0.1PAC*	*0.2PAC*
Trimipramine	4.76	0.17	15	13	13
Venlafaxine	2.74	0.038	15	15	14
Zolpidem	3.02	0.18	12	12	12
Zopiclone	-2.18	0.077	10	10	10
Receptor antagonists					
Atropine	1.57	11.5	8	8	8
Flumazenil	1.39	1.69	9	7	9
Stimulants					
Amphetamine	1.80	24.8	9	7	6
Caffeine	-0.55	1.2	10	10	7
Cannabinol	6.41	0.08	12	13	14
Methadone	5.01	0.84	13	11	13
Methamphetamine	2.24	9.74	10	8	8
Methylphenidate	2.25	11.6	10	7	9
Phentermine	2.08	16.5	9	9	9
THC	5.94	0.072	12	12	14
UV filters					
Octyl methoxycinnamate	5.38	0.026	12	12	12
Veterinary drugs					
Carprofen	3.88	0.19	12	15	12
Diaveridine	1.44	0.36	9	9	9
Difloxacin	1.75	1.55	7	7	9
Dimetridazole	0.23	29.5	7	7	7
Enrofloxacin	0.51	1.61	7	8	8
Flunixin	3.69	0.16	15	15	12
Furaltadone	0.73	19.2	5	5	7
Ipronidazole	1.47	6.6	8	9	9
Marbofloxacin	-0.61	7.78	10	10	8
Monensin	4.82	1.36	12	12	12
Orbifloxacin	0.22	0.024	10	8	10
Oxibendazole	2.52	1.3	8	10	10
Ronidazole	-0.48	16.7	7	10	7
Salinomycin	7.51	0.16	13	13	13
Sarafloxacin	0.52	1.87	8	8	8
Sulfachlorpyridazine	0.85	0.73	9	8	9
Sulfaclozine	0.62	1.09	6	8	8
Sulfadoxine	0.58	1.47	8	8	8
Sulfamonomethoxine	0.74	1.87	8	8	8
Sulfanitran	1.64	0.89	10	10	10
Sulfaquinoxaline	1.55	0.14	10	8	10
Tilmicosin	4.19	0.069	11	13	13
X-Ray contrast media					
Iopromide	-0.44	0.14	8	9	9

Table S10. Total concentration (as a sum of the individual OMP concentrations) of each therapeutic class in sampling point and treatment.

		noPAC				*0.1PAC*				*0.2PAC*		
	# of OMPs	HWW (µg/L)	INF (µg/L)	MBRperm (µg/L)	EFF (µg/L)	HWW (µg/L)	INF (µg/L)	MBRperm (µg/L)	EFF (µg/L)	HWW (µg/L)	INF (µg/L)	MBRperm (µg/L)
Analgesics/anti-inflammatories	29	62.59	70.91	4.87	2.72	83.31	113.35	11.11	8.84	57.68	49.95	3.11
Antiarrhythmic agents	5	0.24	0.29	0.04	0.03	0.44	0.47	0.12	0.11	0.46	0.45	0.04
Antibiotics	40	54.83	43.84	8.19	6.43	131.81	120.27	32.18	34.42	49.14	35.78	6.12
Antifungals	3	0.00	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD
Antihistamines	2	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD
Antihypertensives	1	0.00	0.00	< LOD	< LOD	0.01	0.00	0.00	0.00	< LOD	< LOD	< LOD
Antiparasitics	6	0.26	0.39	0.06	0.04	4.35	0.85	0.09	0.14	0.48	0.47	< LOD
Antiseptics	1	0.17	0.18	< LOD	< LOD	1.45	1.69	2.23	2.42	< LOD	< LOD	< LOD
Beta-blockers	3	1.81	2.44	0.09	0.16	5.41	6.88	0.71	0.82	3.67	3.92	1.53
Calcium channel blockers	1	0.23	0.10	0.00	0.00	0.44	0.63	0.00	0.00	0.14	0.15	0.00
Diuretics	1	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD
Drug metabolites	26	7.04	8.66	2.33	0.75	20.70	23.88	4.59	4.36	12.55	10.92	1.10
Hormones	9	0.95	0.66	0.23	0.33	1.75	1.85	1.35	2.34	0.34	< LOD	< LOD
Illicit drugs	6	4.69	5.76	1.20	0.85	8.52	11.28	2.31	1.71	1.30	0.60	0.40
Plastic additives	2	22.27	23.06	2.39	2.70	33.58	35.08	15.25	16.06	34.35	32.23	19.43
Psychiatric drugs	63	11.43	14.22	3.60	2.91	31.54	49.02	12.04	11.34	21.55	22.21	3.53
Receptor antagonists	2	< LOD	< LOD	< LOD	< LOD	0.02	0.02	0.00	0.00	< LOD	< LOD	< LOD
Stimulants	8	27.10	11.40	2.71	3.03	22.83	31.23	7.42	8.01	13.77	12.86	0.44
UV filters	1	0.24	0.46	0.01	0.00	0.61	1.06	0.01	0.01	0.18	0.23	0.02
Veterinary drugs	22	4.26	3.81	0.70	0.32	8.00	7.82	2.07	2.00	2.61	2.23	0.32
X-Ray contrast media	1	4.89	7.25	0.08	0.00	176.17	122.37	2.10	2.65	81.75	53.52	1.17
Total	232	203.02	193.45	26.49	20.28	530.95	527.75	93.59	95.26	279.98	225.50	37.21

Appendix 2

List of publications

With the exception of the results published in Chapter 5, all the findings reported in this PhD thesis have been published in scientific journals as follows:

1. Gutiérrez, M., Grillini, V., Pavlović, D. M., & Verlicchi, P. (2021). Activated carbon coupled with advanced biological wastewater treatment: A review of the enhancement in micropollutant removal. *Science of The Total Environment, 790*, 148050

2. Gutiérrez, M., Ghirardini, A., Borghesi, M., Bonnini, S., Pavlović, D. M., & Verlicchi, P. (2022). Removal of micropollutants using a membrane bioreactor coupled with powdered activated carbon—A statistical analysis approach. *Science of The Total Environment*, *840*, 156557

3. Gutiérrez, M., Verlicchi, P., & Mutavdžić Pavlović, D. (2023). Study of the Influence of the Wastewater Matrix in the Adsorption of Three Pharmaceuticals by Powdered Activated Carbon. *Molecules*, *28*(5), 2098.

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Review

Activated carbon coupled with advanced biological wastewater treatment: A review of the enhancement in micropollutant removal

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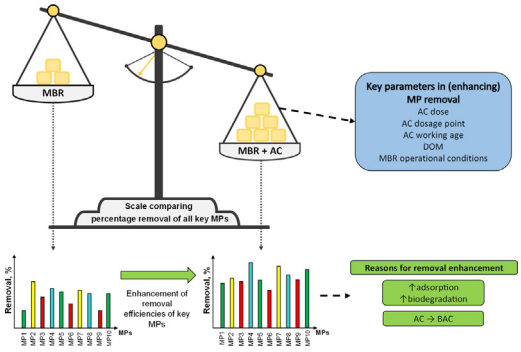
HIGHLIGHTS

- Micropollutants removal by MBR coupled with activated carbon is reviewed.
- Activated carbon in the bioreactor enhances the removal of most compounds.
- Low molecular weight organics are a strong competitor in sorption process.
- At a dose of 0.1 g PAC/L the removal efficiency of many compounds is around 80%.
- Biologically activated carbon column promotes the degradation of MPs.

GRAPHICAL ABSTRACT



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ABSTRACT

This study consists of a review on the removal efficiencies of a wide spectrum of micropollutants (MPs) in biological treatment (mainly membrane bioreactor) coupled with activated carbon (AC) (AC added in the bioreactor or followed by an AC unit, acting as a post treatment). It focuses on how the presence of AC may promote the removal of MPs and the effects of dissolved organic matter (DOM) in wastewater. Removal data collected of MPs are analysed versus AC dose if powdered AC is added in the bioreactor, and as a function of the empty bed contact time in the case of a granular activated carbon (GAC) column acting as a post treatment. Moreover, the enhancement in macropollutant (organic matter, nitrogen and phosphorus compounds) removal is analysed as well as the AC mitigation effect towards membrane fouling and, finally, how sludge properties may change in the presence of AC. To sum up, it was found that AC improves the removal of most MPs, favouring their sorption on the AC surface, promoted by the presence of different functional groups and then enhancing their degradation processes. DOM is a strong competitor in sorption on the AC surface, but it may promote the transformation of GAC in a biologically activated carbon thus enhancing all the degradation processes. Finally, AC in the bioreactor increases sludge floc strength and improves its settling characteristics and sorption potential.

Abbreviations: AC, activated carbon; BAC, biologically activated carbon; BET, Brunauer–Emmett–Teller; BOD_5, biological oxygen demand; CAS, conventional activated sludge; CEC, contaminant of emerging concern; COD, chemical oxygen demand; D617, 3-(3,4-dimethoxyphenyl)-2-methyl-6-methylaminohexane-3-carbonitrile; DEET, N,N-diethyl-m-toluamide; DOC, dissolved organic carbon; DOM, dissolved organic matter; $D_{ow:}$, octanol water partition coefficient; EBCT, empty bed contact time; E1, estrone; E2β, estradiol; E3, estriol; EBV, empty bed volumes; EE2, 17α-ethinylestradiol; EPS, extracellular polymeric substances; GAC, granular activated carbon; HRT, hydraulic retention time; k_{biol}, biological degradation rate; K_d, solid liquid partition coefficient; K_{ow}, octanol water distribution coefficient; LC-OCD, liquid chromatography organic carbon detection; LOD, limit of detection; LOQ, limit of quantification; MBR, membrane bioreactor; MF, microfiltration; MLSS, mixed liquor suspended solids; MLVSS, mixed liquor volatile suspended solids; MP, micropollutant; PAC, powdered activated carbon; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; pH_{PZC}, pH value at the point of zero charge; pK_a, acid dissociation constant at logarithmic scale; PT, post-treatment; RSST, Rapid Small Scale Column Test; SMP, soluble microbial products; SRT, sludge retention time; TMP, trans-membrane pressure; TOC, total organic carbon; UF, ultrafiltration; WWTP, wastewater treatment plant.

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Contents

1. Introduction

In the last two decades, there have been extraordinary developments in membrane technologies applied to wastewater treatment. Membrane bioreactors (MBRs) have become a widely used technology treating urban (Xiao et al., 2019) and industrial wastewater (Cattaneo et al., 2008). The combination of a biological treatment with a membrane separation provides a better-quality effluent over conventional activated sludge systems (CAS) regarding many regulated contaminants, in particular suspended solids and microorganisms.

Among the improved characteristics, MBRs have a lower footprint than CAS, can operate with a wide-ranging loading influent due to a higher biomass concentration and produce less excess sludge (Sipma et al., 2010).

One of the main drawbacks of MBRs is membrane fouling which leads to an increment in the operational and maintenance costs and a reduction in the membrane effective lifespan. However, accurate membrane maintenance planning can counteract it (Xiao et al., 2019).

Depending on the nature of the influent and the required effluent quality, promising insights have been obtained in recent years using advanced biological systems (MBRs) in combination with innovative treatment technologies: these systems are often called hybrid MBRs (Alvarino et al., 2017) or integrated MBRs (Neoh et al., 2016; Woo et al., 2016). Some have been consolidated, such as activated carbon (AC) and ozonation, while others have not yet been intensively implemented, such as advanced oxidation processes, membrane distillation bioreactors, biofilm/bio-entrapped MBRs, and nanofiltration/reverse osmosis (Rizzo et al., 2019). In fact, hybrid MBR is designed not only to guarantee specific effluent quality, but also to improve the MBR operation. In this way, the use of adsorbents, such as AC, to mitigate membrane fouling has been the subject of research efforts in recent years (Iorhemen et al., 2017).

Wastewater treatment plant (WWTP) influent is characterised by a high content of organic matter. Of all the substances commonly found, there has been a focus on micropollutants (MPs) in recent years (Verlicchi et al., 2012). MPs consist of substances from natural and anthropogenic sources and, although their origin can be very diverse, they are strictly correlated to mass-produced materials for anthropogenic activities. While most MPs in WWTP influents range from ng/L to μg/L, some can exhibit higher concentrations (Verlicchi et al., 2012). In this context, biological treatments (mainly CAS and MBR) have not been designed to remove MPs from wastewater, but conventional macropollutants (namely suspended solids, organic substances, nitrogen and phosphorus compounds, microorganisms), and thus some of the most commonly consumed or recalcitrant MPs can be found in WWTP effluents at >1 μg/L (Verlicchi et al., 2012).

Their vast occurrence and diversity, together with the lack of European regulations on their removal in WWTPs and their occurrence in the aquatic ecosystems (Rizzo et al., 2019), entail potential risks for human health and aquatic life, making them *contaminants of emerging concern* (CECs) in the sense clearly stated by Barceló (2003) and remarked more recently by Sauvé and Desrosiers (2014) and UNESCO

(https://en.unesco.org/emergingpollutantsinwaterandwastewater). Their main characteristic is such that they may be subject to future regulations depending on monitoring data on their occurrence in the different aquatic environments, the results of research on their potential health effects and their contribution to the development of antibiotic resistant bacteria. Their persistence in the environment does not necessarily lead to negative effects, as their transformation or removal rates can be compensated by their continuous release into the environment. In the following, the term "micropollutants" will be used.

The high adsorption capacity of AC has been proposed as one of the most promising mechanisms to remove MPs from wastewater. Adsorption processes do not generate toxic by-products in comparison with other advanced technologies used in hybrid MBRs (e.g. ozonation, photocatalysis) and may also remove biological treatment inhibitors at the same time. One drawback to consider is the potential reduction in AC adsorption capacity due to the presence of dissolved organic matter (DOM) which is present in the stream under treatment (Guillossou et al., 2020; Margot et al., 2013). However, adsorbed DOM may contribute to the development of microorganisms on the AC surface, enhancing biodegradation processes by the attached biomass (Fundneider et al., 2021b). In this way, design parameters and operational conditions that could contribute to increase the efficiency of the hybrid systems are crucial (Grandclément et al., 2017).

The inefficacy of conventional treatments in removing MPs determines the need for combined systems able to promote different removal mechanisms which could assure a reduction in MP levels and a lower impact on the receiving waters (Rizzo et al., 2019; Siegrist and Joss, 2012). The enhancement of MP removal by adsorption and biodegradation has therefore been studied among different configurations of MBR integrated with AC, both in the case of powdered activated carbon (PAC) or granular activated carbon (GAC).

This review aims to give a snapshot of the removal achieved for a wide spectrum of MPs from wastewater by means of hybrid MBRs, corresponding to MBRs where AC is added in the bioreactor and also to MBRs coupled with AC (in which the AC stage represents a polishing treatment) as well as of the quality (occurrence of MPs) in the final effluent of hybrid MBRs. The review attempts to respond to the following questions: Is it possible to increase the removal efficiency of selected MPs from wastewater by the addition of AC in an MBR or by coupling the MBR with a polishing AC treatment? What are the best PAC dosages or GAC bed characteristics to achieve the best MP removal efficiency? How does AC influence the MBR operation?

In order to provide the tools needed to answer these questions, an in-depth focus is first carried out on the main MP removal pathways occurring once AC is present in the wastewater under treatment and then a literature survey is presented and discussed on the removal efficiencies of a wide spectrum of MPs referring to different combinations of AC and MBR as well as applied operational conditions. The influence on MP removal of the main MP characteristics, AC properties, design and operational parameters and DOM presence is discussed as well as how AC may influence MBR operations, on the basis of lessons learned from collected studies.

2. Framework of the study

The review refers to a collection of peer reviewed papers identified by applying PRISMA guidelines (Moher et al., 2009). It first reports in detail how this collection was found, and then it discusses quality assurance criteria in order to include or exclude records (studies) and the data reported in them from the selected literature (see the Section 3.1).

Briefly, the overview refers to the removal of MPs from wastewater by different configurations involving advanced biological treatments (namely MBRs) coupled with activated carbon (Table 1). A spectrum of 179 MPs (Table 2), including 20 metabolites, belonging to 30 different classes, was considered: 142 pharmaceuticals, 8 personal care products (antiseptics, synthetic musks and UV filters) and 29 different industrial products (including non-ionic surfactants, stimulants, sweeteners, pesticides and compounds included in the group "Others"). Table S1 reports their main chemical characteristics (molecular weight, Log K_{ow}, Log D_{ow}, pK_a and charge).

A presentation is then reported of the main configurations of hybrid MBRs operating in combination with AC as well as in "ancillary" configurations where conventional activated sludge (CAS) treatments are combined with a post-treatment (PT), including a PAC contact tank followed by a UF membrane unit or a GAC column (Section 3.3). The study continues by focussing on the interactions between AC and organic matter (MPs and DOM) as well as microorganisms when AC is added in the wastewater in the bioreactor or in the PT unit (Section 4). A first comparison is carried out between the removal efficiencies achieved by MBR treatment and in the case of MBR coupled with PAC/GAC in order to highlight the contribution of the AC for many MPs. Then the analysis refers to MP removal efficiencies and concentrations in the final effluent, with regard to the configurations reported in Table 1 and considering different PAC dosages and the volume of wastewater treated in the GAC column, expressed in terms of number of empty bed volumes (EBVs). The discussion which follows deals with the influence of the main factors affecting MP removal: MP properties, AC characteristics and dosage frequency and mode, and operational conditions in the different configurations (sludge retention time SRT, hydraulic retention time HRT, temperature T, PAC contact time, effluent dissolved organic matter DOM, empty bed contact time, EBCT). The study also explores other effects of AC on removal of macropollutants, mitigation of membrane fouling and MBR sludge characteristics. It then concludes with the identification of the fields requiring further research and investigations.

3. Identification of the studies for the qualitative and quantitative analysis

The present systematic review has been developed following the PRISMA guidelines (Moher et al., 2009), a protocol established in 2009 by international experts that defines the steps to follow to obtain a systematic review on a specific topic. The collection of peer reviewed papers was obtained through Scopus, by the key words "MBR" OR "membrane bioreactor" OR "membrane reactor" AND "activated carbon" OR "AC" and following the eligibility criteria discussed in the Supplementary Material (Section S1 and Fig. S1). As a result of this process, a collection of 64 peer reviewed papers, published between 2009 and 2020, was defined including studies presenting and discussing the new trends in the enhancement of the performance of MBR in combination with AC, in terms of removal efficiency of macro- (BOD_5, COD, nitrogen compounds and phosphorus compounds) and micropollutants, and fouling reduction and control (Fig. S1). Based on these studies and following the PRISMA guidelines, a qualitative synthesis was carried out. Then a further refinement was made, leading to the identification of 26 records on which basis a quantitative synthesis was carried out referring to the removal of MPs in MBR coupled AC (PAC or GAC). A few studies (4) referring to CAS where AC was present were included as they provided useful insights into the analysis of MP removal, as will be discussed later. More details about the process followed to define the collection of papers to be included in the review can be found in the Supplementary Material.

3.1. Quality assurance of the literature data

The studies included in this review had to provide a clear description of the plant configuration and report information on sampling (mode and frequency of sampling and sampled matrices) and the adopted analytical methods of the investigated micropollutants. There had to be sufficient collected data to support the study discussion. Moreover, the studies had to state at which plant scale (lab, pilot or full) the investigations were carried out, and also had to give details on the biological

stage (i.e. design parameters and operational conditions), feeding type (real, synthetic or spiked) and mode (continuous or batch), as well as the duration of the investigation in order to evaluate the level of saturation of the AC during the sampling campaigns. As to AC, they had to report the carbon types and main characteristics (see Table 3). Finally, in the case of AC used as a PT, the study had to provide details of a further treatment (often a membrane unit) inserted in the configuration in order to guarantee the separation between treated effluent and AC residues. This separation step is generally adopted in the case of a PAC unit, but in some cases it was placed after a GAC column (Sbardella et al., 2018).

Table S2 (Excel) in the supplementary material collects all the information and shows the main issues addressed in the 26 selected studies providing MP concentrations and removal efficiencies. The remaining 38 out of the preselected 64 papers were included in this review as they contributed to explaining the behaviour of the AC that was added in the secondary or polishing treatment.

Some investigations dealt with the removal mechanisms of specific MPs and often used deionised, modelled water spiked with the key pollutants at the desired concentration (such as Lee et al., 2009). These studies were included in this review as they provide interesting analysis and useful considerations on the removal mechanisms of the investigated compounds. However, the removal achieved is not included in the graphs reported in this paper as they refer to deionised water and no matrix effect was considered. Investigations referring to synthetic water (see Table S2) were included only if details on the characteristics of the water matrix were clearly reported.

Finally, if the concentration of MP in the investigations was found to be less than its limit of quantification (LOQ), half of the LOQ was assumed. If its concentration was found to be less than its limit of detection (LOD), it was assumed equal to the corresponding LOD. If the authors reported a removal efficiency equal to 100% and they did not provide the LOQ or LOD values, it was assumed that the effluent concentration was equal to 10^{-4} μg/L. Removal efficiencies were not considered in the cases in which MP influent concentrations were found to be less than the corresponding LOQ.

3.2. Main characteristics of the reviewed studies

The reviewed studies were carried out in Australia (5), Spain (5), Switzerland (3), Netherlands (3), China (2), Canada (2), Germany (2), Belgium (1), Sweden (1), United Kingdom (1) and Saudi Arabia (1). The plant configurations are schematically reported in Table 1, together with a brief description of the system and the corresponding references. The studies included lab (46%), pilot (42%) and full-scale plants (12%). In 50% of the studies, the feeding was synthetic wastewater, resulting from the addition of specific compounds miming the matrix effect (the composition is provided), and in 50% it was real wastewater. Out of these, only one study spiked MPs into the real wastewater (Remy et al., 2012). Regarding the real wastewater, 69% was urban and 31% hospital effluent (Itzel et al., 2018; Langenhoff et al., 2013; Kovalova et al., 2013b; Paulus et al., 2019). The feeding was continuous in all the studies with the exception of Alvarino et al. (2017) and Serrano et al. (2011).

Among the selected 26 papers dealing with the occurrence and removal of MPs, some reported details of very complex experimental campaigns and it was possible to identify different investigations in the same paper. An investigation consists of an experimental campaign referring to a specific treatment configuration/scenario (MBR equipped with MF or UF membranes, coupled with PAC or GAC), under defined conditions (for instance dosage of PAC or empty bed contact time in GAC column). According to this definition, there was a total of 46 investigations regarding the selected records: their details are reported in Table S2 on the line *Investigations on micropollutants*.

3.3. Configurations included in the review

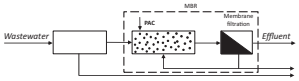
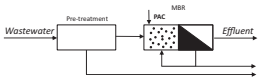
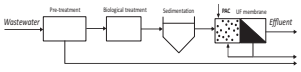
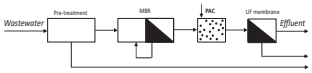
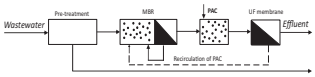
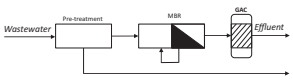
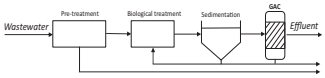
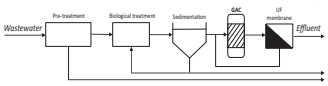
The reviewed configurations belong to three main groups depending on the treatment stage in which AC is present and on AC type: PAC in the bioreactor (configurations I and II in Table 1); PAC in a post treatment (configurations III–V in Table 1); GAC in a post treatment (packed column, configurations VI–VIII in Table 1).

Submerged (I) and side stream (II) MBRs are separated, but the collected results are presented together.

If PAC is used in the PT, it is added in a contact tank receiving the biological effluent to be treated and dispersed in it (Kovalova et al., 2013b; Margot et al., 2013). Sufficient mixing is required to guarantee homogenous conditions. An additional filter is requested in order to retain the AC powder: the UF membrane unit is always equipped after the PAC contact tank (configurations III-V). PAC retained in this unit can be withdrawn (III and IV) or recycled back to the biological reactor (V). If GAC is used as a PT, its granules are packed in a column which is fed and crossed by the biological effluent. In order to clean the GAC filter and remove the retentate, a backwash is planned and periodically carried out (Baresel et al., 2019). A UF unit after the GAC column was found only in one study (VIII). Despite the main aim of this review being the analysis of the performance in a hybrid MBR, four studies referring to CAS coupled with AC (configurations III, VII and VIII) were also included. Two studies explore the effect of a PAC unit after a CAS (Löwenberg et al., 2014; Margot et al., 2013) and another two explore the combination of a CAS with GAC (Grover et al., 2011; Sbardella et al., 2018). The reason for their inclusion is that they further investigate the removal of MPs and provide useful information to also explain MP removal in a hybrid MBR. As reported in Table S2, in 26 out of the 46 investigations, PAC was added in the bioreactor, in 7 PAC was used as a PT and in 13 GAC was used as a PT. In the following sections, it was assumed that if the powder of activated carbon is added in the biological reactor (MBR or CAS), the system is reported as (MBR + PAC) or (CAS + PAC), whereas, if activated carbon is used in a separate tank, the configuration will be represented with these symbols: MBR → PAC or GAC; CAS → PAC or GAC.

It is important to remark that the operation, in case AC is added in the bioreactor or AC acts as a PT by means of PAC or GAC, is regulated by different parameters depending on the three main configuration groups. In MBR + PAC they are (i) the *hydraulic retention time* (*HRT*) of the wastewater in the bioreactor which must be long enough to guarantee MP transfer from the liquid phase to the PAC surface or its absorption in the floc; (ii) *the sludge retention time* (SRT) which must be long enough to promote the development of different species of microorganisms able to degrade different MPs, (iii) the *AC retention time* in the bioreactor which is the time AC spends in the tank before its disposal or before it leaves the bioreactor embedded into the floc (in general it is ≥SRT); finally (iv) the *AC working age* which measures the time since it was added in the system (an indirect measure of AC saturation) which is ≤AC retention time. In PAC acting as a PT, the specific parameters influencing its performance are: (i) the *HRT* of the (waste)water in the PAC contact tank; (ii) the *AC retention time* in the tank that is the time AC stays in the tank before its withdrawal; and (iii) the AC *working age*. In GAC acting as a PT, parameters defining its behaviour are: (*i*) the *HRT* of the (waste)water within the AC column which is measured by the empty bed contact time (EBCT); (*ii*) the *filtration velocity* v_f which is the ratio between the influent flow rate and the surface area of the GAC filter and (*iii*) the *working age* which depends on the EBV. EBCT has to be set in order to guarantee the time for the MPs transfer from the bulk phase to the GAC surface and also inside its grain. According to the suggested design parameters in well-known manuals (among them Metcalf and Eddy, 2014), EBCT should be at least 5–30 min and v_f 5–15 m/h. EBCT may be replaced by the *effective contact time* that is defined as the product of EBCT and the bed porosity. These specific parameters are reported for each study In Table S2, together with many other details on the investigations. Finally, the period of investigations

Table 1
Configurations of biological treatment coupled with AC considered in the review together with the corresponding references.

Configuration	Comments	References
I Side stream (MBR + PAC) 	PAC is added directly in the bioreactor. The membrane unit is in a separate tank. The sludge recycled into the bioreactor contains an amount of (embedded) PAC. A fraction is lost with the excess sludge.	Alvarino et al., 2016; Asif et al., 2020; Echevarría et al., 2019; Remy et al., 2012; Serrano et al., 2011, Wei et al., 2016
II Submerged (MBR + PAC) 	PAC is added directly in the bioreactor. The membrane unit is in the same reactor. The sludge recycled into the bioreactor contains an amount of (embedded) PAC. A fraction is lost with the excess sludge.	Alvarino et al., 2017; Li et al., 2011; Nguyen et al., 2013a; Nguyen et al., 2014; Yang et al., 2010; Yang et al., 2012; Yu et al., 2014
III (PT) CAS → (PAC + UF) 	PAC is used in the post treatment. The CAS effluent is sent to the PAC and a UF membrane unit retains the powder. A small amount is recycled. In Margot et al., 2013, 5% of the influent is treated in an MBBR and then mixed with the CAS effluent.	Löwenberg et al., 2014, Margot et al., 2013
IV (PT) MBR → PAC → UF 	PAC is used in the post treatment. The permeate is sent to the PAC and a UF membrane unit retains the powder. In the MBR there is no PAC.	Kovalova et al., 2013b
V (PT) MBR → PAC → UF & recirculation 	PAC is used in the post treatment. The permeate is sent to the PAC and a UF membrane unit retains the AC powder and is completely recycled in the bioreactor.	Lipp et al., 2012
VI (PT) MBR → GAC 	GAC is used as a post treatment. The permeate is sent into the GAC column and then directly discharged. In two studies (those with the asterisk in the adjacent column) there is an ozonation step between MBR and GAC.	Baresel et al., 2019; Itzel et al., 2018*; Langenhoff et al., 2013; Nguyen et al., 2012; Nguyen et al., 2013a; Nguyen et al., 2013b; Paredes et al., 2018; Paulus et al., 2019*
VII (PT) CAS → GAC 	GAC is used as a post treatment. The CAS effluent is sent into the GAC column and then directly discharged.	Grover et al., 2011
VIII CAS → GAC → UF 	GAC is used as a post treatment. The CAS effluent is sent into the GAC column, then filtered (by UF membrane) and then discharged.	Sbardella et al., 2018

* An ozonation step is present between MBR and GAC column.

on micropollutant removal in hybrid MBRs with PAC or GAC varied between 9 days (Kovalova et al., 2013b; Wei et al., 2016) and 3 years (Grover et al., 2011). Out of the 46 investigations, only a few provided detailed trends of the removal efficiencies in the presence of AC over time. These included Nguyen et al. (2013a), Serrano et al. (2011), Alvarino et al. (2016, 2017), Li et al. (2011) and Lipp et al. (2012).

3.4. The selected compounds

The analysed micropollutants included 179 compounds belonging to 30 classes (Table 2). The compounds in italics and with an asterisk were investigated, but they were never detected. As a result, 163 compounds are included in the graphs and belong to 28 classes (those with an acronym in Table 2).

The class of calcium channel blockers (M) was included in the list in Table 2 as the compound amlodipine was found in raw wastewater (Baresel et al., 2019). It was removed below its LOD in the MBR and for this reason it does not appear in any figure resulting in the investigated configuration MBR → GAC.

3.5. Activated carbon used in the investigations

The activated carbon adopted in the reviewed studies was in most cases in powder form (PAC) and in a few studies in granules (GAC). It was generally supplied by: Norit, Chemviron, Desotec, Sigma Aldrich and ChiemiVall, as reported in Table S2. The size generally ranges were <50 μm for PAC and 100–2400 μm for GAC, in accordance with Metcalf and Eddy (2014), only (Sbardella et al., 2018) adopted a GAC with a higher size range (2360–4750 mm). Among the selected 66 papers, it was also found that sometimes AC up to 300 μm was considered PAC (Ng et al., 2013; Yang et al., 2019; Zhang et al., 2017). A few authors provide more details about the particle size distribution of the adopted AC (Ng et al., 2013; El Gamal et al., 2018). Many studies also considered the influence and role of pore size (Alves et al., 2018), which was classified, in accordance with IUPAC (Rouquerol et al., 1994), in micropores (diameter < 2 nm), mesopores (diameter between 2 nm and 50 nm) and macropores (diameter > 50 nm).

The main characteristics of AC are reported in Table 3. The most important ones are Brunauer–Emmett–Teller *BET specific surface area* as it is a measurement of the potential surface area available for promoting the different removal mechanisms which will be discussed later on; *iodine number* which is a measure of the pore volume available in the AC mass; *pore diameter* defining the size of the particles which can enter the porous structure of the grain; and the *apparent* or *bulk density*, that is the mass of AC contained in a unit volume (including particle, inter-particle void and internal pore volume).

In addition, the point of zero surface charge (pH_{PZC}) is another important characteristic, reported in some study (Alves et al., 2018; De Ridder et al., 2011; Kovalova et al., 2013a, b), which defines the pH at which there are as many positively charged functional groups as negatively charged functional groups on the AC surface (pH_{PZC} between 6.5 and 8 indicating that their surface is slightly positively charged or negatively charged at neutral pH, De Ridder et al., 2011). At wastewater pH below pH_{PZC}, the carbon surface is mostly positively charged and, above the surface, it is mostly negative charged. It is important to know this threshold, as the adsorption process is most effective for uncharged apolar adsorbates (Alves et al., 2018).

Only one study (Alves et al., 2018) investigated the influence of the activation type (by steam or by chemicals) of the carbon and compared the results at lab level and (Choi et al., 2005; Paredes et al., 2018) explored the effect of the GAC type on removal efficiencies and GAC lifetime.

On the basis of origin and activation mechanism, ACs present a high heterogeneity (Benstoem et al., 2017). However, it is worth noting that the selection of virgin and reactivated carbon and the operation time may influence the adsorption capacity as their characteristics may change over time (Benstoem et al., 2017; Choi et al., 2005).

Table 2
Compounds included in the review grouped according to their class. In brackets, the number of compounds for each class considered in this study.

Class	Class symbol	Compound
Analgesics/anti-inflammatories (18)	A	4-Acetamidoantipyrine; 4-aminoantipyrine; 4-formylaminoantipyrine; 4-methylaminoantipyrine; antipyrine/phenazone; diclofenac; formyl-4-aminoantipyrine; ibuprofen; indometacin; ketoprofen; mefenamic acid; morphine; *n*-acetyl-4-aminoantipyrine; naproxen; paracetamol/acetaminophen; salicylic acid; tramadol; *meclofenamic acid**
Anaesthetics (2)	B	Lidocaine; thiopental
Antibacterials (29)	C	Amoxicillin; ampicillin; azithromycin; cefalexin; ciprofloxacin; clarithromycin; clindamycin; erythromycin; flumequine; lincomycin; metronidazole; N4-acetylsulfamethoxazole; norfloxacin; ofloxacin; oxolinic acid; oxytetracycline; rifaximin; roxithromycin; sulfadiazine; sulfamerazine; sulfamethoxazole; sulfamethoxypyridazine; sulfamoxole; sulfapyridine; sulfathiazole; sulfisoxazole; trimethoprim; *doxycycline**; *tetracycline**
Anticoagulants (1)	D	Warfarin
Antidiabetics (1)	E	Metformin
Anti-hypertensives (3)	F	D617; verapamil; *enalapril**
Antimycotics (4)	G	Carbendazim; fluconazole; propiconazole; *ketoconazole**
Antineoplastics (5)	H	Cyclophosphamide; flutamide; hydroxytamoxifen; ifosfamide; tamoxifen
Antiseptics (1)	I	Triclosan
Antiviral (3)	J	Oseltamivir; oseltamivir carboxylate; ritonavir
Beta-agonists (1)	K	Terbutaline
Beta-blockers (6)	L	Atenolol; atenolol acid; bisoprolol; metoprolol; propranolol; sotalol
Calcium channel blockers (1)	M	Amlodipine
Contrast media (7)	N	Amidotrizoic acid (diatrizoate); diatrizoate and iothalamic acid; iohexol; iomeprol; iopamidol; iopromide; ioxitalamic acid
Diuretics (2)	O	Furosemide; hydrochlorothiazide
Gastrointestinal disorder drugs (1)	P	Mebeverine
Hormones (14)	Q	17α-Ethinylestradiol (EE2); 17β-estradiol (estradiol/E2β); 17β-estradiol-acetate; boldenone; boldione; cyproterone acetate; dihydrotestosterone; estriol (E3); estrone (E1); etiocholanolone; nandrolone; testosterone; *norethindrone**; *progesterone**
Lipid regulators (5)	R	Bezafibrate; fenofibric acid; gemfibrozil; simvastatin; *clofibric acid**
Non ionic surfactants (2)	S	4-Tert-octylphenol; nonylphenol
Others (15)	T	4(5)-Methylbenzotriazole; 4-n-nonylphenol; 4-tert-butylphenol; 5-methylbenzotriazole; benzalkonium chloride; benzothiazole; benzotriazole; bisphenol A; bisphenol A diglycidyl ether; bisphenol F diglycidyl ether; irgarol (cybutryne); methylbenzotriazole; octylphenol; perfluorooctanoic acid (PFOA); perfluorooctanesulfonic acid (PFOS); *tris (2-carboxyethyl)phosphine (TCEP)**; *tris(1,3-dichloroisopropyl)phosphate (TDCPP)**
Pesticides (8)	U	Atrazine; diuron; fenoprop; isoproturon; mecoprop; N,N-diethyl-meta-toluamide (DEET); pentachlorophenol; terbutryn
Psychiatric drugs (16)	V	10,11-Dihydro-10,11-dihydroxycarbamazepine; carbamazepine; citalopram; diazepam; fluoxetine; gabapentin; levetiracetam; N,N-didesvenlafaxine; oxazepam; primidone; risperidone; sertraline; venlafaxine; *amitriptyline**; *dilantin**; *thioridazine**
Receptor antagonists (7)	W	Eprosartan; irbesartan; losartan; ramipril; ranitidine; valsartan; valsartan acid
Stimulants (3)	X	Caffeine; ritalinic acid; theophylline
Sweeteners (1)	Y	Aspartame
Synthetic musks (3)	Z	Celestolide; galaxolide; tonalide
UV filters (4)	AA	2-Phenyl-5-benzimidazolesulfonic acid; benzophenone-3; butyl methoxydibenzoylmethane; oxybenzone
Veterinary drugs (12)	BB	Enrofloxacin; marbofloxacin; sarafloxacin; sulfachloropyridazine; sulfaclozine; sulfadimethoxine; sulfadimidine; sulfadoxine; sulfamonomethoxine; trenbolone; tylosin; *monensin**
*Anti-histamines (1)***		*Diphenhydramine**
*Urological drug (1)***		*Finasteride**

* Compounds investigated and nsever detected.
** For these classes a symbol is not set as they are not included in the graphs.

In the investigations with PAC added in the bioreactor, the dosage was between 0.004 g/L (Remy et al., 2012) and 20 g/L (Asif et al., 2020). In the following analysis the dosages considered are discretized as: <0.05 g/L, 0.051 g/L; 0.25 g/L, 0.5 g/L; 0.75 g/L, 1–2 g/L and 20 g/L. The highest dosage (20 g/L) was selected on the basis of the batch test carried out by Asif et al. (2020). It had to guarantee a very high removal (>90%) of soluble microbial products (SMP) in the biological tank and under unsaturated conditions for PAC over the whole investigation.

As to the GAC column, the removal efficiency is often expressed as a function of the number of empty bed volumes (EBV), defined as the ratio between the treated (waste)water volume and the GAC column volume.

Table 3
Main characteristics of the activated carbon used in the reviewed studies.

Type	PAC	GAC
BET specific surface area (m^2/g)	328 to 1363	895 to 1250
Particle size (μm)	15 to 40*	1000 to 4750
Pore volume (cm^3/g)	0.228 to 0.88	0.043
Pore diameter (nm)	2.6 to 3.13	3 to >100
Iodine number (mg/g)	850 to 1250	920 to >1200
Bulk density (g/cm^3)	0.25 to 0.42	0.42 to 0.50
pH_{pzc}	7 to 11	
Ash content (%)	6 to 14	3

* (In 2 cases up to 150).

4. The role of activated carbon in the removal of micropollutants

Activated carbon may be added in the bioreactor or it can be used as a PT fed by the secondary effluent or the permeate, as reported in Table 1. Its presence favours similar removal mechanisms for the micropollutants in the case of granules (GAC) or powder (PAC). As shown in Table 3, PAC and GAC are characterised by a high specific surface (m^2/g) due to the presence of micro-, meso- and macropores. The internal structure of a grain, without taking into consideration its specific size, is reproduced in Fig. 1A. On its whole surface there is a high number of *active* sites where compounds (micro- and macropollutants) occurring in the wastewater can bind, depending on their affinity with the AC surface, and thus they are removed from the liquid phase via sorption mechanisms. Pores in the granule or in the powder are of different sizes resulting in different thresholds for the size of the molecules which can penetrate and then adsorb on the internal surface of the AC grain.

Micropollutant affinity towards an AC is strictly correlated to the physical and chemical characteristics of the AC (Section 3.5), namely pore size and texture, surface functional groups (Fig. 2C) and charge, and mineral matter content (Alves et al., 2018; Choi et al., 2005; Fuente et al., 2003; Kovalova et al., 2013b). Micropores are directly responsible for MP adsorption (El Gamal et al., 2018) as shown in Fig. 1B.

Adsorption is expected to decrease over time due to a gradual saturation of the active sites during operation (Choi et al., 2005). Dissolved

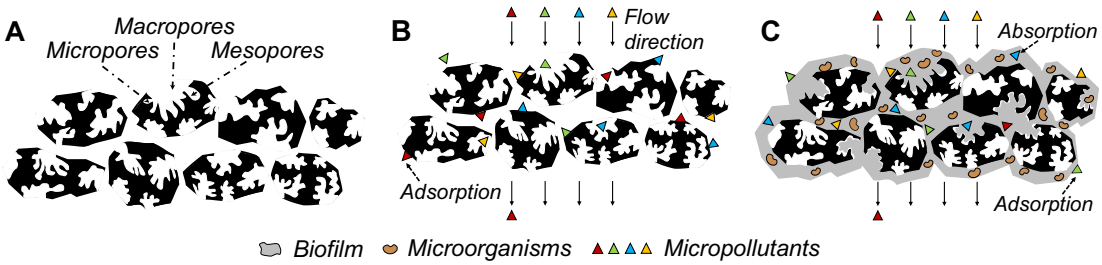


Fig. 1. Schematic representation of (A) the structure of activated carbon; (B) adsorption of micropollutants on the surface of the AC; (C) BAC, with micropollutants absorbed and adsorbed on its surface.

organic matter (DOM), and in particular the fraction of low molecular weight organics (see Section 6.1.8), if present in the liquid phase in contact with AC, tends to adsorb on the AC surface (Filloux et al., 2012). Organic particles may enter the macropores, thus they may represent a barrier for the MPs in their movement to reach the active sites of meso- and micropores. DOM and MPs are numerically present at different levels. In this context, Rattier et al. (2012) found that DOM acts as a strong competitor when it occurs 10^3–10^6 times higher than MPs. In the presence of DOM in the liquid phase (wastewater under treatment), microorganisms may develop on the AC surface area and macropores (Alves et al., 2018), promoting the growth of a biofilm, thus favouring biodegradation processes due to microorganism metabolic reactions. The AC thus becomes *biologically activated carbon* (BAC) (Fig. 1C). The MP biodegradation processes are enhanced here due to the development of a more specialised biomass, and the coexistence of aerobic and anoxic zones in this biofilm (Alvarino et al., 2016). MPs occurring in the wastewater may be sorbed by two mechanisms: *adsorption* due to electrostatic interactions between MP charged groups and the oppositely charged biofilm or AC surface, and *absorption* into the biofilm stratum due to MP hydrophobic interactions of the aliphatic and aromatic groups with the lipophilic cell membrane of the microorganisms or the lipid fractions of the suspended solids. Then some may biodegrade by means of microorganisms in the biofilm, transform and even mineralise; others may remain as they are (Baresel et al., 2019) (Fig. 1).

When AC is added in the bioreactor, it comes into contact with the flocs (activated sludge): some AC particles are incorporated within them, others are suspended within the liquid phase, depending on the AC added quantity (Ng et al., 2013; Remy et al., 2010) (Fig. 2A).

Sludge flocs are dynamic systems where incorporated AC particles may be covered by the biofilm becoming BAC or they may have their surface partially free (Fig. 2B). In this last case, MPs may directly adsorb on the AC surface. If the AC is covered by the biofilm, MPs may be absorbed in the biofilm, desorbed from it and adsorbed on the smallest AC pores. Bacteria can only colonise macropores due to size exclusion. Extracellular polymeric substances (EPS) instead can also enter into meso- and micropores and thus act as a catalyst for the biodegradation processes of MPs which manage to reach the surface of these pores and attach to it (Alves et al., 2018).

If AC acts as a PT, by PAC (as reported in Pills Report, 2012) or GAC (Sbardella et al., 2018), the development of the biofilm on its surface is still possible: DOM may be retained by the granules (Seo et al., 1996; Sun et al., 2020) and, over time, it may promote the growth of an autochthonous biomass (Sbardella et al., 2018). Sorption and biodegradation are complementary mechanisms that extend the AC life. During backwashing operations of the GAC filter, some MPs could be detached from the filter and found in the backwash water (Baresel et al., 2019). At long operating times, mature or aged biofilm developed on the AC surface may detach giving rise to the biological regeneration process. This cleans the AC surface, and the AC active sites are now free for MP adsorption even at long operating times. The regeneration is not able to create the original conditions and AC replenishment may become necessary to guarantee optimal operating conditions.

To sum up, MP removal mechanisms are the results of continuous interactions among MPs and AC particles, biofilm and organic matter. For this reason, BAC has to be considered a dynamic system where MP sorption and biodegradation occur simultaneously (El Gamal et al., 2018).

4.1. Common parameters and coefficients used in predicting MP removal

The sorption potential of an MP onto an AC is given by its solid water distribution coefficient K_d defined by Eq. (1):

$$K_d = \frac{c_{sorbed}}{c_{dissolved}} \quad (1)$$

where c_{sorbed} is the concentration of the compound of interest sorbed on the AC (μg/kg), $c_{dissolved}$ is the MP concentration in the liquid (μg/L). K_d is expressed in L/kg. It is strictly correlated to the nature of the adsorbent (case specific). A rapid look at the literature on MP sorption on AC shows that experimental values are very scarce (Yang et al., 2012).

As remarked in Dickenson and Drewes (2010), Mailler et al. (2015), McArdell et al. (2011) and Rattier et al. (2012), MP sorption onto the surface of a particulate matter (activated sludge or AC) is due to MP hydrophobicity (absorption) and to electrostatic interactions between positively charged compounds and negatively charged solid surface (adsorption).

The octanol water distribution coefficient D_{ow} can be used to predict its behaviour.

It is a modification of the octanol-water partition coefficient (K_{ow} defined by Eq. 2) accounting for ionisation of the compound (for non-ionisable compounds D_{ow} and K_{ow} have the same value) and it also considers attraction by the solid (correlated to pK_a). Eqs. (3) and (4) corresponds to the correlations between K_{ow} and D_{ow} for acidic and basic compounds respectively.

$$K_{ow} \equiv \frac{\text{concentration in } n-\text{octanol}}{\text{concentration in water}} \quad (2)$$

$$\text{Log } D_{ow} = \text{Log } K_{ow} + \text{Log}\frac{1}{1+10^{pH-pK_a}} \text{ (acidic compound)} \quad (3)$$

$$\text{Log } D_{ow} = \text{Log } K_{ow} + \text{Log}\frac{1}{1+10^{pK_a-pH}} \text{ (basic compound)} \quad (4)$$

For neutral compounds Log D_{ow} = Log K_{ow} and for ionic solutes Log D_{ow} < Log K_{ow}.

However, even if D_{ow} is corrected for charge (through pK_a), it only reflects how polar the compound is. Adsorbability prediction for charged compounds is more complex, as different mechanisms are involved as it will be better discussed in Section 6. Table S1 reports Log K_{ow}, p K_a and Log D_{ow} at different pH as well as charge at pH = 7 for the different compounds included in this study.

As to biodegradation, the kinetic constant k_{biol} is influenced by the operational conditions set in the bioreactor (mainly biomass concentration and type, HRT, and temperature), MP characteristics, and the

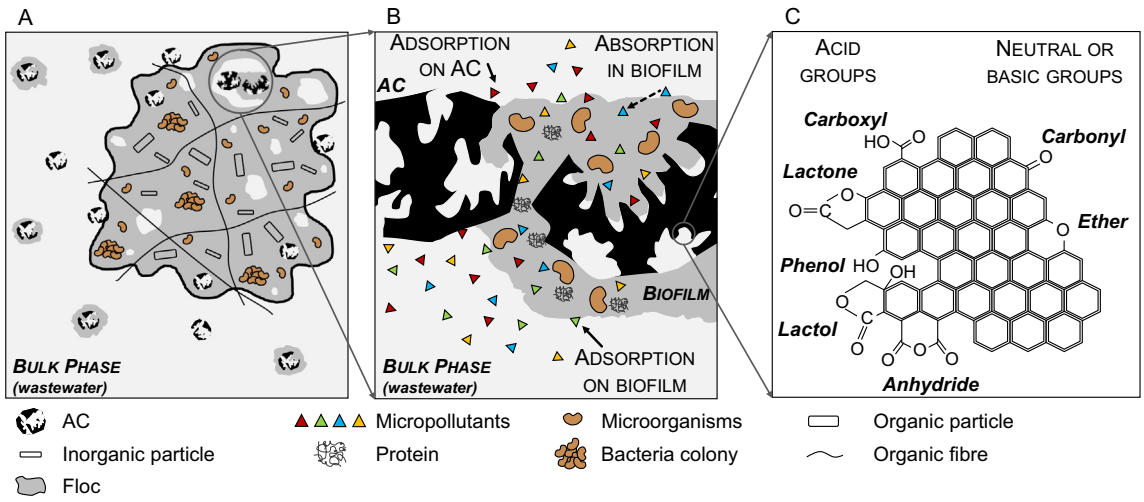


Fig. 2. Schematic representation of a sludge floc in the bioreactor in the presence of AC (A); MP removal mechanisms in an AC particle incorporated in the sludge floc (B); main functional groups on the surface of AC (C).

availability or limitation of substrates which define the type of biodegradation process (by metabolism or cometabolism) (Alvarino et al., 2018). These considerations explain the reasons why predictions are quite difficult and experimental data are often not in agreement with such data.

5. Results

Collected data provided by the investigations included in this review were processed in order to compare the MP removal achieved by the selected configurations in Table 1, at different AC dosages and under different operational conditions. Moreover, AC working age and behaviour over time were also explored and discussed. The first analysis carried out refers to the contribution of AC in removing MPs in the case of PAC added in the bioreactor (Fig. 3) or GAC used as a PT (Fig. 4) in comparison with the removal achieved by a biological treatment alone. It was not possible to compare MP removal achieved by the biological step alone or in the case of the biological step being followed by a PAC unit due to lack of corresponding values in the biological stage (Kovalova et al., 2013b; Lipp et al., 2012; Löwenberg et al., 2014; Margot et al., 2013).

In Figs. 3 and 4, lower case letters at the top of the graph correspond to the specific studies reported below the figure. In some cases, the same compound has been the subject of more than one investigation (for instance, in Fig. 3, diclofenac was investigated in 6 studies called: *a*, *b*, *d*, *f*, *g* and *i*). Compounds belonging to a class are grouped together and the name of the class is reported in upper case (according to Table 2) at the bottom of the graph. Finally, the separate grid shows when the micropollutant was released. This means that negative removal efficiencies were reported in the reviewed papers, occurring in MBR alone (more often) and/or in MBR combined with AC (only for carbamazepine, Li et al., 2011). Figs. 3 and 4 do not correlate removal efficiencies with specific operational conditions and configurations: the hybrid MBR is considered a *black box* and the details regarding quantity of added PAC or operational conditions referring to PAC or GAC are not reported, or when the PAC is added (in the anoxic or in the aerobic compartment): they will be discussed in Section 6.

In more detail, Fig. 3 refers to the removal achieved for 48 compounds belonging to 13 classes in MBR and (MBR + PAC). It emerges that the presence of AC added in the biological tank improves the removal of most of the compounds: it occurred in 79 out of the 108 reported cases. In 13 of the remaining 29 cases, MP removal did not improve and, according to the authors, this was due to the fact that the compound was almost completely removed in MBR and, due to the presence of AC, the contribution was not relevant (Nguyen et al., 2013a). In the last 16 cases, the MBR presents a higher removal efficiency than the corresponding case of MBR + PAC. Details of these analyses are reported in Table S3. Briefly: higher MP removal values found in MBR alone compared to MBR + PAC were related to removal data referring to different AC working age (Alvarino et al., 2017; Nguyen et al., 2013a), different sludge properties resulting in different characteristics of the cake developed against the membrane and thus cake filtration performance (Alvarino et al., 2017) and accidental temperature drop (Li et al., 2011). As to Fig. 4, it includes 22 compounds belonging to 9 classes and 44 columns. The removal in MBR → GAC was higher in 27 cases than in MBR alone. In 16 cases, MBR reached almost complete removal efficiencies and the removal efficiency did not increase after the GAC stage. In only one case referring to paracetamol, the trend is not clear.

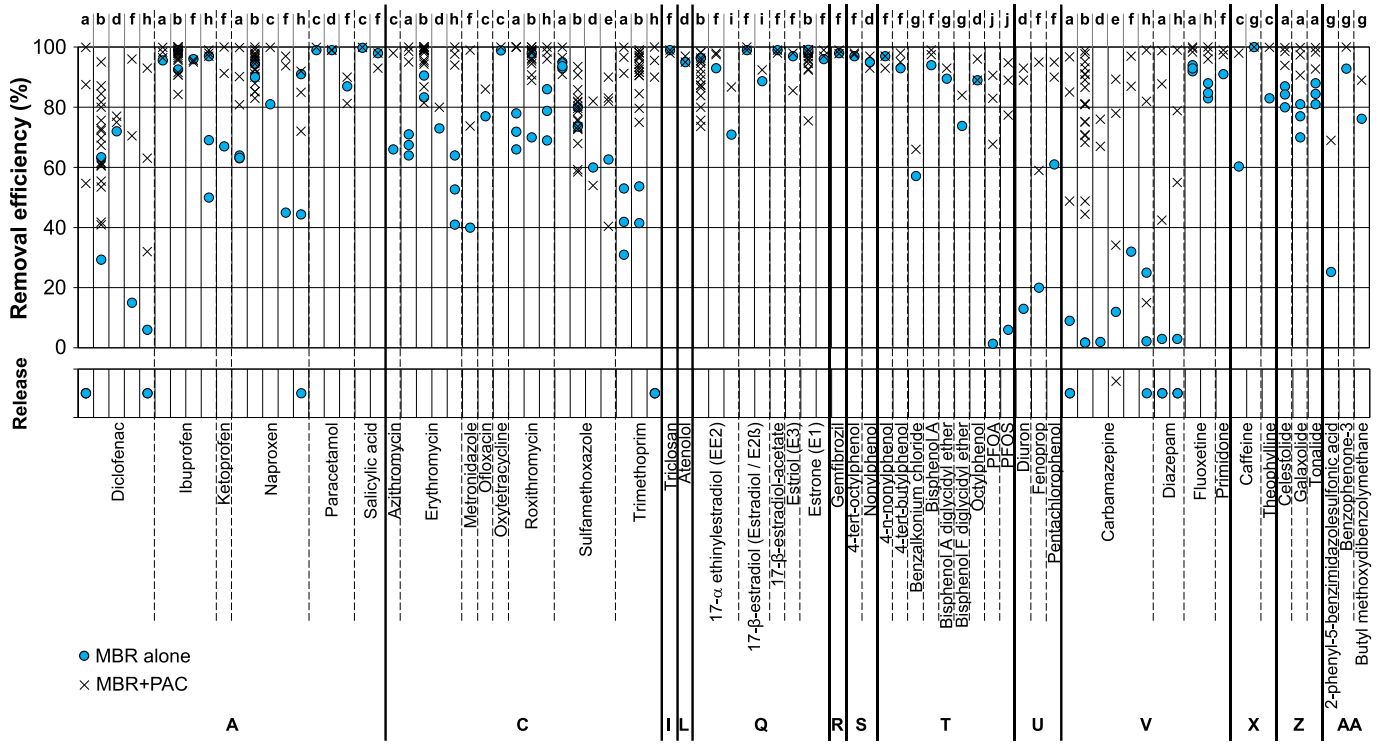
Table S4 reports further details about this analysis. Due to a lack of data referring to the removal efficiencies for MPs achieved in MBR alone, but only in GAC as a PT, data reported in Baresel et al. (2019), Grover et al. (2011), Langenhoff et al. (2013) and Sbardella et al. (2018) were not included in this figure.

Fig. 3 shows that MP release occurred occasionally with the only exception of trimethoprim, which was always released in the investigations by Serrano et al. (2011). The authors explained this finding by the fact that nitrifier bacteria were absent in the biomass within the MBR and trimethoprim was not degraded by the different species developed in the microbial community. In the other cases, MP release was ascribed to the following causes: changes in operational conditions (for instance a sharp increment of the MP concentration in the influent) (Li et al., 2011), environmental conditions such as a decrement in temperature which strongly affects biological reaction rates (Li et al., 2011); AC saturation (Alvarino et al., 2016), re-generation of parent compounds starting from the corresponding metabolites or transformation products (for diclofenac and carbamazepine) (Alvarino et al., 2016). Another possible reason, not reported in the reviewed studies, but often remarked in the literature (Verlicchi et al., 2012), is an inappropriate sampling protocol.

These first rough comparisons lead to the consideration that the presence of AC has the potential to improve removal for most compounds. The influence of the main operational parameters will be analysed in detail in Section 6.

5.1. Removal in MBR + PAC

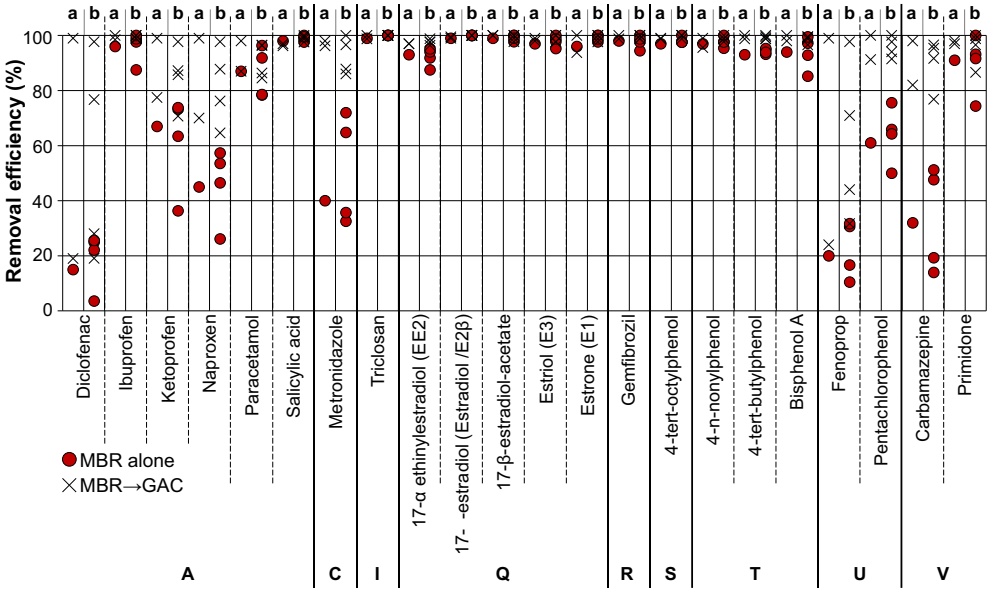
In order to better investigate the influence of the *amount of PAC added* in the bioreactor, literature data were reported in Fig. 5



a Alvarino et al. 2016; **b** Alvarino et al. 2017; **c** Asif et al. 2020; **d** Echevarría et al. 2019; **e** Li et al. 2011; **f** Nguyen et al. 2013a; **g** Remy et al. 2012; **h** Serrano et al. 2011; **i** Yang et al. 2012; **j** Yu et al. 2014

Fig. 3. Comparison among removal efficiencies achieved in MBR alone and MBR coupled with PAC.

considering the different PAC dosages, between <0.05 g/L and 20 g/L of PAC. PAC dosages were classified as: <0.05 g/L, 0.05–0.1 g/L; 0.25 g/L, 0.5 g/L, 0.75 g/L, 1–2 g/L and 20 g/L. In Fig. S2, the same data are reported according to the Authors. Based on the collected data, 48 compounds belonging to 13 different classes were analysed, and the most studied were: carbamazepine (31 values), diclofenac (28), naproxen and sulfamethoxazole (27), ibuprofen (26), trimethoprim (24), erythromycin (23), roxithromycin (22), EE2 (21) and E1 (20). The remaining compounds have only 1–6 values of removal efficiency. It emerges that all the compounds can be removed by MBR + PAC, even the most recalcitrant diclofenac and carbamazepine. The variability ranges are 32% to 99% for diclofenac, the highest values were found in Alvarino et al. (2016), and 15% to 99% for carbamazepine, with the top removal reported in Alvarino et al. (2017). At the lowest doses of PAC (<0.05 g/L), the removal efficiency is at least 60% with the only exception of sulfamethoxazole (it needs at least 0.25 g/L to achieve 60%



a Nguyen et al. 2013a; **b** Nguyen et al. 2013b

Fig. 4. Comparison among removal efficiencies achieved in MBR alone and MBR coupled with GAC.

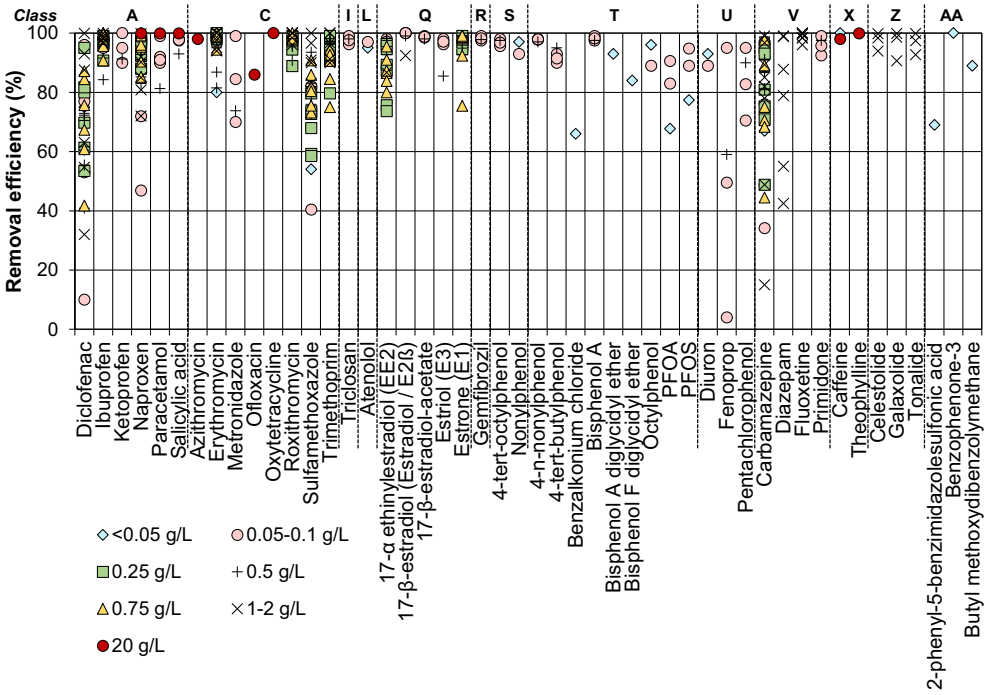


Fig. 5. Removal efficiencies for the compounds investigated in MBR + PAC with a submerged or side stream membrane unit.
Data from: Alvarino et al. (2016, 2017); Asif et al. (2020); Echevarría et al. (2019); Li et al. (2011); Nguyen et al. (2013a); Remy et al. (2012); Serrano et al. (2011); Yang et al. (2012); and Yu et al. (2014).

removal). The high dosage of 20 g/L in Asif et al. (2020) was selected in order to guarantee a homogeneous integration of PAC and sludge and to achieve the best rheological properties of the sludge.

An analysis of the collected data highlights that the addition of PAC as low as 0.1 g/L is sufficient to achieve a removal of 80% for 34 out of the 37 compounds which were investigated in this range of PAC addition.

PAC addition in the MBR leads to a relevant increment in PFOS and PFOA removal (Fig. 3): from <7% in the MBR to the range 68% to 94% in the MBR + PAC, depending on the concentration of AC and the compound (Yu et al., 2014). Their removal is only due to adsorption on PAC and 0.08 g/L seems to be enough to reach 80% of removal. The Authors underline that the expected removal with the addition of PAC should be much higher, especially at the highest PAC dosages, but probably because of fouling due to sludge and DOM, the available PAC surface for PFOA and PFOS adsorption was greatly reduced and this was more evident for PFOS, the compound with higher sorption potential (higher D_{ow}, see Table S1). For the most investigated compounds (diclofenac, sulfamethoxazole and carbamazepine), the addition of PAC leads to an increment in removal efficiency, despite its value varying in a range greater than 50%. This leads to the conclusion that PAC added in the MBR does not guarantee a minimum removal for the compounds due to many factors that influence their behaviour, which will be discussed in Section 6.

5.2. Removal when AC is used as a post treatment

An analysis of the removal efficiencies achieved when PAC is used as a post treatment is reported in Fig. 6: PAC treatment follows the biological step consisting of a CAS (Löwenberg et al., 2014; Margot et al., 2013) or an MBR (Kovalova et al., 2013b). The tested doses were < 0.05 g/L for CAS and MBR and 1–2 g/L for CAS. With regard to the first interval, the tested dosages were 0.008; 0.023 and 0.043 g/L for MBR → PAC (light blue square in Fig. 6) and 0.0171 g/L for CAS → PAC (dark square in Fig. 6). Referring to the light blue square values, the wide variability emerging from Fig. 6 is strictly correlated to the different dosages. An in-depth analysis is available in the report (McArdell et al., 2011) as well as in Kovalova et al. (2013b).

Removal values of compounds in MBR → PAC < 20% were found at the lowest doses of PAC (0.008 g/L). This was the case for all the contrast media (class N) with the only exception of iopromide which exhibited a removal of 47% already at these dosage conditions. Diatrizoate and ioxitalamic acid were always poorly removed: between 1% and 18% at the different tested doses. Moreover, it was found that poor removal (21% to 35%) is achieved for all contrast media in MBR alone (Margot et al., 2013; data not shown) and PAC addition may remove them, depending on the added dose. Fluctuations in the removal efficiencies of such recalcitrant compounds also leading to negative values (not shown) may be ascribed to variations in their influent concentrations (Lipp et al., 2012) and to a sampling mode that implies the analysis of the grab or composite samples taken not considering the HRT of the monitored treatment stage (Verlicchi et al., 2012). It emerges that a higher dose is not able to enhance the removal achieved for diclofenac, sulfamethoxazole, mecoprop and carbamazepine. At the same dose of PAC as a PT after a CAS or an MBR, the removal achieved after an MBR is higher with respect to the removal achieved after a CAS for diclofenac (95% to 99% versus 82% to 85%) and carbamazepine (99% versus 90% to 99%), lower for sulfamethoxazole (2% to 60% versus 58% to 64%) and partially overlapped in the case of benzotriazole (68% to 92% versus 90% to 92%). This can be ascribed to the interactions between the organic matter and the AC surface, which are more relevant in the case of CAS effluent due to its higher concentration with respect to MBR permeate. In these configurations, there was a higher number of compounds with a variability of more than 50% in their removal efficiency compared to configurations I and II (Fig. 6) where only three compounds presented such a variability range.

Fig. 7 refers to MP removal efficiencies in a GAC column acting as a PT, after the biological step at different empty bed volumes (EBV), that is during the GAC working period. They varied between <1000 EBV (Nguyen et al., 2013b, 2012) and 60,000 EBV (Baresel et al., 2019). Some investigations did not report the EBV correlated to the removal values and thus their data are not included in Fig. 7 (Grover et al.,

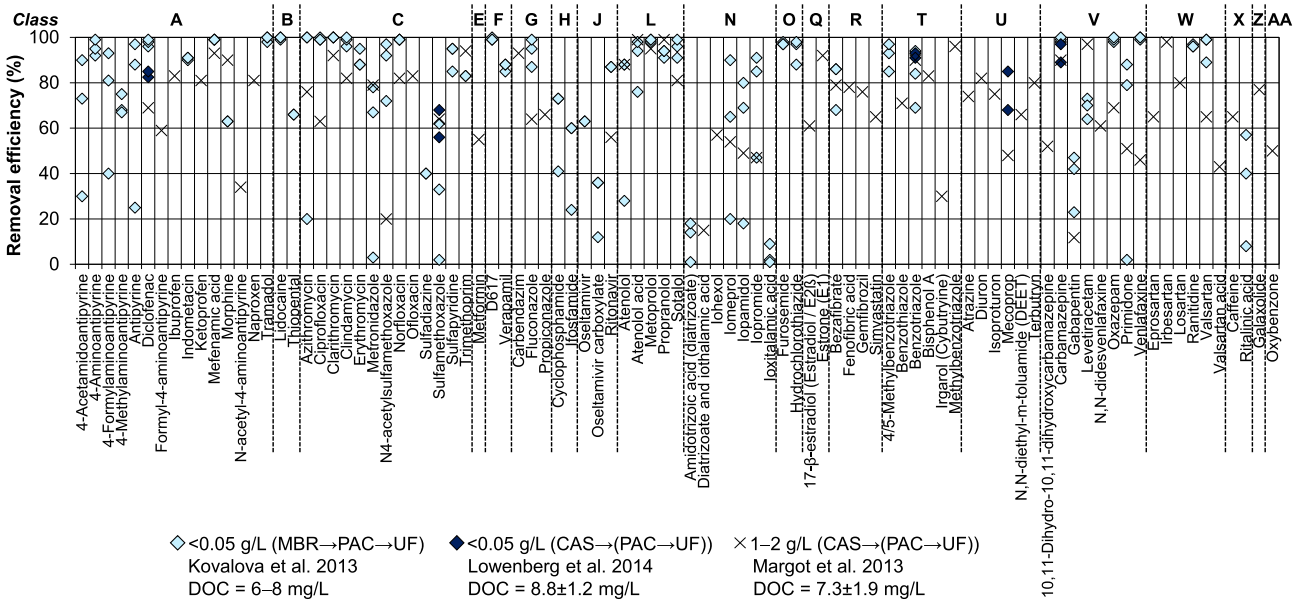


Fig. 6. Removal efficiencies of the compounds included in the reviewed studies referring only to the PAC polishing treatment, following a CAS or an MBR. DOC concentrations refer to the secondary effluent fed to the PAC unit.
Data from: Kovalova et al. (2013b); Löwenberg et al. (2014); and Margot et al. (2013).

2011; Itzel et al., 2018; Langenhoff et al., 2013; Paulus et al., 2019). On the contrary, all the collected data on removal efficiencies in a polishing GAC unit are reported in Fig. S3, grouped according to the Authors. It emerges that for most investigated compounds the removal efficiencies vary greatly. The smallest variability intervals were found for bisphenol A (6%, between 77% and 83%), ciprofloxacin (23%, between 63% and 83%), and 4-n-nonylphenol and 4-tert-butylphenol (25% respectively 50% to 75% and 74% to 99%).The widest interval was found for diclofenac (3% to 99%), with the lowest value found in Nguyen et al. (2013b) and the highest values collected in Paredes et al. (2018) and Baresel et al. (2019). The extremely low removal was ascribed to the saturation of the GAC column, whereas the highest removal values may be ascribed to the biological regeneration within the BAC which thus allowed a high and continuous MP removal from the real wastewater, even at high EBVs. As diclofenac is poorly removed in biological processes (20% to 30% as in Fig. 4), the contribution of the GAC column in its removal is fundamental. The removal achieved with the GAC filtration is related to MP nature, its biodegradability and sorption potential, the degree of saturation level of the AC filter, the EBCT, as well as MP concentration in the GAC influent. If a compound is highly removed in the bioreactor, the resulting concentration in the treated effluent is low. In this case, MP removal efficiencies are around 40% to 50% in the GAC column are still to be considered very good as they lead to a very high overall removal. This is the case for ibuprofen, paracetamol, E3, 4-tert-octylphenol, 4-tert-butylphenol and 4-n-nonylphenol. When MP removal in the bioreactor is moderate and also variable in a wide range (20% to 70%), it emerges that the GAC can have two different behaviours, which mainly depend on the nature of the compound. GAC can exhibit a fairly constant removal efficiency up to its saturation (ketoprofen); on the other hand, it seems that GAC performance may adapt to the variations in the permeate concentration. This was the case for metronidazole for which GAC was able to guarantee a very high removal efficiency leading to an overall removal between 86% and 99%, as shown in Fig. 4 (Nguyen et al., 2013b). This issue will be discussed later and compared with recent literature findings. In the case of compounds with very low removal efficiencies in the bioreactor,

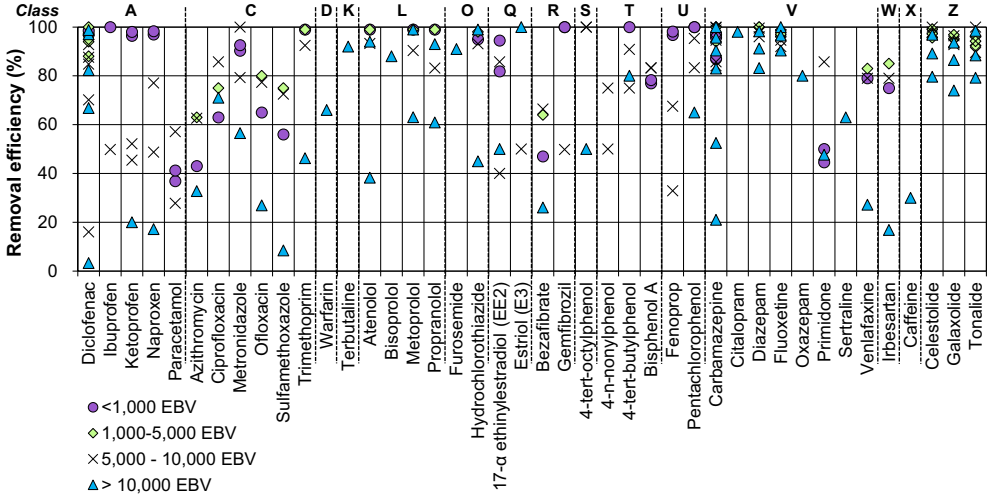


Fig. 7. Removal efficiencies obtained in the GAC unit acting as a PT for the compounds under review at different empty bed volumes.
Data from: Baresel et al. (2019); Nguyen et al. (2013b, 2012); Paredes et al. (2018); and Sbardella et al. (2018).

GAC may greatly contribute to their removal and its presence is essential for assuring a good removal of such recalcitrant compounds. If a decrement occurs, it may be correlated to GAC saturation conditions (fenoprop, carbamazepine and diclofenac). If biological regeneration occurs (see Section 4), MPs may still be removed by adsorption. This explains the behaviour of atenolol, metoprolol and propranolol, the antibiotic trimethoprim and the diuretic hydrochlorothiazide, and also diclofenac, which maintain a medium-high removal efficiency for a long working time (Baresel et al., 2019; Sbardella et al., 2018). In the case of GAC saturation, biodegradable compounds absorbed in BAC or adsorbed in GAC, may still undergo biodegradation processes which maintain a good removal efficiency at long operation times (azithromycin, ciprofloxacin, ofloxacin, and sulfamethoxazole) (Sbardella et al., 2018).

5.3. MP concentrations in MBR + PAC effluent

Figs. 8 and 9 refer to MP concentrations in the effluent from an (MBR + PAC) system included in the review. The different symbols used for these effluent quality data depend on the value of the corresponding biological stage influent. Ranges were set for the influent concentrations: 0.01–0.1 μg/L, 0.1–0.5 μg/L, 0.5–1 μg/L, 1–25 μg/L, 100–120 μg/L and 750 μg/L. This discretisation was defined on the basis of the collected literature data and there is no constant interval width for this reason. Data reported in Figs. 8 and 9 refer to different types of MBR (in particular they could include UF or MF membrane units, different microbial community species, for instance the presence of nitrifier bacteria as discussed in Alvarino et al. (2017), different AC dosages in the reactor, different AC ages, different influent characteristics in terms of micro- and macropollutants. They thus provide ranges of effluent concentrations corresponding to different operational conditions in the treatment systems. For this, the analysis of the reported trends requires great caution.

MP concentrations lower than 0.01 μg/L correspond to a very good quality of the effluent. They refer to compounds which have a high sorption potential ($\mathrm{Log}D_{ow} > 3$, as for E2β), or are highly degradable (caffeine), or have a low influent concentration (naproxen). Additionally, they refer to high PAC dosages (naproxen, paracetamol, salicylic acid and oxytetracycline, azithromycin, caffeine) (Asif et al., 2020; Alvarino et al., 2017) or to fresh PAC (erythromycin, roxithromycin, sulfamethoxazole, fluoxetine) (Alvarino et al., 2016; Alvarino et al., 2017).

The highest effluent concentrations correspond to the highest influent values or ranges of concentrations: this was the case for sulfamethoxazole (Li et al., 2011) (in Fig. 8), PFOA and PFAS (Yu et al., 2014) and carbamazepine (Li et al., 2011) (in Fig. 9). There is an exception: carbamazepine in Fig. 9 has an effluent concentration similar to the influent one (around 22 μg/L). According to the authors (Serrano et al., 2011), this might be ascribed to the saturation of the AC after three months of continuous operations. The release of carbamazepine (see Fig. 3) reported in Li et al. (2011) was related to an accidental low temperature which may have reduced the kinetics of the biological processes and the transfer of the MP from the solid (sludge or AC) to the liquid phase. The effluent concentration increased to 190 mg/L from 100 mg/L in the influent. Paracetamol (Fig. 8), an easily degradable compound, was found at a very low concentration also with an influent concentration equal to 118 μg/L (Echevarría et al., 2019) and with an AC dosage in the range 0.025–0.050 g/L.

On the other hand, diazepam (Fig. 9), a poorly degradable compound, was found in the effluent at 0.1–11 μg/L with the corresponding influent in the range 10–25 μg/L (Serrano et al., 2011). The highest effluent concentrations are due to PAC saturation (Alvarino et al., 2016).

If a threshold is set equal to 1 μg/L for the effluent concentration of an AC treatment, out of the 48 reported micropollutants in Figs. 8 and 9, 32 compounds are always below such threshold, and 16 compounds are at least one value above. If the threshold is set at 0.1 mg/L, the compounds with at least one value above it become 39 out of 48. This means that most of the selected MPs may occur in the MBR + PAC permeate in the range 0.1–1 mg/L.

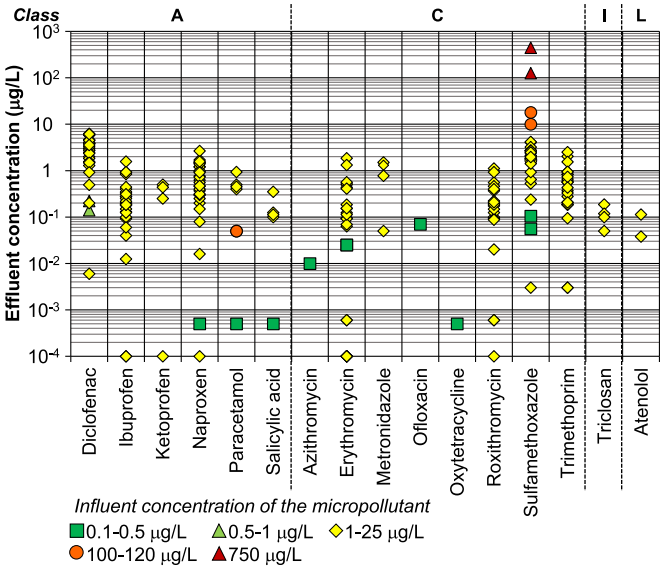


Fig. 8. Concentrations of micropollutants in the effluent of MBR + PAC for some classes of micropollutants. Data are provided with respect to the micropollutants concentration in the corresponding influent.
Data from: Alvarino et al. (2016, 2017); Asif et al. (2020); Echevarría et al. (2019); Li et al. (2011); Nguyen et al. (2013a); Serrano et al. (2011); and Yang et al. (2012).

5.4. MP concentrations in the effluent of an AC stage (post treatment)

Figs. S4 and S5 refer to the effluent quality if PAC or GAC are used as a PT. Reported data are related to the influent concentrations and to PAC dosage or GAC EBV. Compounds in light pink (64) refer only to PAC, those in light grey (22) only to GAC, and the remaining 29 to both AC types. It emerges that the maximum concentrations in the effluent were found in general for PAC treatment, with the contrast media (class N) being the compounds exhibiting the highest concentrations (10–2750 mg/L) based on the findings by Kovalova et al. (2013b). In discussing these data, it is important to remark that they refer to high influent concentrations (Fig. 9), and to investigations which exhibited an average (good) removal of around 60% (Fig. 6). Limiting the attention to the 29 common compounds (Fig. S6), and to the applied conditions (see Figs. S4 and S5), it seems that the quality of a PAC unit effluent is better for analgesics/anti-inflammatories, hormones and carbamazepine, whereas in case of a GAC column effluent the quality is better for antibiotics, beta-blockers and diatrizoate. A reduction in the concentrations is more evident for those compounds occurring at higher influent concentrations, underlining that the observed removal efficiencies (Figs. 6 and 7) are strictly dependant on the influent concentrations, as also discussed for other treatments, such as the biological stage (Verlicchi et al., 2012).

If a threshold is set at 1 mg/L, out of the 115 compounds analysed, 22 have at least one value exceeding it (20%). They are mainly analgesics, anti-inflammatories and contrast media.

A comparison was carried out between the quality in the case of MBR + PAC (Figs. 8 and 9) and MBR → PAC with regard to the most common investigated compounds: sulfamethoxazole, trimethoprim, carbamazepine and metronidazole. The collected concentrations in MBR + PAC permeate were obtained by an addition of 0.025–1 g/L of PAC in the bioreactor for sulfamethoxazole, trimetroprim and carbamazepine and 0.1 g/L and 0.5 g/L for metronidazole and those referring to the PT unit effluent by an addition of 0.008–2 g/L for all the compounds. It was found that the concentrations of sulfamethoxazole, trimethoprim and carbamazepine are lower when AC acts as a PT, and for metronidazole, the variability ranges of the effluent concentrations are similar in both cases.

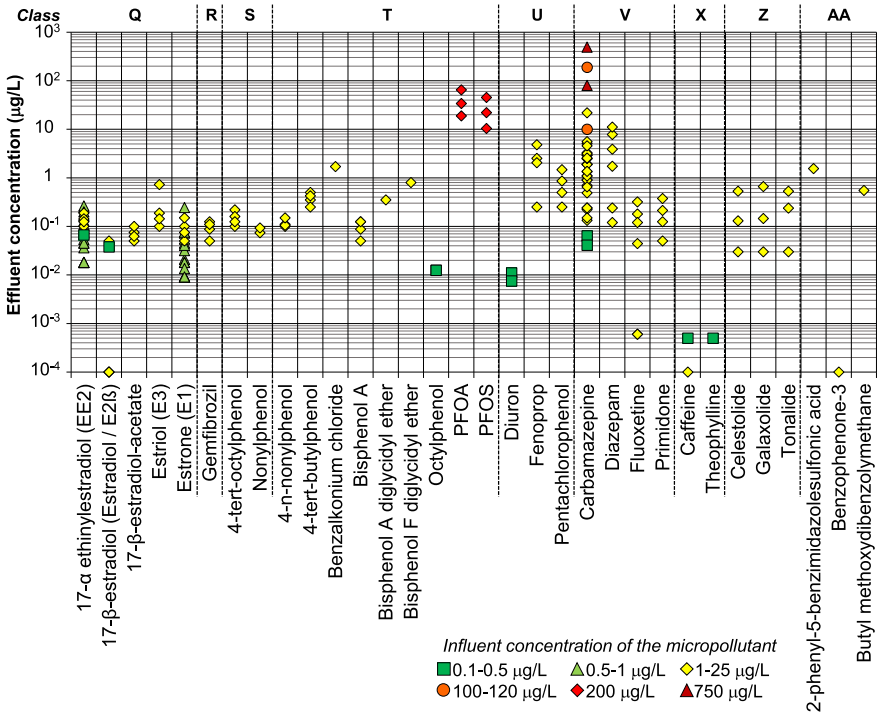


Fig. 9. Concentration in the effluent of MBR + PAC for micropollutants belonging to the other classes included in the review.
Data from: Alvarino et al. (2016, 2017); Asif et al. (2020); Echevarría et al. (2019); Li et al. (2011); Nguyen et al. (2013a); Remy et al. (2012); Serrano et al. (2011); and Yu et al. (2014).

Ciprofloxacin shows very good removal in PAC as a PT and in the case of influent concentrations around 15 mg/L.

5.5. Further results

A few studies investigated or estimated the mass load of micropollutants sorbed onto the activated carbon and the activated sludge, with different dosages of PAC in the bioreactor in long-term investigations: PFOS and PFOA in Yu et al. (2014), and E2 and EE2 in Yang et al. (2012). Yang et al. (2012) found that the main contribution due to the presence of PAC is in a greater sorption percentage of the investigated compounds, whereas the impact on biodegradation is quite modest, with the k_{biol} being quite similar (for E2 it was 8.38 1/d in MBR and 9 1/d in MBR + PAC, for EE2 it was 4.41 1/d in MBR and 4.8 1/d in MBR + PAC). Alvarino et al. (2016) stated that PAC addition leads to an enhancement in the biotransformation for some MPs mainly for those exhibiting moderate kinetics.

As to K_d, they found that the presence of PAC greatly improves the adsorption of EE2, which is more hydrophobic than E2: its K_d in MBR sludge was 1.431 L/gTSS whereas in MBR + PAC sludge it was equal to 4.123 L/gTSS. As to E2, its K_d was 0.916 L/g TSS in MBR sludge and 1.671 L/gTSS in MBR + PAC sludge. As a consequence, the enhanced sorption capacity in MBR + PAC sludge could increase the amount of EE2 and E2 adsorbed onto sludge.

6. Discussion

The potential of AC in removing MPs from wastewater prompted specific investigations on adsorption batch tests under controlled conditions (e.g. aqueous solutions and synthetic water with a simulated matrix effect) (de Ridder et al., 2010; Dickenson and Drewes, 2010). However, removal mechanisms of MPs in hybrid MBRs are not limited to adsorption processes as described in Section 4.

AC and MP structure and properties, wastewater composition, and operational conditions strongly influence the overall removal of MPs in MBR coupled with AC. At the same time, AC presence can influence MP fate during treatment, change sludge properties and also have an effect on membrane fouling. These issues will be discussed in the following sections.

6.1. Factors influencing the removal of MPs by the presence of AC

The main factors influencing MP removal are related to compound properties, AC characteristics and dosage frequency and mode, wastewater composition (namely DOM and its content of large molecules and low molecular weight organics), and treatment operational conditions. The interactions between MP and AC depend on their properties. The extent at which these interactions may develop is related to the available quantity of AC and MP and the conditions under which these interactions occur.

6.1.1. Micropollutant properties

The main properties affecting MP removal mechanisms include molecule charge, Log K_{ow} or better Log D_{ow}, pK_a, molecular size, and specific functional groups within the molecule. Most of these properties are available in Table S1 for the reviewed compounds.

6.1.1.1. Charge. MP charge is a leading parameter if its removal is due to electrostatic interactions with AC in a hybrid MBR. An analysis of the removal efficiencies of the selected MPs on the basis of their charge (anionic, neutral, zwitterionic and cationic compounds at the operating pH) and Log D_{ow} is reported in Fig. S7 referring to a PAC unit acting as a PT. Similar trends were found considering removal in GAC column as a PT.

It emerges that cationic compounds (including clarithromycin) seem more prone to be removed by AC treatment due to electrostatic interactions between the positively charged surface of the pollutants and the negative surface of the carbon, confirming the findings by Kovalova et al. (2013b). Cationic compounds seem to be mostly well removed regardless of their other properties (Mailler et al., 2015; Margot et al.,

2013). This fact justifies their small removal variability range compared to anionic or neutral ones. In the case of neutral compounds, removal is influenced by hydrophobicity and molecule structure (mainly functional groups that allow H-bonds and π-π bonds) (de Ridder et al., 2010). A significant positive correlation has been found regarding MP removal and Log D_{ow} (Mailler et al., 2015). For anionic compounds, electrostatic repulsion is expected between the AC and MP surface. Although it seems to be a relation between hydrophobicity and removal efficiency in the case of PAC as a PT (see Fig. S7), no clear evidence of this phenomenon was found in the literature (Mailler et al., 2015; Margot et al., 2013). However, high MP hydrophilicity can result in low adsorption capacity for charged compounds even when electrostatic interactions are expected between AC and MPs (Kovalova et al., 2013a). Moreover, it seems that saturation is more prone to take place for anionic compounds in wastewater (Mailler et al., 2015).

6.1.1.2. Log D_{OW}. An analysis of the removal as a function of Log D_{ow} has been carried out by Alves et al. (2018), Kovalova et al. (2013b) and Rattier et al. (2014) for many MPs and they do not show a clear correlation. Referring to neutral compounds, Fig. S7 shows that at higher Log D_{ow} values the removal efficiencies are higher and have a lower variability range. According to de Ridder et al. (2010) at log D_{ow} greater than 3.7 hydrophobic interactions become the dominant removal mechanism.

6.1.1.3. Molecular weight. Alves et al. (2018) found that if AC is added to spiked water, there is a clear correlation between molecular weight and removal efficiency: they stated that the higher the molecular weight, the higher the amount of AC to guarantee the same removal efficiency, confirming that steric hindrance of the large molecules hinders their adsorption rate. This behaviour is more pronounced in the case of hydrophilic compounds, such as iopromide (Log $D_{ow} = 0.45$).

6.1.2. Characteristics of activated carbon

The main characteristics of AC are reported in Section 3.5. Their influence on the removal of selected MPs were investigated by Alves et al. (2018), Choi et al. (2005), Mailler et al. (2016) and Paredes et al. (2018). In particular, Alves et al. (2018) compared the removal efficiencies for a wide selection of compounds with different types of AC in terms of activation (with steam or chemical), textural properties, chemical properties (related to the functional groups in the outer layer of the grain and in particular to the presence of oxygen surface groups, such as carboxylic, ethers and lactones as reported in Fig. 2C), pH-point of zero charge, as well as surface charge at pH = 8. They found that in pure water, chemical activated carbons are more prone to attract and bind MPs than steam activated carbons and they guarantee 80% removal at lower doses. Choi et al. (2005) linked AC characteristics (specific surface area, pore volume and material) to MP adsorption in GAC columns. They found a negative correlation between pore volume and the BET specific surface area; they remarked that the BET specific surface area and pore volume reduce as the operation time increases, their reduction occurs mostly in micro-pores and that MP and DOM adsorbed onto macropores can subsequently cause a micropore blockage. The extent of this reduction depends on the carbon type. According to the investigations by Fundneider et al. (2021a), a balanced proportion of macro-, meso- and micropores in the GAC improve the MP removal in the presence of DOC, whereas GAC with a high proportion of micropores is more affected by pore blockage due to DOC adsorption leading to a lower MP removal. MP removal is strongly affected by the presence of DOM which may partially cover the AC surface. If an AC is positively charged, it attracts DOM (negatively charged) and thus its surface will have positively and negatively charged zones, thus attracting anionic and cationic MPs respectively (Fig. 2). Finally, it was also found that pore volume is more important than specific area and a larger pore volume generally allows a higher removal of MPs (Rossner et al., 2009).

Mailler et al. (2016) studied the influence on the removal efficiencies of 15 MPs of the physical and characteristics of four PACs. They found that the BET surface area is positively correlated to MP removal. On the other hand, the BET surface area is negatively correlated to bulk density, that is, a high BET surface area corresponded to low bulk densities. As bulk density is an easy-to-measure parameter it could be used as an indicator to select AC.

6.1.3. PAC dosage and losses

PAC dosage seems to be one of the crucial operational parameters regarding the influence on MP removal. Tested dosages were generally defined on the basis of preliminary batch tests aiming at investigating the sorption potential of the specific MP on an AC in pure water. Unfortunately test data regarding adsorption of MPs in the case of PAC added in an MBR did not fit well with the adsorption isotherms (Li et al., 2011; Nguyen et al., 2013b).

PAC was added at the beginning of the investigations (Alvarino et al., 2016) or periodically during the experimental period (Alvarino et al., 2017; Li et al., 2011). In this last scenario, fresh AC mixes with "older" AC which is partially saturated. It was found that the addition leads to an improvement in the removal of recalcitrant MPs such as carbamazepine and diclofenac and, for this reason, carbamazepine (concentration) was suggested as an indicator of the AC saturation level (Alvarino et al., 2017).

The loss of the *potential* adsorption capacity of the AC is reduced not only by its progressive saturation, but also by its losses from the system by withdrawal of excess sludge or retentate from membrane PT units. PAC addition (replenishment) is thus necessary to maintain its desired concentration in the tank.

6.1.4. Dosage point

In some investigations PAC was added in the anoxic tank (Remy et al., 2012), in others in the aerobic one (Asif et al., 2020; Echevarría et al., 2019). In Asif et al. (2020), PAC was added in the aerobic compartment of the anoxic/aerobic side stream MBR and due to sludge recirculation a fraction of PAC embedded in the sludge flocs was fed to the anoxic compartment, promoting MP removal in this environment. AC may also reach the biological reactor in a different way. This is the case in schematic representation V in Table 1: PAC is used as a PT followed by a UF unit for its separation. The recirculation of the retained PAC back to the MBR, promotes its mixing with activated sludge and thus improves MP sorption and degradation (Lipp et al., 2012). Based on previous studies, it emerges that useful considerations can be found in Streicher et al. (2016) who suggested that the long contact time in the activated sludge processes might enhance the PAC removal efficiency of many MPs compared to the short contact times in case of PT and that PAC addition in the anoxic tank seems to be the best option. Finally, Boehler et al. (2012) reported that similar removal of MPs can be achieved by adding 10–20 mg PAC/L in the case of a PT (DOM in the range 5–10 mg/L) and 30–40 mg/L of PAC if it is added in the biological tank.

6.1.5. Duration of the added PAC

The removal of an MP is strictly related to the working age of the AC: once it is added in the bioreactor, the whole surface is available for sorption and all the active sites are free (Fig. 1B). After a period of operation, some sites are occupied by MPs and DOM and the removal may be lower than in the case of fresh AC. Once sorbed, the MP can be stable or subjected to biodegradation processes, leading to transformation products which could leave the carbon surface or remain sorbed on it (Baresel et al., 2019). As reported in Section 3.5, doses of PAC added in the biological treatment varied between 0.004 g/L (Remy et al., 2012) and 20 g/L (Asif et al., 2020). Removal data provided in the studies are seldom correlated to the AC working age: only 8 studies provided removal as a function of time (Alvarino et al., 2016, 2017; Li et al., 2011; Löwenberg et al., 2014; Nguyen et al., 2013a, 2014; Serrano et al., 2011; Wei et al.,

2016). In order to guarantee a good performance of the AC present in the treatment, Alvarino et al. (2017) validated a dosage of 250 mg/L added every 35 days.

6.1.6. Sludge retention time

(Ng et al., 2013) evaluated the influence of SRT in hybrid MBRs (configurations I and II in Table 1, SRT = 10 d, 30 d and >100 d). At lower SRTs, a higher amount of fresh PAC is required to maintain a fairly constant AC concentration in the bioreactor. This would provide a higher adsorption of MPs and DOM and at the same time this practice would reduce the risk of membrane fouling. Higher SRTs promote the development of a diverse biomass species within the biological compartments and thus they would favour MP biodegradation processes. Specific investigations on the influence of SRT on the removal of MPs were not carried out in the reviewed studies: SRT ranged between 12 d (Echevarría et al., 2019) and 300 d (Nguyen et al., 2014) and no relevant removal differences were found.

6.1.7. Hydraulic retention time in PAC tank

According to kinetic studies, such as those by Kovalova et al. (2013a), Mailler et al. (2016) and Meinel et al. (2015), contact time influences the MP removal rate. They found that short HRT (30–60 min) may be enough to guarantee an efficient adsorption of most MPs (including atrazine, norfloxacin, ofloxacin and sulfamethoxazole). Larger molecules, such as erythromycin and roxithromycin require more than 1 h to achieve high removal. Moreover, adsorption is faster in the case of finer AC. In the reviewed studies, the tested HRT for the PAC tank as a PT varied between 0.5 h and 24 h and it allows the transfer of most of the MPs from the liquid to the solid phase. According to Lee et al. (2009), in submerged MBR, high HRT, low flux and intense mixing in the bioreactor are the best operational conditions to maintain the PAC in the bulk phase and reduce its deposition against the membrane. In fact, they found that PAC against the membrane reduces its sorption available surface thus its potential removal capacity. These findings refer to investigations carried out with deionised water, where biodegradation cannot occur for the investigated compound (E2). It is important to remark that the retention time of the PAC in the tank is another fundamental parameter, as remarked in Section 4, but unfortunately it is not possible to correlate MP removal data to PAC retention time due to lack of data.

6.1.8. Dissolved organic matter

DOM is due to large organic molecules (biopolymers, humic substances and building blocks) and smaller molecules (low molecular weight organic acids and neutrals). Similar DOM concentrations (expressed as mg DOC/L) were found in the different compartments of the bioreactor as well as in a CAS effluent and in an MBR permeate, ranging between 5 mg/L and 18.4 mg/L (Altmann et al., 2014b; Fundneider et al., 2021a; Kovalova et al., 2013b; Meinel et al., 2015; Streicher et al., 2016). Based on Liquid Chromatography–Organic Carbon Detection (LC-OCD), it was found that different percentages of DOM constituents may occur (Altmann et al., 2014b; Filloux et al., 2012; Guillossou et al., 2020; Streicher et al., 2016; Zietzschmann et al., 2016, 2014) depending on the initial raw wastewater and the treatment. Interesting analyses of DOC in the wastewater under treatment were carried out in Fundneider et al. (2021a, 2021b) also by size exclusion chromatography coupled with online DOC and UV_{254}, together with fractionation of the DOC and sorption potential of each fraction. They found that the non-adsorbable DOC in wastewater was around 20%, in agreement with the results achieved by Zietzschmann et al. (2014).

As mentioned above, DOM may affect MP removal as it can compete for available surface/sorption sites and, to a lesser extent, pore blockage, depending on its characteristics (average molecular weight and hydrophobicity) and AC porosity (De Ridder et al., 2011). This fact is clearly evident in Dickenson and Drewes (2010), Guillossou et al. (2020) and Zietzschmann et al. (2016) who compared the removal curves of a selection of MPs at the same dosage of PAC in ultrapure water, drinking water and wastewater. According to the investigations by Dickenson and Drewes (2010), the observed removal was almost complete for all the compounds in the first case and in the range 50% to 75% in the presence of DOM.

Background DOM decreases adsorption capacities to a greater extent than pH, ionic strength, and temperature. This occurs especially at low carbon doses where the competition for sorption sites is strong (Kovalova et al., 2013a). According to Zietzschmann et al. (2014) the different fractions of DOM present a different adsorption behaviour: small molecules adsorb quickly and overall better, instead large molecules show slow and lower adsorption. The effect of small DOM molecule competition seems to affect particularly medium and low adsorbable MPs. In this context, Zietzschmann et al. (2016) found that low molecular weight organics are the main competitors for the active sites in AC, and the estimation of their concentration can be useful in evaluating the required AC dose to reach a desired MP removal. On the other hand, Guillossou et al. (2020) found that in the case of wastewater characterised by a modest fraction of low molecular weight organics, the competition in adsorption is due to biopolymers and hydrophobic molecules. Moreover, MPs may also interact with non-adsorbable DOM and thus remain in the liquid phase (Mailler et al., 2016).

Many authors suggest correlating MP removal to the PAC dose normalised to the respective DOC (that is the specific PAC dose, expressed in terms of mg PAC/mg DOC) (among them: Kovalova et al., 2013b; Streicher et al., 2016; Zietzschmann et al., 2016). This parameter makes it possible to estimate the required dose of a given PAC able to achieve the desired removal of the selected MP from the wastewater under treatment.

DOM adsorbed onto activated carbon is generally negatively charged at the pH of the wastewater and thus can decrease the adsorption of negatively charged MPs through repulsive electrostatic interactions (De Ridder et al., 2011) and increase the attraction of positively charged compounds (Mailler et al., 2015). At the same time, MPs may interact with DOM through Van der Waals bonds, as well as covalent and hydrogen bonds, resulting in a higher removal in MBR systems. This was found for bisphenol A which can interact with microbial by product-like and humic acid-like DOM in wastewater, and carbamazepine and ibuprofen with fulvic acid-like compounds (Hernandez-Ruiz et al., 2012). These complex phenomena are also affected by a high ionic strength in the liquid phase which can reduce the effect of electrostatic repulsion and attraction (De Ridder et al., 2011). Moreover, the DOM attached to the surface may be a barrier for those compounds whose removal is mainly due to adsorption on the activated sites, such as carbamazepine, diclofenac, diazinon and naproxen (Rattier et al., 2012). Guillossou et al. (2020) showed that sufficiently long contact times allow a high removal of many MPs, despite an increase in DOM sorption on AC. This fact was ascribed to a slow diffusion of MPs through the adsorbed DOM on the PAC surface or to the formation of DOM-MPs complexes which are progressively adsorbed on the PAC surface. As highlighted above, proper HRTs can guarantee the transfer of MPs from the liquid to the solid phase.

The interest towards DOM in the study of adsorption processes has increased in recent years being the adsorbed DOM (mg DOC/g GAC) the proposed assessment parameter of the performance of the GAC column instead of the commonly adopted EBV (Fundneider et al., 2021a).

6.1.9. Main factors affecting MP removal by GAC

In a GAC column it is crucial to adopt proper EBCT and filtration velocity v_f. EBCT is a key factor for the design of the GAC column, influencing the breakthrough curves of MPs. Generally, shorter EBCTs may lead to a lower adsorption of MPs. In this context, v_f and column height can be adjusted in order to guarantee a proper EBCT for removing the different MPs (Fundneider et al., 2021a). In the reviewed investigations, EBCT

was between 7 and 50 min and the filtration velocity in the range 0.4–4.67 m/h (Baresel et al., 2019; Nguyen et al., 2013a, 2013b, 2012; Paredes et al., 2018; Sbardella et al., 2018). Investigations were carried out at a lab scale with the only exception of Baresel et al. (2019) who was at a pilot scale plant. A comparison of the adopted values of EBCT and v_f and those provided by the literature (Metcalf and Eddy, 2014) (510 min; 515 m/h as well as filter bed height in the range 24 m) shows that:

- EBCT in these investigations is generally higher (with the exception of Nguyen et al. (2013b, 2012) where EBCT is around 7 min);
- v_f is always less than the minimum literature recommended value;
- as to the height, in lab scale investigations it was between 0.12 m and 0.42 m, in the pilot plant it was 1 m.

The adopted operational conditions (very slow filtration velocity and high EBCT) promoted the transfer of MPs from the liquid to the solid phase and counterbalanced the fact that the bed height was always less than the suggested one.

As to EBCT influence it is important to underline some main results. According to Fundneider et al. (2021a) the smaller the grain size, the larger the specific surface area of the GAC and the shorter the EBCT to reach the equilibrium conditions for the MP mass transfer from the liquid phase to the solid phase. In their investigations, they correlated the MP removal capacity of the GAC column with the DOC sorbed on the GAC mass. They found that operating with EBCT between 6 and 24 min, the measured sorbed DOC on the GAC was higher for GAC columns operating with higher EBCT. With EBCT in the range 24–33 min, no differences were found. Moreover, they found that EBCT ≤ 20 min has a stronger influence on the removal of well adsorbable MPs (among them benzotriazole, carbamazepine and ibersartan) than on the removal of poorly/moderately adsorbable compounds (such as primidone, and gabapentin). This leads to suppose that there is a value for EBCT after which the utilisation capacity of the GAC cannot be further improved. Moreover, they found that longer EBCTs have a positive effect on biological processes which take place within the grains of the GAC column. They reported that the EBCT increment promotes the substrate uptake by the biofilm developed on the grain surface in agreement with Terry and Summers (2018). They concluded that there is a minimum value of EBCT allowing MP removal by sorption and that an EBCT increment leads to an enhanced removal of MP and a better utilisation of the sorption capacity of the GAC column.

As to MP influent concentration, Zietzschmann et al. (2016) found that, below the threshold of 50 mg/L, it did not impact the breakthrough curve of the investigated compound (benzotriazole, carbamazepine and primidone)which was instead impacted by the low molecular weight organics occurring in the wastewater fed to the GAC filter.

Finally, some attempts to investigate MP removal by Langmuir and Freundlich isotherm adsorption curves (Nguyen et al., 2013b; Paredes et al., 2018) pointed out that there is no clear evidence of direct correlations between isotherm parameters and any of the governing parameters such as Log D_{ow}, number of hydrogen bond donor/acceptor groups, dipole moment or aromaticity ratio of the compounds (Nguyen et al., 2013b).

6.1.10. Behaviour of the GAC filter over time

GAC filter removal capacity decreases over time due to the granules increasing saturation by MPs and DOM. MP and DOM loads (mass/time) are crucial parameters affecting the expected operation time. Many authors investigated the GAC filter saturation process through the so called breakthrough profiles which report the ratio between MP effluent concentration c_{eff} and its influent concentration c_{inf} vs EBV (Baresel et al., 2019; Nguyen et al., 2012; Kovalova et al., 2013a; Nguyen et al., 2013b; Paredes et al., 2018). Rapid small-scale column tests (RSSCTs) represent a suitable option to determine breakthrough curves faster than pilot GAC columns. RSSCTs are a scaled-down version (by simple design equations) of pilot GAC beds allowing sorption studies to minimise removal via biodegradation (Crittenden et al., 1991; Zhiteneva et al., 2020).

Once adsorbed on AC, as discussed in Baresel et al. (2019) and Fundneider et al. (2021b), some MPs (among them oxazepam, carbamazepine and diclofenac) may undergo biodegradation, leading to transformation products which may leave the AC surface, thus contributing to AC filter bioregeneration. They noted that for oxazepam it was clearly evident that after 25,000 EBV there was a sharp increment in the ratio c_{eff}/c_{inf}, followed by a consistent decrement due to GAC bioregeneration which allows new molecules of oxazepam to be sorbed. This fact is discussed in Benstoem et al. (2017) who found a good removal of adsorbable MPs when DOM equilibrium in the GAC column is reached. Moreover, it was also observed (Sbardella et al., 2018) that when the carbon is completely saturated (at long operating times), some MPs (for instance azithromycin) exhibit a modest but constant removal which could be ascribed to the biodegradation process still occurring within the BAC.

Fig. 7 reports the removal efficiencies for the reviewed compounds as a function of EBV. It emerges that for some compounds, good removal occurs after a long operation time (really high EBV) for the reasons just discussed, but also for a low influent MP and DOM load (Paredes et al., 2018; Sbardella et al., 2018).

Investigations on the GAC filter lifespan are in any case necessary in order to plan periodical regeneration or replacement of the exhausted AC, as recommended (Nguyen et al., 2013a, 2013b, 2012).

Very recent studies remarked that the parameter EBV does not take into consideration the fluctuations in influent in terms of MP concentration and load which are fundamental for the GAC column lifetime and the breakthrough point. In addition, a variation in the influent flow rate results in an EBCT variation. For these reasons, Fundneider et al. (2021a) propose the adsorbed DOC (mg DOC/g GAC) as the assessment parameter of GAC column performance as it is independent of the influent fluctuations of concentrations and flow rate and Zietzschmann et al. (2016) propose the low molecular weight organics per mass of GAC (mg C/g GAC) and the UV_{254} per mass of GAC. According to Fundneider et al. (2021a) recommendations and guidelines will be available in the near future for the efficient design and operation of GAC columns acting as a PT in WWTP by DWA, the German Association for Water, Wastewater and Waste.

6.1.11. Other parameters influencing MP removal in MBR coupled with AC

6.1.11.1. Temperature. It is well known that an increment in temperature leads to a decrement in sorption of an MP (Nam et al., 2014), whereas it enhances its biodegradation (Alvarino et al., 2018).

6.1.11.2. Addition of the coagulant $FeCl_3$. An addition of the coagulant (4–15 mg/L) to the secondary effluent already mixed with PAC may lead to an improvement in membrane permeability and to control the TMP increase (Löwenberg et al., 2014). It may also favour the separation of the PAC (Margot et al., 2013). In the patented fluidised PAC bed (CarboPlus©), acting as a PT following an attached biomass system, $FeCl_3$ was added (2.5 mg/L) to stabilise the PAC bed and prevent PAC leakage (Mailler et al., 2015). They found a slight enhancement in the removal of carbamazepine, beta-blockers and diclofenac (5% to 15%), probably due to coagulation of the colloidal fraction, a lower removal for sulfamethoxazole (−30%) and no change for lorazepam and bezafibrate.

6.1.11.3. Redox conditions. Once PAC is added, a biofilm may develop on its surface, with aerobic and anoxic zones, thus creating a gradient in redox potential. Over time, the anoxic zone develops and the community structure changes, favouring the species diversity in the anoxic zone (Zhang and Zhao, 2014).

In particular, it was found that PAC addition promotes the development of nitrifiers which favour the degradation of some MPS, mainly hormones and ibuprofen (Alvarino et al., 2018). Alvarino et al. (2016) found that denitrification might occur to some extent also during the aerobic phase. This was due to the growth of a biofilm on the added PAC able to adsorb nitrate ions. This implies the coexistence of anoxic and aerobic zones and thus the development of MP degradation processes occurring under different redox conditions.

6.1.11.4. Type of membranes. The size of the membranes (MF and UF), equipped in MBRs, slightly influences the removals of MPs. It was found that for diclofenac the removal was higher in the case of UF (Alvarino et al., 2017). This fact can be ascribed not to MP size exclusion, but to its sorption on smaller particles retained by the cake layer grown against the membrane.

6.2. Influence of the AC on the MBR operation

Most of the investigations on MBR coupled with AC in recent years have dealt with the removal of macropollutants, membrane fouling, analysis of the operational conditions and factors influencing and enhancing micropollutant removal. This section briefly discusses the main issues related to macropollutant removal, membrane fouling mitigation and sludge property changes.

6.2.1. Effluent quality

The presence of AC favours the development of the biomass leading to a slightly higher concentration of the biomass. This could be ascribed to the sorption of organic matter onto the AC surface in the reactor which is then available to microorganisms for their anabolic activities (Cho et al., 2011; Guo et al., 2008; Johir et al., 2013). As to organic matter (COD, BOD_5, DOC) and suspended solids, it was found that the presence of AC may slightly improve their already high (>95%) removal in MBR (Guo et al., 2008; Johir et al., 2013). A DOC removal of 81% was observed in the MBR investigated by Gao et al. (2016) and a very low removal of aromatic compounds with unsaturated bonds which led to a 34% reduction in UV_{254}. The addition of 1 g/L of PAC in the bioreactor not only incremented the DOC removal up to 91%, but strongly increased the removal of UV_{254} up to 83%. This was explained with the fact that organic compounds, both recalcitrant and easily degradable ones, are directly adsorbed on PAC, then they gather around the bacteria favouring the biodegradation of the recalcitrant compounds. Decrease in UV_{254} is therefore related to the adsorption of aromatic rings, both from MPs and DOM constituents of wastewater (Altmann et al., 2014a; Streicher et al., 2016). As to nitrogen removal, studies remarked that PAC addition may lead to an increment of around 10% (Echevarría et al., 2019; Serrano et al., 2011) due to the formation and growth of a biofilm layer on the adsorbent surface that creates anoxic zones enabling denitrification, as well as an enhancement of nitrifiers (Alvarino et al., 2018). As to P, the observed removal efficiencies in MBR are low to moderate and do not significantly change with the presence of AC (Johir et al., 2013). It was found that the addition of 20 g/L of PAC may promote the development and growth of polyphosphate-accumulating-organisms (PAOs) which led to a 10% increment in the removal of total phosphorus from the wastewater (Asif et al., 2020). To sum up, the different removals achieved may be ascribed to a change in the composition of the mixed liquor (Pan et al., 2016).

6.2.2. Mitigation of the membrane fouling

Most of the studies have dealt and are still dealing with the mitigation effects on the membrane fouling, one of the most critical problems to face and manage with membrane technologies (Iorhemen et al., 2017; Zhang et al., 2019). According to the nature of foulants, fouling can be divided into: *bio-fouling* related to the attached microorganisms on the membrane surface; *organic fouling* due to polysaccharides, proteins, colloidal and humic substances, and bio-polymers and *inorganic fouling* caused by salts, scalants, metal oxides and other inorganic substances (Gkotsis and Zouboulis, 2020). Deposition and attachment of foulants on the membrane surface lead to an increment in hydraulic resistance. As a result, the transmembrane pressure (TMP) increases and the flux through the membrane declines (Woo et al., 2016). Curves of TMP versus operation time shows a first stage in which the membrane does not require cleaning and TMP slightly increases, then in the second stage a sudden increase occurs. Jamal Khan et al. (2012) and Lin et al. (2011) found that the addition of 0.751 g/L of PAC approximately doubles the duration of the first stage, whereas Zhang et al. (2019) suggest 2 g/L as the optimum dosage of PAC as a mitigation strategy of membrane fouling control. In the field of the urban wastewater treatment, the principal fouling which may occur is organic fouling. In order to avoid fouling, it is necessary to retain foulants with adequate pretreatments that are able to reduce their content in the water under treatment.

As described in Section 4, once AC is added in the biological tank, microorganisms and DOM are retained on its surface: their lower concentrations in the liquid phase reduce the membrane organic fouling and biofouling (Gao et al., 2016). Another positive effect of AC addition in the MBR is that it leads to an enhancement of the sludge floc strength (as will be discussed later on). As a consequence, the strong floc structure with incorporated AC will release fewer foulants (soluble COD, proteins and polysaccharides, Ca^{2+}, Mg^{2+}) and thus will reduce the formation of the gel-layer on the membrane (Remy et al., 2010; Johir et al., 2011). The velocity with which the membrane fouls depends on the TOC concentration in the water under treatment; the *flux*, that is the specific flow rate through the membrane, expressed in L/m^2 h, and the added AC size (Ng et al., 2013). They found that membrane fouling prevention can be optimised by using: (*i*) fine rather than coarse PAC as it better reduces the TOC in the bulk phase; and (*ii*) relatively short SRTs (around 10 days), as they favour organic matter adsorption. At the same time, in order to reduce smaller AC particle deposition, flux must be carefully set also on the basis of the aeration system used to detach foulants.

6.2.3. Changes in sludge properties after the PAC addition

PAC addition in the bioreactor leads to an enlargement of the floc size: the average sludge particle size was found around 90 μm in an MBR (70% in the range 10–100 μm) and 128 μm in an MBR + PAC (37% in the same range) (Pan et al., 2016). The sludge flocs enlarge because added PAC neutralises their negative surface charge, causing them to agglomerate (Zhang et al., 2017). The larger flocs increase their strength and are able to withstand greater impacts during aeration (Pan et al., 2016). They lead to a low content of SMP and/or EPS contents in the mixed liquor (Pan et al., 2016; Zhang and Zhao, 2014; Remy et al., 2010).

PAC addition also leads to a change in the chemical composition of the sludge floc which results in a different sorption potential (Yang et al., 2012; Yu et al., 2014). It was also found that the PAC-embedded sludge floc exhibited a higher sorption capacity of recalcitrant aromatic compounds, resulting in a reduction in UV_{254} (Gao et al., 2016; Pan et al., 2016).

The sludge with incorporated PAC has better settling characteristics since less compressible flocs are formed. In this context, Johir et al. (2013) and Pan et al. (2016) found that the sludge volume index (SVI) for MBR sludge was around 90–110 mL/g and in the case of MBR + AC, it was reduced to 50–70 mL/g. The presence of PAC within a sludge floc leads to a cake layer against the more porous membrane than in the absence of PAC: a higher volume percentage of particles was found in the range 300–700 mm in the case of MBR + PAC than in MBR operating with the same MLVSS (Jamal Khan et al., 2012; Lin et al., 2011).

7. Conclusive considerations and need for further research

The current overview shows the effective contribution of AC in (advanced) biological wastewater treatment in enhancing the removal of

many MPs and at the same time the improvement of MBR performance (increment in the removal of the discussed macropollutants, mitigation in membrane fouling and improvement in sludge characteristics). Collected results are strictly related to MP nature, AC characteristics and the presence of DOM in wastewater and the complex interactions among these three actors define the MP removal efficiencies. Although there is not a well-defined PAC dose to add in the MBR to reach a minimum removal for all the MPs, with a PAC of 0.1 g/L, 80% of removal was achieved for most of the tested compounds. MP removal efficiencies show a greater variability when PAC is in the PT in comparison to when it is added in the bioreactor. Moreover, it emerges that the effect of the presence of DOM is more evident in the case of PAC as a PT. MP removal efficiency in the GAC unit working as a PT is highly dependent on MBR performance. For compounds with a moderate removal efficiency in MBR (such as ketoprofene), GAC can exhibit fairly constant removal until its saturation. It was also found that GAC may adapt to the MP loading fluctuations in the column influent and guarantee fairly constant effluent quality (such as for metronidazole). If GAC becomes BAC, biodegradable compounds retained on its surface may still maintain a good removal efficiency at long operation times due to biodegradation processes in biofilm. In the case of MPs whose main removal mechanism is adsorption, GAC column bioregeneration is essential in order to allow a high and continuous MP removal.

A loss in AC *potential* adsorption capacity occurs due to its progressive saturation and its removal from the system through excess sludge withdrawal or the retentate from the membrane PT unit. PAC addition (replenishment) is thus necessary to maintain its desired concentration in the tank.

AC influences the MBR operation mainly by changing the composition of the mixed liquor. The concentration of organic compounds in the liquid phase of the biological tank is reduced by the attachment of DOM onto the AC surface. The presence of AC in the floc increases its strength and improves its settling characteristics. The cake layer against the membrane becomes more porous than when AC is absent. AC added in the bioreactor prolongs MBR operation by mitigating membrane fouling.

Recent studies proposed to analyse MP removal as a function of the DOC adsorbed on the AC (mg DOC/mg AC) as it better reflects the saturation level of the AC present in the studied system over time.

Further studies are necessary to better investigate the interactions between DOM and the different MPs with regard to the characteristics of DOM (biopolymers, hydrophobic molecules) and the role played by inorganic ions (for instance cations). Moreover, the contributions due to adsorption and biodegradation to MP removal may be identified under controlled conditions, by comparing the performance of a biologically inactivated GAC with a BAC. Values of biological constant rate k_{biol} when AC is added in MBR could be useful to predict the potential enhancement of the biodegradation of selected MPs as well as K_d values showing MP sorption potential when PAC is added in MBR or AC unit acting as a PT. Their knowledge will make it possible to understand which removal pathway mostly contributes to the removal of a specific compound, despite the fact a multiparametric equation is not available to predict the behaviour of a compound in such a complex system.

Analysis of the performance of specific configurations should also include the monitoring of UV_{254}. This parameter quickly provides an indirect measure of the occurrence of many low molecular weight organics. For this reason, it was considered a surrogate for MP occurrence in influent and effluent, but it could also become a reliable surrogate of low molecular weight organics belonging to the DOM.

Finally, investigations on real wastewater are necessary to better understand the removal mechanisms with regard to compounds of great concern or which could represent a group of compounds characterised by a similar behaviour in hybrid MBRs like those coupled with AC. Investigations on synthetic wastewater represent a useful step in the research, but they should be validated with real wastewater.

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Declaration of competing interest

The author stated that there is no conflict of interest in publishing this paper.

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Removal of micropollutants using a membrane bioreactor coupled with powdered activated carbon — A statistical analysis approach

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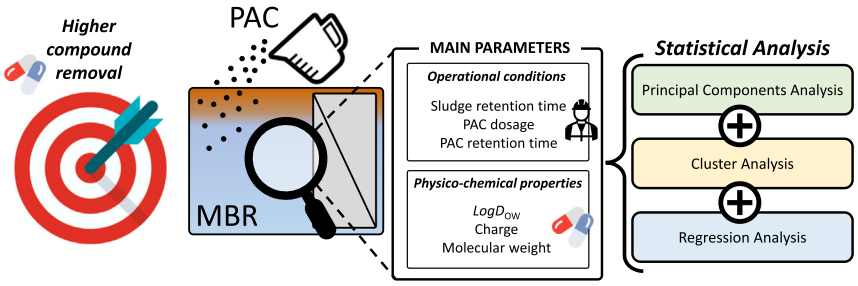
HIGHLIGHTS

- Main factors influencing micropollutant removal in an MBR coupled with PAC.
- The main operational conditions and physico-chemical properties were considered.
- Comparison of the influence of the selected factors based on statistical analysis.
- Principal component analysis, cluster analysis and regression analysis were done.
- Micropollutant charge and log D_{ow} result significantly correlated to the removal.

GRAPHICAL ABSTRACT



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ABSTRACT

The occurrence of micropollutants in wastewater is largely documented as well as the environmental risk posed by their residues in the aquatic environment. Many investigations have been carried out and plan to study and improve their removal efficiency in existing wastewater treatment plants. At the same time, efforts are being made to develop new technologies or upgrade existing ones to increase the removal of a selection of micropollutants. Due to the great variability in their chemical and physical properties, it would be advisable to find representative compounds or identify the factors which most influence the removal mechanisms under specific conditions. This study analyses the removal efficiencies of a great number of micropollutants in wastewater treated in a membrane bioreactor coupled with powdered activated carbon (PAC), which was the subject of a review article we have recently published. The main operational parameters (i.e. PAC dosage, PAC retention time and sludge retention time) and compound physico-chemical properties (i.e. octanol-water distribution coefficient, charge and molecular weight) were first selected on the basis of a dedicated screening step and then an attempt was carried out to clarify their influence on the removal of micropollutants from wastewater during its treatment. To this end, a statistical analysis, mainly based on exploratory methods (cluster analysis and principal component analysis) and regression analysis, was carried out to compare and discuss the different results published in the scientific literature included in the cited review article. It emerged, that, based on the collected dataset, micropollutant charge and LogD_{ow} seem to play the most important role in the removal mechanisms occurring in MBR coupled with PAC.

1. Introduction

The occurrence of micropollutants in the aquatic environment has been well documented by many investigations worldwide (Wilkinson et al., 2022) and their effect on the environment as well as on human health is an issue of increasing concern. Wastewater treatment plants are considered

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one of the most important pathways for their emission into the environment (Ghirardini et al., 2021). Environmental quality standards and legal limits regarding treated effluent release into surface water bodies have been set for only a few of them (e.g. pesticides, plasticisers and insect repellents as in Directive 2013/39/EU of the European Parliament and of the Council (EC, 2013)) and only in some countries (e.g. some European Union member States and Switzerland). Despite this fact, great efforts are being made worldwide to test solutions that are able to improve the removal of selected micropollutants from wastewater (namely, antibiotics, analgesics and anti-inflammatory drugs, psychiatric drugs and antidiuretics). End-of-pipe treatments based on advanced oxidation processes (e.g. ozonation, $O3/H_20_2$), filtration and sorption on activated carbon (AC) are some of the options suggested for secondary effluent polishing. This is the case in Switzerland, according to their Micropol strategy (https://www.eawag.ch/en/department/eng/projects/abwasser/strategy-micropoll/). In addition, the upgrading of or changes to existing wastewater treatment steps may represent another strategy to guarantee a higher removal of a selection of micropollutants (Rizzo et al., 2019). In this context, limiting the attention to the secondary biological treatment, it was confirmed that the removal efficiencies are higher in a membrane bioreactor (MBR) than in a conventional activated sludge system for a great number of micropollutants (Choi et al., 2022; Radjenović et al., 2009; Verlicchi et al., 2013, 2012). In recent years, many, diverse attempts have been made to further improve MBR performance (Neoh et al., 2016; Woo et al., 2016) by combining MBRs with innovative treatment technologies such as consolidated ones (i.e. activated carbon and ozonation) or others that have not yet been fully implemented (i.e. advanced oxidation processes, membrane distillation bioreactors, biofilm/bio-entrapped MBRs, nanofiltration and reverse osmosis) (Rizzo et al., 2019). In all the investigations, the common aim has been to foster degradation and/or sorption removal mechanisms for a selection of micropollutants, by favouring or optimising the operational conditions. Among these modified MBRs, often called "hybrid systems" (Alvarino et al., 2017), the combination of an MBR coupled with powdered activated carbon (PAC) has attracted the interest of many researchers worldwide.

In a recent review paper (Gutiérrez et al., 2021), we presented and discussed the enhancement of the removal achieved for a multitude of MPs by the addition of PAC to the MBR or by means of a specific post-treatment using powdered or granular AC. Limiting the attention to the case of PAC added in the bioreactor, in the cited study, the removal efficiencies were related to different factors: micropollutant properties, AC characteristics, PAC addition point and duration, operational conditions (sludge and hydraulic retention times, SRT and HRT respectively) and characteristics of the wastewater under treatment (mainly dissolved organic matter, DOM). It was remarked that for weakly charged substances, the lipophilicity of a compound plays a crucial role in its adsorption to the PAC surface, while in the case of charged substances, also the electrostatic interactions between the PAC surface and the functional groups become relevant (Alvarino et al., 2017). Furthermore, DOM present in the aeration tank is likely to interfere with the PAC and the occurring micropollutants, leading to either direct competition with the micropollutants for the PAC adsorption sites or pore constriction (Delgado et al., 2012). As a result, the parameters involved in the phenomenon are manifold.

Considering the compounds, it is worth mentioning (i) the octanol-water partition coefficient (K_{OW}), or better the octanol-water distribution coefficient (D_{OW} which accounts for acid-base speciation), which provides an indication of the lipophilicity of a substance, (ii) the acid dissociation constant (pK_a), (iii) the charge and the presence of specific functional groups for its electrostatic affinities, and (iv) the molecular weight (MW) and size, which give a view of the potential to be intercepted by the PAC pores (Kovalova et al., 2013).

Otherwise, considering the adsorbent, the properties that mainly influence the fate of micropollutants in an MBR coupled with PAC regard (i) the characteristics of the adopted PAC (e.g. pore size and texture), (ii) the addition quantity and mode (PAC dosage, PAC retention time and dosage point in the reactor), and (iii) the reactor operational parameters (e.g. redox, pH, temperature, HRT, SRT, mixed liquor suspended solids) (Alvarino et al., 2018a; Mailler et al., 2016).

The cited review, which includes 64 peer-reviewed papers published between 2009 and 2020, emphasizes the complexity of the *phenomena* under study. Furthermore, it emerged that the different operational conditions and wastewater characteristics adopted in the past investigations sometimes led to different findings that, in some cases, did not coincide. As a result, a more rigorous approach to elaborate and interpret the collected data is needed to identify the main parameters affecting the removal of micropollutants in MBRs coupled with PAC. This could be useful in designing such a hybrid system or in optimising its performance. The novelty of our study consists in evaluating the joint effect of all the factors. In other words, instead of considering the predictors once at the time, we included all of them as explanatory variables. With such approach it is possible to assess the effect of each factor less other effects. Since the goal is to find new scientific results based on empirical evidence, generalizable beyond the observed cases, in our opinion, the most appropriate modeling practice is that based on inferential approach and not the one typical of machine learning. One of the goals of the paper is also to provide rigorous tools for interpreting data by providing robust modeling tools for the benefit of water treatment professionals.

In this context, the main operational parameters (i.e. PAC dosage, PAC retention time and SRT) and the physico-chemical properties of the compounds (i.e. $\text{Log}D_{OW}$, charge and MW) were selected on the basis of a dedicated screening step and then an attempt was made to clarify their influence on the removal of micropollutants from wastewater during its treatment. To this end, a statistical analysis, mainly based on exploratory methods (principal component analysis and cluster analysis) and regression analysis, was carried out to compare and discuss the different results published in the scientific literature included in the cited review article.

2. Material and methods

2.1. Characteristics of the adopted dataset

The dataset adopted in this work was retrieved by Gutiérrez et al. (2021) and refers only to the data (observations) provided by 10 studies investigating the fate of micropollutants in an MBR coupled with PAC. Those referring to PAC or granular activated carbon (GAC) as a polishing treatment after an MBR were excluded. Table S1 of the Supplementary Material lists the studies and the relative observations included in the current analysis. Among these, only the observations in which all the parameters necessary for this study are available (i.e. SRT, PAC dosage, PAC retention time, D_{OW}, charge and MW) were maintained. Therefore, 26 observations (namely, the ID observations from Table S1 8–9, 37–38, 52, 57, 73–74, 89–90, 99, 102, 119–120, 125, 128–131, 138–139, 151–152, 167 and 172–174) were excluded from the original dataset (red records in Table S1). Then, the observation number 154, referring to carbamazepine, was excluded as its removal value (-90%) was considered an outlier of the dataset.

The resulting dataset includes 146 observations referring to 37 compounds (of which 6 non-steroidal anti-inflammatories drugs (NSAID), 7 antibacterials, 1 antiseptic, 5 hormones, 1 lipid regulator, 1 non-ionic surfactant, 2 pesticides, 4 psychiatric drugs, 2 stimulants, 3 synthetic musks and 5 others uncategorised compounds) collected from 7 studies (namely, Alvarino et al., 2017, 2016; Asif et al., 2020; Li et al., 2011; Nguyen et al., 2013; Serrano et al., 2011; Yu et al., 2014) (Table S1).

All the data included in the refined dataset refer to laboratory-scale plants, with the exception of the 9 observations reported by Serrano et al. (2011) which refer to a pilot-scale study. All the experimental reactors were fed with synthetic wastewater, made by adding specific compounds in water to simulate the matrix effects expected in real wastewater. Its compositions in the different studies were provided as reported in Gutiérrez et al. (2021).

The durations of the investigations range between 65 days (Asif et al., 2020) and 306 days (Nguyen et al., 2013). The configurations of the reactors adopted in the selected studies are reported schematically in Table 1. Here, in 4 out of 7 studies (providing a total of 117 observations) the membrane unit is placed in the biological reactor, while in the other 3 studies (29 observations) the membrane unit is in a separate tank (Table 1). The variability ranges of the operational conditions adopted in the studies are reported in Table 2.

Six parameters were chosen on the basis of a dedicated screening of data availability. In addition they were selected only if they present a wide and heterogeneous variability range. Their influence on the micropollutant removal mechanism during treatment in an MBR coupled with PAC is well known (Gutiérrez et al., 2021). Other variables which could affect the removal (e.g. membrane shape, pore size, biomass characteristics) were not considered as the investigations available in the literature do not provide the full set of data to be included in the dataset or few data were found.

2.2. Statistic tools

A univariate linear regression analysis was initially carried out to predict average removal as a function of the other considered variables. To test the Goodness of Fit, both the parametric and non-parametric ANOVA were applied. In both the cases the *p*-value indicated no significance. After that, non-linear relationships were considered through the application of linear models to transformed variables. In particular, it was taken into account the logit of average removal as dependent variable, the inclusion of the squared explanatory variables and of the interactions in the set of predictors, the logarithmic transformation of the explanatory variables and combinations of these modifications of the original model. Then, the same previous attempts were done with the bivariate model, considering the average of removal and the standard deviation of removal as response variables and finally it was repeated the analysis on a multivariate version of the model with average, standard deviation, minimum and maximum of removal as dependent variables. In no case the Goodness of Fit tests were significant. Finally, the univariate two-sample NPC test approach was applied. The logit of average removal took the role of response and $\log D_{ow}$ as a "treatment". Again there was not empirical evidence of a significant effect of the factor on the dependent variable. Based on these results other tools were considered.

2.2.1. Principal component analysis

Principal component analysis (PCA) was applied in order to reduce the dimensionality of the dataset. The application of PCA aims to reduce the number of variables by eliminating a small proportion of data variability. PCA transforms the original correlated observed variables into new uncorrelated variables (principal components), with minimum loss of the original information represented by the observed variability. The principal components (PCs) are linear combinations of the original observed variables. The first component is the linear combination with maximum variance. It corresponds to the dimension along which the dispersion of data is maximum. The second component is the linear combination with maximum variance among those corresponding to orthogonal directions with respect to the first component. The subsequent components are detected in a similar way, considering orthogonal directions and maximising the variance. Hence, the resulting PCs are uncorrelated themselves and represent a new set of variables, related to the original variables by a defined linear combination (Lever et al., 2017).

The loadings are the correlations between the principal components and original variables. They correspond to the weights of the linear combinations explaining the variables by the components. The scores of the principal components map the different samples in the new dimensional space of the principal components facilitating the investigation of the different relationships between the variables (Vasilaki et al., 2018).

In this study, PCA was performed using R software ((Beiras, 2018), (R Core Team, 2020, software available at https://www.r-project.org). Then, Varimax orthogonal rotation was applied for the PCA axes and to reduce the contribution of the less relevant parameters within each PC (Jollife and Cadima, 2016).

2.2.2. Cluster analysis

Clustering techniques are widely applied in order to identify and group underlying patterns in high dimensional datasets. It is not easy to categorize them clearly, nevertheless they can be classified into four classes: partitioning, hierarchical, density-based and grid methods. Cluster Analysis (CA) aims to group datapoints (or equivalently statistical units) into homogeneous groups (clusters). Therefore, in the current study it was used to analyse the similarities among the different observations and gather potential relationships between them and their removal. The latter then were investigated better using the regression analysis.

In this study, CA was carried out adopting the *K*-means method which is one algorithm of the partitioning method. *K*-means is a partitional clustering algorithm which creates a defined number (K) of groups (also called clusters, c_k) of datapoints x_i. The within-cluster sum of squares S between the datapoints and the cluster empirical mean (i.e. the centroid, μ_k) (which measures the within-cluster heterogeneity) between the datapoints is minimised (Hennig et al., 2016), according to eq. 1:

$$S = \min \sum_{k=1}^{K} \sum_{x_i \in c_k} \|x_i - \mu_k\|^2 \quad (1)$$

In particular, this algorithm begins by fixing the number of clusters K and their corresponding centroids. Then, each statistical unit is included in the cluster with the nearest centroid. Once all the units have been classified, every centroid is recalculated as the value providing the lowest distance to all the members of its class. As the centroids have changed, the distance between each datum and the centroids must be calculated again so that the units are reassigned to the closest cluster. The process is repeated until no improvement in the classification process is obtained (de la Vega and Jaramillo-Morán, 2018).

Table 1
The two configurations of MBR coupled with PAC together with the corresponding references included in this study.

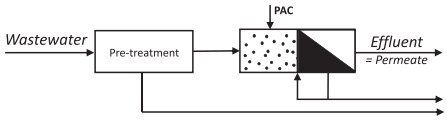
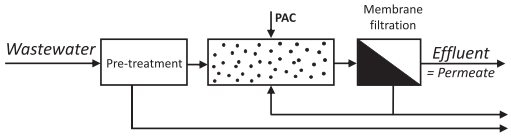
Configuration scheme	Description	Referring studies (number of observations)
	Submerged MBR: The membrane is placed in the biological reactor, where PAC is added.	Alvarino et al. (2017) (60); Li et al. (2011) (7); Nguyen et al. (2013) (44); Yu et al. (2014) (6).
	Side-stream MBR: The membrane is placed in a separated tank. PAC is added in the biological reactor.	Alvarino et al. (2016) (13); Asif et al. (2020) (7); Serrano et al. (2011) (9).

Table 2
Selected operational conditions and corresponding values in the included investigations.

References (no. of observations)→ Operational conditions ↓	Alvarino et al. (2016) (13)	Alvarino et al. (2017) (60)	Asif et al. (2020) (7)	Li et al. (2011) (7)	Nguyen et al. (2013) (44)	Serrano et al. (2011) (9)	Yu et al. (2014) (6)
SRT [d]	118	200	30	92	100	288	30
PAC dosage [g L^{-1}]	1	0.25–0.75	20	0.1–1	0.1–0.5	1	0.03–0.1
PAC retention time [d]	118	35–105	65	28–60	37–63	86	88–246

As this algorithm needs a fixed number of clusters prior to starting the clustering process, in some cases several possible K values must be tested and evaluated to find out which one provides the best classification. The number of clusters must not be too high in order to guarantee that the classification obtained is both useful and meaningful (de la Vega and Jaramillo-Morán, 2018).

The number of clusters (K) which better describes the similarities within the dataset is often tricky to evaluate and there is no predefined criterion for its evaluation (Jain, 2010). In this work, the well-known Elbow and Silhouette methods were adopted to overcome this issue (Kassambara, 2017). The first was used to identify a range of K graphically which may be adopted for the analysis. In the former method, the sum of squares for each possible number of clusters is calculated and plotted, in order to detect an evident slope change point (a bend) that corresponds to the optimal number of clusters. The latter method provides a measurement of the similarity of each unit with those inside its own cluster compared with those outside the cluster. Now, if the silhouette of each datum inside a cluster is represented in decreasing order, a graphic representation of the quality of the allocation of data inside them is provided for all the clusters. The mean value of the silhouettes for all the clusters will provide a measurement of the quality of the clustering carried out, so that the higher the value, the better the classification. Therefore, the different clustering configurations were compared based on their average Silhouette value (Sil_{ave}) in order to assess the consistency of the solutions proposed by the graphical interpretation of the Elbow method results. Before the analysis, the dataset values were standardised to reduce outliers which may drive the grouping (Mohamad and Usman, 2013).

2.2.3. Regression analysis

Finally, regression analysis was used to investigate the influence of the selected parameters on the removal of micropollutants in an MBR coupled with PAC.

The regression analysis was conducted to find a possible relationship between average removal (response of the model) and some explanatory variables in order to predict the response values. The function *lm* in the R software environment was used to carry out the analysis, with a significance level $\alpha = 0.05$.

We performed two equations: the first, with data in three out of the four identified clusters (e.g. Cluster A, B and D), in which the response variable is the average removal and the explanatory variables are SRT, PAC retention time, PAC dosage, logD_{ow}, charge and MW; in the second, concerning only two clusters (Cluster B and D), we have the same response variable and the explanatory variables are SRT, PAC retention time, PAC dosage, logD_{ow} and MW.

In the current study, the analysis was carried out considering two different sub-datasets. The first one included all the observations except for the seven provided by the study by Asif et al. (2020), which were considered outliers due to the especially high PAC dosage adopted (20 g L^{-1}, compared to 0.1 to 1 g L^{-1} in the other studies). In this context, although the influence of PAC is not proportional to the added dosage, as discussed in Section 4.1, the especially high dosage may result in different *phenomena* in the reactor (e.g. changes in the rheological properties of the mixed liquor) which make the experiment difficult to compare to the others. Accordingly, the differences between these seven observations and the others were observed also in the exploratory data analysis (Sections 3.1 and 3.2).

Otherwise, the regression analysis was conducted considering only the observations related to negatively charged and neutral compounds (which correspond to clusters B and D, respectively, as defined in Section 3.2), in order to investigate their expected behaviour in the reactor, as suggested by different studies (such as Alves et al., 2018, Kovalova et al., 2013, and Mailler et al., 2016, to name just a few). A variable was considered significantly correlated to the removal when the p-value was <0.05.

Finally, regression analyses were always completed with diagnostic assessments on residuals (see Fig. S2 in Supplementary Materials).

3. Results

3.1. Principal component analysis

The results of the PCA in terms of loadings of the considered variables are reported in Table 3, while biplots of the first 4 principal components are shown in Fig. 1. These biplots of the PCs two by two were used to visualise the combined behaviour of the significant variables that affect the system. The biplots enable the simultaneous visualization of the variable loadings and scores of the principal components (Vasilaki et al., 2018).

The dimensionality of the dataset was reduced to 4 principal components (hereinafter PC1, PC2, PC3 and PC4) explaining the 87% of the total cumulative variance (27% up to PC1, 50% up to PC2, 70% up to PC3 and 87% up to PC4. For PC1, the highest loadings were exhibited by charge (0.901), followed by MW (0.804). As a result, high positive values of PC1 in Fig. 1 represent high values of the physico-chemical properties charge and MW of the compounds. SRT and the opposite of the PAC dosage are mostly represented in PC2 (0.844 and −0.788, respectively) which mainly describes the variation of the operational conditions under study, as no considerable values of the physico-chemical property-related loadings emerged (Table 3). High positive values of PC2 in Fig. 1 corresponds to high values of SRT, while negative values of PC2 represent high PAC dosages. PC3 and PC4 mainly represent the PAC retention time operational conditions (0.962) and the physico-chemical property D_{OW} (0.962), respectively. These two variables appear to be represented only by the respective principal components, with negligible loadings in the others (Table 3).

3.2. Cluster analysis

The result of the elbow method is represented in Fig. S1 of the Supplementary Material. The obtained curve suggests an optimal number of clusters (K) ranging between 3 and 5. The highest Sil_{ave} for these different clustering configurations was found for $K = 4$ ($Sil_{ave} = 0.44$). Therefore, the dataset was partitioned in 4 clusters.

The centroids of the clusters obtained in terms of SRT, PAC dosage, PAC retention time, LogD_{OW}, charge and MW, together with the number of observations included in each cluster and their corresponding average removal efficiency after the treatment, are reported in Table 4.

Table 3
Details of the PCA loadings. The numbers in parenthesis represent the percentage of variance explained by each component.

Variable	PC1 (27%)	PC2 (23%)	PC3 (19%)	PC4 (18%)
SRT	0.253	0.844	−0.112	−0.147
PAC dosage	0.164	−0.788	−0.127	−0.375
PAC retention time	<0.10	<0.10	0.962	<0.10
LogD_{OW}	<0.10	<0.10	<0.10	0.962
Charge	0.901	<0.10	−0.131	0.253
MW	0.852	0.126	0.239	−0.137

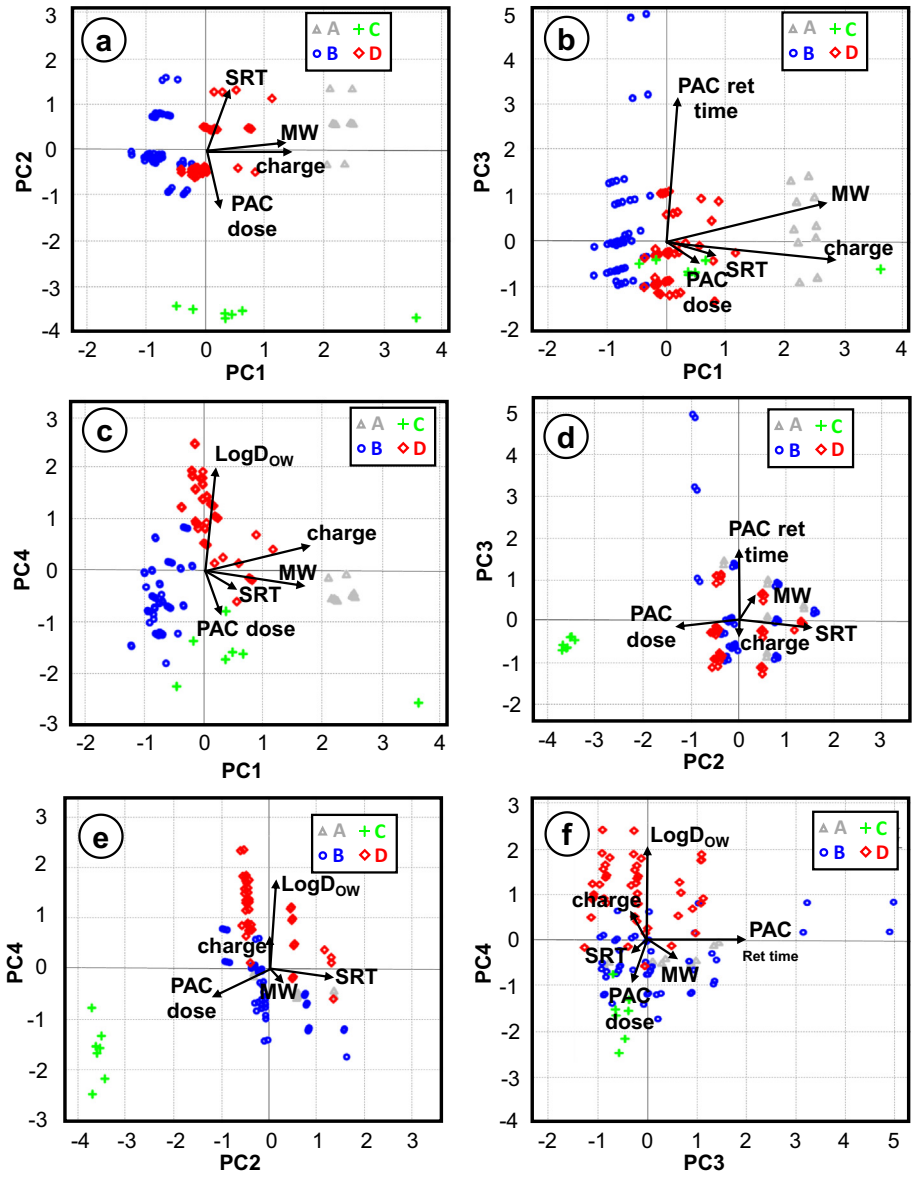


Fig. 1. Biplots of the principal components (PCs) with a representation of the PCA scores (referring to the experimental observations) included in each cluster (A-D, according to the results of Section 3.2). The vectors represent the loadings of the PCA (i.e. how strongly each variable influences a PC).

As shown in Table S2 of the Supplementary Material, it emerges that while clusters A, B and D include datapoints from various studies, cluster C grouped the observations of the only investigation conducted by Asif et al. (2020). This can be explained by the fact that cluster C grouped the observations characterised by an extremely high PAC dosage value (Table 4), of which the centroid shows the highest value (20 g L^{-1}) compared to the other clusters in which the centroids are centred around a similar value of mean PAC dosage (0.4 to 0.6 g L^{-1}). This reflects the particular experimental features of the investigation conducted by Asif et al. (2020), in which the adopted PAC dosage (20 g L^{-1}) was considerably higher than those added in the other studies (0.03 to 1 g L^{-1}, as shown in Table 2). For this reason, the relevant distance between the observations included in cluster C and all the others points in Fig. 1a, d and e is not surprising, due to the high relevance of the PAC dosage in PC2. Furthermore, cluster C also exhibited the lowest average value of SRT (30 days). Indeed, with the exception of the 6 observations by Yu et al. (2014) referring to PFOA and PFOS (with an SRT of 30 days), the experiment conducted by Asif et al. (2020) was the only one in which an SRT lower than 92 days was adopted (as better described below). The combination of a different PAC dosage and SRT make it an outlier, in terms of operational conditions.

The other clusters (A, B and D) are characterised by greater heterogeneity in terms of included studies and compounds as well as a higher number

Table 4
Characteristics of the clusters, in terms of number of observations included in each cluster, average removal efficiency and centroids of each of the six selected variables.

Cluster ID	Number of observations included	Average removal [%]	SRT [d]	PAC dosage [g L^{-3}]	PAC retention time [d]	LogD_{OW}	Charge	MW
A	16	97.9	200.7	0.6	78.0	1.39	0.95	785.5
B	65	84.4	139.7	0.4	73.9	0.69	−0.90	261.5
C	7	97.4	30.0	20.0	65.0	−0.56	−0.07	286.3
D	58	91.0	156.1	0.5	67.8	3.35	0.12	261.8

of included observations (Table S2). Clusters A and B are characterised by the highest and the lowest average charge value (0.9 and −0.9, respectively). In particular, cluster B includes observations regarding mainly anionic compounds, grouping the majority of them (59 out of 62) among the whole dataset. In detail, the datapoints grouped in B refer to the anionics sulfamethoxazole (11 values), diclofenac (10), ibuprofen (10), naproxen (10), PFOA (3), PFOS (3), 17β-estradiol-acetate (2), fenoprop (2), gemfibrozil (2), ketoprofen (2), pentachlorophenol (2), salicylic acid (2) but also the neutrals metronidazole (2), primidone (2) and paracetamol (2). On the contrary, cluster A grouped only cationic substances, including erythromycin (8 values) and roxithromycin (8), which represent the majority of cationic substance-related observations in the dataset (16 out of 27).

Finally, cluster D mainly grouped neutral or zwitterionic compounds (48 observations out of 57 of the whole dataset), with the only exception being the neutral/cationic trimethoprim (8 values) and the cationic fluoxetine (2). The compounds included in D refer to carbamazepine (13), 17β-ethinylestradiol (8), estrone (8), 4-n-nonylphenol (2), 4-tert-butylphenol (2), 4-tert-octylphenol (2), 17β-estradiol (2), bisphenol A (2), diazepam (2), estriol (2), triclosan (2), celestolide (1), galaxolide (1) and tonalide (1) (Table S2). This cluster is not only characterised by the neutral average charge, but also for the highest $\mathrm{Log}D_{\mathrm{OW}}$ (= 3.3, Table 4), which drove its partitioning.

The stratification of charge is clearly visible in Fig. 1a, b and c, in which PC1 is displayed. It is also interesting to observe that for similar values of charge, clusters B and D are well differentiated by their $\mathrm{Log}D_{\mathrm{OW}}$ values represented by PC4 (Fig. 1c).

3.3. Regression analysis

The results of the regression analysis are reported in Table S3 and S4.

We carried out a multiple linear regression analysis with parameter estimates based on the ordinary least squares method. Given the outcome of the diagnostic analysis in which we have no evidence supporting the assumption of normality of the errors, instead of the classic parametric t or F tests, we applied the permutation test on the coefficients' significance and the permutation ANOVA, which are more flexible and robust with respect to the departure from normality (see Bonnini and Cavallo, 2022).

In the first regression, considering Clusters A, B and D, we obtain an Adjusted R-squared equal to 0.1299, while in the second regression in Cluster B and D we have an Adjusted R-squared equal to 0.0984. Considering the dataset in which all the observations except the seven provided by Asif et al. (2020) were included (for a total of 139 observations), it emerged that the removal of micropollutants in an MBR coupled with PAC was significantly correlated to their charge ($p = 0.049 < 0.05$). Here, also $\mathrm{Log}D_{\mathrm{OW}}$ appears to be important in the removal process, albeit the corresponding coefficient estimate appears weakly significant ($p = 0.088 < 0.10$). According to the estimates of the coefficients, a + 1 increase in $\mathrm{Log}D_{\mathrm{OW}}$ determines a variation of +2.23 in average removal, while a + 1 variation in charge corresponds to a change equal to +3.13 in the response. No significance was observed for MW or any of the operational condition-related variables ($p > 0.1$) (Table S3).

The results of the regression analysis conducted when considering the dataset in which there were 123 observations of clusters B and D revealed that, when excluding the effect of the charge, the $\mathrm{Log}D_{\mathrm{OW}}$ has a strongly significant effect on removal ($p < 0.001$) and MW gains importance in the removal process, although its regression coefficient is weakly significant ($p = 0.076 < 0.10$). The expected variation of removal when $\mathrm{Log}D_{\mathrm{OW}}$ and MW increase by one is +4.16 and −7.36, respectively. None of the three operational condition-related variables resulted in significantly affecting the removal of micropollutants in the MBR coupled with PAC ($p > 0.1$).

However, given the small values of the coefficients of determination, the results of the regression analysis should be evaluated prudently because the goodness-of-fit of the model is low. This may be because other explanatory variables (e.g. redox potential, biomass concentration and membrane pore size) not included in the model could be more important than those considered as predictors of removal. Another possible reason for the low goodness-of-fit could be the non-linear relationship between the variables under study and the consequent incorrect specification of the model. In other words, the reasons why the Adjusted R-square is low and therefore we do not have very satisfactory results can be: (a) the specification of the model is not appropriate (perhaps the relationship is not linear and a different specification of the equation of the regression model should be considered) or (b) important explanatory variables are missing in the model as predictors of the response. Since, as also mentioned in Section 2.2, we tested various model specifications that also include nonlinear relations, we can say that most likely the Adjusted R-squared is low because important explanatory variables are missing. Hence, in future studies, better models could be obtained by adding new predictors. Anyway, even if from the descriptive point of view the goodness-of-fit is not high because the specification of the model could be improved, from the inferential point of view, we have significances indicating non-null effects of some predictors on the response.

4. Discussion

4.1. Influence of the operational conditions

Taken together, the collected results provide interesting insights regarding the main factors involved in the removal of micropollutants during wastewater treatment by an MBR coupled with PAC.

The high average removal efficiency of the datapoints grouped in cluster C (97%) suggests that the PAC dosage may play an important role in micropollutant removal, especially when a particularly high quantity is added in the bioreactor (20 g L^{-1}, as in the case of Asif et al., 2020). Indeed, it is well known that the presence of PAC improves the physico-chemical properties of the sludge (i.e. it promotes floc growth and structure strength) entailing increased adsorption and, potentially, biodegradation (Alvarino et al., 2020; Hu et al., 2015). On the other hand, the variability in the average removal obtained by more commonly adopted values of PAC dosages (0.03 to 1 g L^{-1}) ranging from 84% (cluster B) to 98% (cluster A) seems to downsize the relevance of this factor. Moreover, the results of the regression analysis that was conducted taking into account all the datapoints with the exception of those of cluster C, considered as outliers, showed that selected PAC dosages, alone, do not significantly influence the removal of micropollutants during the treatment ($p = 0.115$, Table S3). This result may be due to different factors. Although different studies highlighted that the PAC dosage is a crucial operational condition with respect to micropollutant removal (among them Alvarino et al., 2017 and Li et al., 2011), its activity may be influenced by (i) PAC addition timetable (and therefore PAC aging in the reactor); (ii) wastewater matrix effect (as it affects the micropollutant saturation rate and floc biological activity (Alvarino et al., 2018b; Paredes et al., 2018)); (iii) characteristics of the selected PAC (mainly: pore size, specific surface area and bulk density (Alves et al., 2018; Mailler et al., 2016)); and (iv) physico-chemical characteristics of the micropollutants (Alvarino et al., 2018b). Furthermore, although not found in the selected studies, also (v) PAC potential losses due to excess sludge withdrawal, and vi) PAC addition point (e.g. in the anoxic tank as done by Remy et al., 2012, or in the aerobic tank as done by Asif et al., 2020 and Echevarría et al., 2019, to name just a few), may influence the sorption on the PAC surface. Therefore, the sum of all these factors makes it difficult to discuss statistically the significance of the PAC dosage on micropollutant removal efficiency.

Nevertheless, dedicated works (among them Cecen and Aktas, 2011; Loos et al., 2013 and Yu et al., 2014) highlighted that, strongly limiting the influence of the six above listed factors, the positive influence of the PAC dosage becomes statistically significant. In this regard, Mailler et al. (2016) observed that the positive correlation between the PAC dosage and removal efficiency follows a logarithmic pattern. Therefore, the addition of particularly high dosages of PAC may not entail proportional benefits.

In accordance with the findings of different studies (among them Alvarino et al., 2017, Löwenberg et al., 2014, and Wei et al., 2016), the

PAC retention time appeared to be non-significantly correlated to the removal of the investigated micropollutants in both the regression analyses conducted ($p = 0.745$ considering the whole dataset with the exception of cluster C, and $p = 0.592$ considering only the neutral and anionic substances of clusters B and D). Briefly, once PAC is added in the bioreactor, its porous surface is entirely available, while after a period of time, its active sites start to be occupied by the sorbed micropollutants and the competitor DOM, which are present in the mixed liquor. This leads to a decrement of PAC potential sorption capacity, but at the same time, it provides an environment suitable for the development of a microbial community in the sludge flocs where the PAC is embedded. A more complex and heterogeneous microbial community can potentially enhance the biodegradation processes (Baresel et al., 2019). In other terms, the removal mechanisms of the substances may differ based on PAC age, promoting the removal of recalcitrant compounds that are more prone to be sorbed in/on fresh PAC (e.g. carbamazepine), or those which are more likely to be sorbed and biodegraded in the PAC-sludge floc complex. As a result, the effect of the PAC retention time on the removal of micropollutants strongly depends on their corresponding physico-chemical properties. In this regard, to achieve a good performance of PAC during the treatment for both cited types of substances which are more prone to be sorbed or biotransformed, Alvarino et al. (2017) recommend a dosage of 0.2 g L^{-1} added every 35 days.

Similar considerations may be applied to the SRT. As shown by Ng et al. (2013), low SRT values (i.e. 10 days) implies the addition of fresh PAC, providing a higher sorption of compounds which are prone to be sorbed on the PAC surface. On the contrary, high SRTs (> 100 days) promote the development of different species in the biomass, entailing a better biotransformation of the compounds (Alvarino et al., 2018a). In accordance with these considerations, both regression analyses conducted showed that the SRT is not significantly correlated with the removal ($p > 0.465$). Nevertheless, except for the 7 observations related to Asif et al. (2020) in which the SRT was 30 days, SRTs in the dataset are always particularly high (from 92 in Alvarino et al., 2017 to 288 days in Serrano et al., 2011) compared to those expected in common conditions adopted in MBR reactors (20–50 days, Metcalfe, 2014). Indeed, compounds with low biodegradability are not expected to increase their removal at high SRTs (Yu et al., 2014) and therefore an exhaustive conclusion cannot be provided due to the lack of heterogeneity of the values.

4.2. Influence of the physico-chemical characteristics of the micropollutant

Concerning the physico-chemical characteristics of the compounds, it is interesting to observe that the highest and lowest average removal efficiencies refer to the observations grouped in clusters A and B, respectively (98% and 84%). These are also distinguishable by the highest and the lowest average charge values. This evidence suggests that the removal of micropollutants is positively correlated to their corresponding charge.

Though this may seem counterintuitive, as the surface of the PAC added in the experiments is generally neutral to positively charged at a pH higher than 7, this fact was observed in many studies (among them Boehler et al., 2012; Loos et al., 2013; Mailler et al., 2016; Margot et al., 2013). This can be explained bearing in mind that the covering of the DOM, typically negatively charged at neutral pH, on the PAC surface entails a consistent decrease in its overall charge (Yu et al., 2012). As a result, a high *adsorption* (indicating the potential of electrostatic interactions, according to Ternes et al., 2004) of positively charged micropollutants (i.e. cationic) and the negatively charged PAC-DOM complex surface is expected, as well as for repulsion in the case of anionic compounds (de Ridder et al., 2011).

The reduced average removal efficiency (84%) characterising the observations grouped in cluster B is not surprising, as it mostly refers to anionic compounds which are, additionally, also characterised by a low $LogD_{OW,}$ and therefore characterised by a low lipophilicity. Hereinafter they are referred to as compounds with low *absorption* potential (Ternes et al., 2004). However, for these compounds, removal may be driven by biotransformation and can be enhanced by the presence of the specific functional groups of the compound which interact between the PAC-DOM complex, explaining an average removal of 84% (Alvarino et al., 2017).

On the contrary, even if the particularly high average removal efficiency characterising the observations of cluster A seems to reflect the same behaviour, this might also be due to other reasons. Indeed, cluster A grouped the observations related to 2 substances (namely, erythromycin and roxithromycin) which have been demonstrated to be readily biodegradable in bioreactors in which high nitrification is reached, making their removals only slightly influenced by the addition of PAC in such reactors (Alvarino et al., 2017).

The results of the regression analysis confirmed the importance of the role of the charge in the removal of micropollutants during wastewater treatment. Excluding the 7 observations related to the study by Asif et al. (2020), the removal of the compounds under study showed to be significantly correlated to their charge ($p = 0.049$).

Despite this, as mentioned above, the sorption of micropollutants on the PAC surface is not only driven by adsorption due to electrostatic interactions by their functional groups and the PAC surface. On the contrary, especially in the case of non-charged substances, the adhesion of the micropollutants in the PAC-sludge floc complex may also be due to absorption and, therefore, to compound lipophilicity (Mailler et al., 2015).

The results of the statistical analysis that was conducted confirm these considerations. A relatively high average removal efficiency was found for the observations grouped in cluster D (91%) in which the high presence of non-charged compounds is counteracted by a high average value of $LogD_{OW}$ (= 3.3, Table 4).

In addition, it is interesting to observe that the removal efficiency appears to be significantly correlated to $LogD_{ow}$ only when considering the neutral and anionic compounds ($p < 0.001$). On the contrary, considering the whole dataset, no significance was observed ($p = 0.088$), suggesting that in the absence of strong electrostatic interactions, the lipophilicity of a compound plays a crucial role in the sorption mechanism.

Finally, the outcomes of the statistical analysis suggest that the molecular weight does not play a crucial role in the fate of micropollutants in an MBR coupled with PAC. Considering the whole dataset, with the exception of cluster C, the regression analysis shows that MW is not significantly correlated to the removal efficiency data ($p = 0.453$). Nevertheless, considering only the negatively charged and neutral compounds (clusters B + D), MW gains relevance in the removal process, albeit remaining non-significant ($p = 0.076$). This suggests that in absence of strong electrostatic interactions, MW may moderately influence the removal of compounds with high MW (and therefore high molecular size). These findings are in line with those shown in the investigation conducted by Alves et al. (2018) who found that, considering weakly charged compounds, a slight positive correlation between the adsorption potential and MW occurs. Furthermore, Tadkaew et al. (2011) noted that compounds with relatively high MW may be more prone to biodegradation processes, as they present more branches susceptible to be attacked by specialized microorganisms developed on the PAC-sludge floc complex, especially in the case of high lipophilic compounds. It is important to remark that the cited study refers to MBR. On its basis, it seems that there is a *weak* correlation between the removal efficiencies and MWs. In particular, compounds with higher MWs resulted to be more lipophilic (e.g. with higher $LogD_{ow}$). These findings are in agreement with our statistical analyses, confirming that in the case of a lack of strong electrostatic interactions between cationic MPs and negatively charged PAC-sludge complex, MW gains importance. Tadkaew et al. (2011) also suggested that the presence of a specialized biomass in the MBR could justify the increased biodegradation. In our selected studies, biomass characterization was not investigated and therefore no specific conclusions about the specialized microorganisms can be obtained.

5. Final remarks and further research

The statistical analysis highlights and suggests interesting conclusions regarding the fate of micropollutants in MBR treatments coupled with PAC.

No significant correlation was found between PAC dosage and micropollutant removal efficiency in the studied range of PAC concentrations (0.03–1 g L^{-1}). Nevertheless, the complexity of the factors influencing the sorption of micropollutants on the PAC surface during treatment (e.g. PAC addition timetable and point, compounds characteristics and matrix effect), and the difficulty in comparing observations provided by different experimental conditions, prevent a clear view in this regard. Further research is needed to clarify the role of the PAC dosage on micropollutant removal, as well as to investigate the good practices (e.g. timetable and point of addition) leading to a better exploitation of the potential of PAC in the reactor, instead of only the variation in the PAC dosage.

The same applies to the PAC retention time, the relevance of which appears to be strongly related to the micropollutant physico-chemical properties. The adoption of a short PAC retention time may enhance the removal of those substances which are more prone to be sorbed on PAC-sludge flocs complex, while a long PAC retention time may entail an increased biotransformation of the compounds due to a more complex and heterogeneous microbial community in the reactor.

Inconclusive results were found for the SRT as it generally varied between very high values (92 and 288 days) and an exhaustive interpretation of all the expected values was not possible.

Considering the physico-chemical properties, the charge demonstrated to be significantly correlated to the removal of micropollutants in an MBR coupled with PAC. This can be explained by the electrostatic interactions between the positively charged substances and the negatively charged surface of the PAC covered by DOM.

In addition, LogD_{OW} showed to be significantly correlated to the removal of neutral and anionic substances, suggesting that the absence of electrostatic interactions, or even the repulsion to the flocs for the anionic compounds, is counteracted by the high relevance of the compound lipophilicity.

Similar behaviour was observed concerning the MW of the substances, which showed to gain importance for neutral and anionic compounds, although not being as statistically significant as LogD_{OW}.

Overall, the results of this study suggest that the variation of the defined operational conditions (i.e. SRT, PAC retention time and PAC dosage) does not always entail a better removal efficiency of a broad spectrum of micropollutants. On the contrary, confirming the scientific literature on the topic, the specific physico-chemical characteristics (in particular, charge and LogD_{OW}) of each compound seem to play the most important role in such a complex process.

Nevertheless, precise management of the operational conditions may significantly entail the removal of specific micropollutants or groups of them.

The results obtained may provide a better understanding of the role played by the selected factors in the removal of micropollutants in an MBR coupled with PAC.

It is important to underline that most of the observations included in the dataset referred to lab scale studies and synthetic wastewater. This implies that the useful considerations suggested by the results of the current statistical analysis should be strengthened by dedicated experiments in full scale plants according to (O'Flaherty and Gray, 2013).

The findings mentioned above may help in the management of such advanced biological treatment in view of achieving a higher removal efficiency of the compounds considered in this study, as well as others that were not included but that exhibit similar physico-chemical characteristics, and thus behaviour. In addition, this study showed that basic statistic means and exploratory data analysis applied to the results of different investigations may be an effective tool to elucidate the influence of the main parameters involved in the complex *phenomena* behind the removal of micropollutants in MBR systems coupled with PAC. As remarked above, future investigations on this type of upgraded MBR should include other parameters including membrane shape, pore size, biomass characteristics, reactor configurations in order to allow a more complete statistical analysis.

CRediT authorship contribution statement

Marina Gutiérrez: writing original draft, review and editing, data curation, investigations, resources.

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Michela Borghesi: formal analysis, writing original draft, review and editing.

Stefano Bonnini; formal analysis, writing original draft, review and editing.

Dragana Mutavdžić Pavlović: visualization, funding acquisition.

Paola Verlicchi: conceptualization, methodology, writing original draft, review and editing, visualization, supervision, project administration, funding acquisition.

Declaration of competing interest

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

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Appendix A. Supplementary data

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Study of the Influence of the Wastewater Matrix in the Adsorption of Three Pharmaceuticals by Powdered Activated Carbon

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Abstract: The use of powdered activated carbon (PAC) as an absorbent has become a promising option to upgrade wastewater treatment plants (WWTPs) that were not designed to remove pharmaceuticals. However, PAC adsorption mechanisms are not yet fully understood, especially with regard to the nature of the wastewater. In this study, we tested the adsorption of three pharmaceuticals, namely diclofenac, sulfamethoxazole and trimethoprim, onto PAC under four different water matrices: ultra-pure water, humic acid solution, effluent and mixed liquor from a real WWTP. The adsorption affinity was defined primarily by the pharmaceutical physicochemical properties (charge and hydrophobicity), with better results obtained for trimethoprim, followed by diclofenac and sulfamethoxazole. In ultra-pure water, the results show that all pharmaceuticals followed pseudo-second order kinetics, and they were limited by a boundary layer effect on the surface of the adsorbent. Depending on the water matrix and compound, the PAC capacity and the adsorption process varied accordingly. The higher adsorption capacity was observed for diclofenac and sulfamethoxazole in humic acid solution (Langmuir isotherm, $R^2 > 0.98$), whereas better results were obtained for trimethoprim in the WWTP effluent. Adsorption in mixed liquor (Freundlich isotherm, $R^2 > 0.94$) was limited, presumably due to its complex nature and the presence of suspended solids.

Keywords: adsorption; diclofenac; sulfamethoxazole; trimethoprim; dissolved organic matter; powdered activated carbon; wastewater

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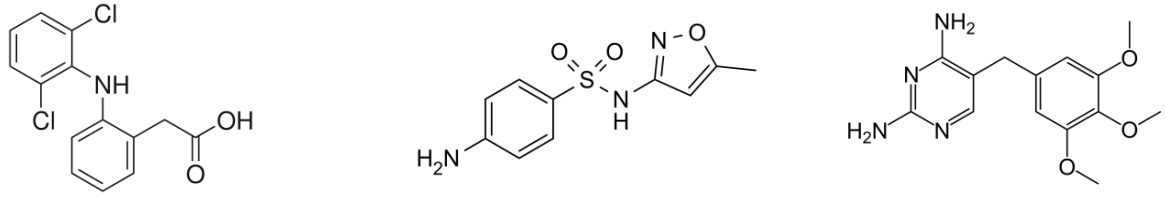
1. Introduction

Pharmaceuticals are one of the most common organic micropollutants found in wastewater. Among pharmaceuticals, nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics are in the spotlight due to their high consumption and/or recalcitrant nature [1,2]. In wastewater treatment plants (WWTPs), the core treatment is biological degradation, and even though some pharmaceuticals are highly biodegradable, the concentrations found in WWTP effluent are still an issue, because WWTPs are not designed to remove them [3]. In this way, advanced treatments have gained interest and have been gradually implemented over the last few years [4–6]. These treatments include activated carbon adsorption (in powder or granules), which offers the advantage of being able to remove a wide range of compounds. This is particularly relevant in wastewater treatment, where organic micropollutants often occur as a "cocktail", and tens to hundreds of substances can be found at the same time [7]. Indeed, the removal of many recalcitrant substances relies almost uniquely on sorption processes [8]. Powdered activated carbon (PAC) is known for being a very flexible option that can be added to existing treatment lines (i.e., addition to the biological tank) or as a polishing treatment to treat the secondary effluent (i.e., in a new contact tank) [9,10]. PAC is used to enhance the removal of substances via adsorption and to promote diverse removal mechanisms with the main aim of obtaining synergistic effects (such as enhanced biodegradation).

Adsorption onto activated carbon, which is driven by the properties of the adsorbent and absorbate as well as the water quality, is a complex process that is not fully understood [11]. When considering the application of PAC in WWTPs, the potential enhancement of the removal of pharmaceuticals depends on many factors for which the extent of their influence is challenging to consider altogether [12]. Activated carbon is a porous adsorbent of which the adsorption capacity depends on its surface properties (specific surface area, pore volume, functional chemical groups) [13]. Pharmaceuticals instead depend on their physicochemical characteristics (compound charge, hydrophobicity, molecular weight, etc.) to be adsorbed, which usually leads to competition effects such that some substances tend to adsorb more easily than others. Moreover, the overall adsorption process depends also on the conditions in which it occurs, such as the water matrix. The constituents of the water matrix and, more specifically, the dissolved organic matter (DOM), may influence the adsorption process. DOM is formed by many fractions that differ in size (building blocks, biopolymers, humic acids, low molecular weight organics, etc.), which may limit the adsorption of pharmaceuticals by blocking the pores on the PAC surface or by direct competition for the adsorption sites [14,15]. Pharmaceuticals may also interact with the DOM present in the liquid phase or the DOM that is adsorbed onto the PAC surface. The results of the interaction may enhance or diminish the adsorption onto PAC, depending on the tested compounds and conditions [11,16,17]. In our previous paper [18], the removal efficiencies of a vast selection of organic pollutants at trace levels were compared and discussed in different MBR coupled to PAC treatment configurations. Specifically, the PAC was added either inside the biological tank of the bioreactor (mixed liquor) or in a post-treatment unit to treat the MBR permeate. Results indicated that the effect of the PAC dosage point was dependent on the compound under study. In general, the presence of suspended solids and the complex nature of the mixed liquor requires higher doses of PAC compared to the MBR permeate to achieve equivalent removal efficiencies [19]. Due to the presence of the micro- or ultra-filtration membranes in the bioreactor, the MBR permeate is free of suspended solids [20]. In light of the foregoing information, the use of synthetic water matrices (i.e., humic acid solution) can act as a means to understand the adsorption process under certain DOM constituents [17].

Because the adsorption onto PAC is influenced by the adsorbate's properties, three pharmaceuticals (Figure 1), namely diclofenac (DCF), sulfamethoxazole (SMX) and trimethoprim (TMP), were selected. These compounds have been subjected to several studies due to their low-to-moderate removal in WWTPs and the potentially harmful effects on the environment that they may entail [21,22]. Additionally, they differ in hydrophobicity (octanol–water partition coefficient, K_{ow}) and charge at the pH of the wastewater. These parameters are commonly used to predict the effectiveness of the addition of PAC on the wastewater treatment line [23].



(**a**) (**b**) (**c**)

Figure 1. Molecular structure of (**a**) diclofenac, (**b**) sulfamethoxazole and (**c**) trimethoprim.

DCF is a non-steroidal anti-inflammatory drug (NSAID) used to treat pain and inflammatory disorders. Banned in many countries of Southeast Asia [24], DCF was selected for the first Watch List (Decision 2015/495) for Union-wide monitoring in Europe [25]. DCF is a weak electrolyte (Figure 1) with high hydrophobicity (logK_{ow} = 4.3) [26] that predominates in its anionic form in wastewater [27]. Compared to other NSAIDs, DCF shows inefficient and variable removal efficiencies in WWTPs, with great discrepancy among the literature

data [28]. In this way, the addition of PAC has been shown to be beneficial, albeit the removal efficiencies found in the literature still show great variability (32–99%) [18].

SMX is a bacteriostatic antibiotic commonly prescribed in combination with TMP. SMX is an anionic compound with very low hydrophobicity ($\log K_{ow}$ = 0.8) [26]. Although these chemical properties are disadvantageous for the direct adsorption of SMX onto PAC, it has been shown that the addition of this adsorbent to the biological tank of a membrane bioreactor (MBR) may increase the removal of this compound [29]. Moreover, batch adsorption isotherms obtained by Li et al. [8] estimated a maximum adsorption of (q_m) 0.017 mg/g.

TMP is an antibiotic that was included in the European Watch List in 2020 (Decision EU 2020/1161) and was maintained in the recent update published in 2022 (Decision 2022/1307) [30,31], for which its monitoring and related research are promoted. It is a relatively hydrophilic compound with a low tendency for sorption onto the sludge of the WWTPs [21]. It has been generally classified as moderately removed in WWTPs, with better removal efficiencies when PAC is added inside the bioreactor compared to when it is added as a post-treatment [18].

Adsorption batch experiments and mathematical models can be useful tools to examine the conditions under which PAC adsorption takes place and to predict adsorbent response to such conditions [32]. In previous research, the application of adsorption models has been of great value to understand the mechanisms of adsorption of certain pollutants on porous adsorbents such as PAC [33]. However, only a few studies have applied these models to study the effect of varying concentrations of DOC [6] and DOM constituents [15–17] in the adsorption of pharmaceuticals in wastewater. Indeed, the potential positive effect of these interactions between DOM and pharmaceuticals has been rarely documented and quantified [11,16]. With regard to the adsorbates, the influence of their physicochemical properties (polarity, charge and hydrophobicity) in adsorption has been the subject of study in the literature [6], but rarely has the literature focused on the subsequent potential competition effect caused by their different affinity towards PAC under realistic conditions of wastewater treatment [34].

For all the above-mentioned reasons, the adsorption of three pharmaceuticals onto PAC is investigated under different conditions using four different approaches. First, the adsorption capacity of PAC for the three target compounds is determined experimentally, and the adsorption process is described by three isotherm models (Linear, Langmuir and Freundlich) and three kinetic models (Lagergren's pseudo-first-order, pseudo-second-order and intraparticle diffusion model (IPD)). Second, the potential competition effect among pharmaceuticals due to their different physicochemical properties (charge, hydrophobicity) is evaluated. Third, the potential influence of the water matrix is assessed by comparing the adsorption process (kinetics, isotherms, experimental adsorption capacity) in ultra-pure water, humic acid solution, permeate of a full-scale membrane bioreactor (MBR) and mixed liquor from the nitrification tank of the same MBR. Finally, the interaction between the pharmaceuticals and the DOM on the adsorption onto PAC is studied.

2. Results and Discussion

2.1. Effect of the Contact Time and Initial Concentration of Pharmaceuticals

In order to determine the time needed to reach the maximum adsorption of the target pharmaceuticals onto PAC, adsorption experiments at various contact times were conducted. For this purpose, individual solutions of each pharmaceutical were tested at three concentrations (5, 15 and 25 mg/L) with two concentrations of PAC (0.1 and 1 g/L) at various contact times (10, 20, 30, 40 and 50 min and 1, 2, 4, 6, 12, 18 and 24 h). Figure 2 shows the removal (in terms of % of adsorption) of the three target compounds over time (10 min–24 h) in Milli-Q water with 1 and 0.1 g/L of PAC. All target compounds reached the equilibrium within 24 h, with very little difference in the adsorption between 18 h and 24 h, indicating that no more molecules could be adsorbed. In this way, 24 h was taken as the equilibrium time for the adsorption isotherms.

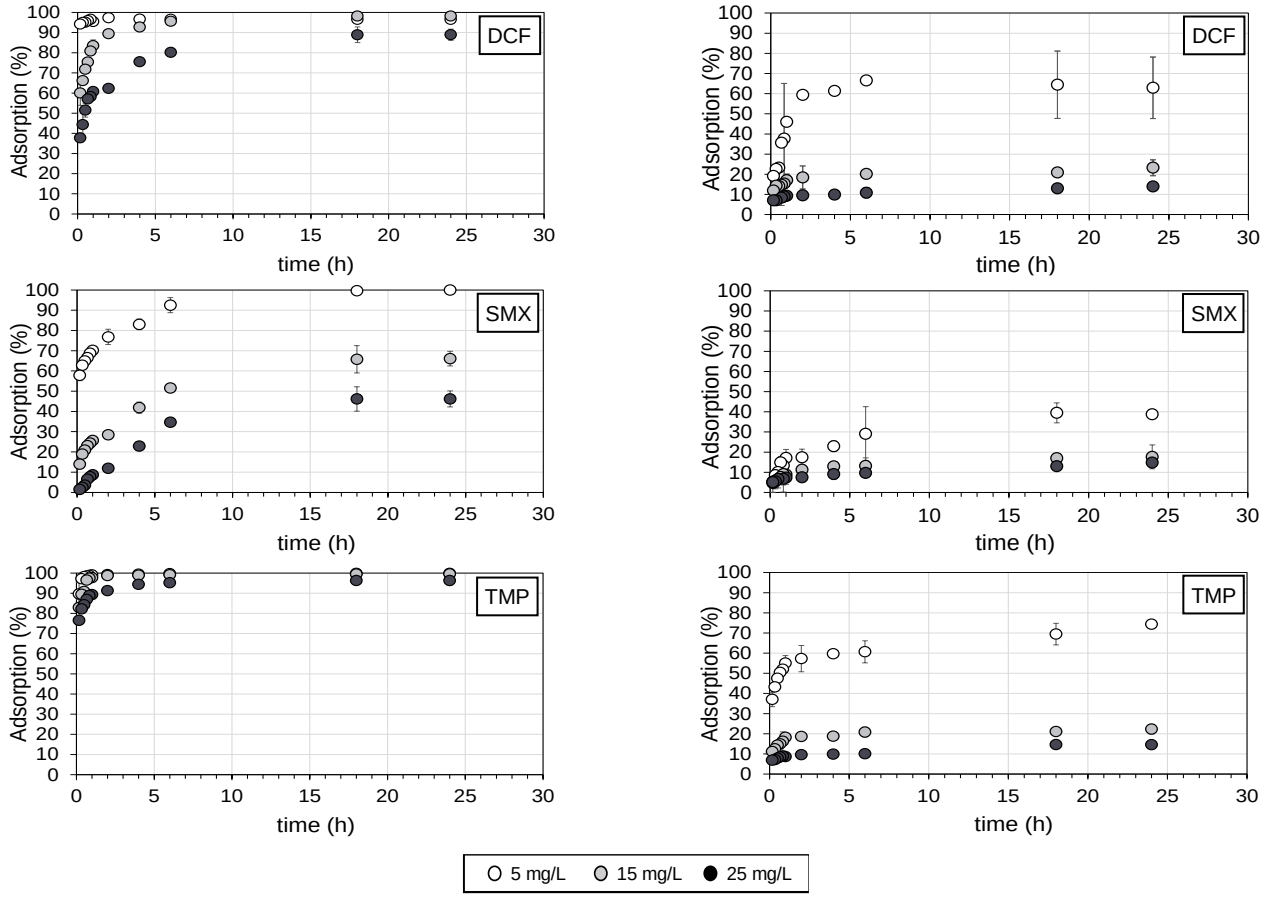


Figure 2. Kinetics of adsorption of DCF, SMX and TMP at three different concentrations in Milli-Q water with (**a**) 1 g/L of PAC and (**b**) 0.1 g/L of PAC at different contact times (10 min–24 h). Error bars indicate the standard deviation.

TMP was almost completely removed by the adsorption onto PAC (1 g/L) at 24 h (96–99.8%), followed by DCF (88–97%) and SMX (46–99.9%). TMP was the compound with the fastest kinetics, with removal from 77% (for the initial concentration of 25 mg/L) to 90% (for the initial concentration of 5 mg/L) in the first 10 min of agitation. SMX instead was the compound with the lowest rates and overall adsorption, depending on the initial concentration. In the first 10 min, 57% of the compound was adsorbed for 5 mg/L (maximum adsorption of 99.9% after 24 h), whereas only 1.5% was adsorbed for 25 mg/L (at 24 h, only 46% of the compound was adsorbed).

Lower adsorption percentages were found when PAC was added at 0.1 g/L for all OMPs in all tested shaking times (Figure 2). At an initial concentration of 5 mg/L, adsorption of 39%, 63% and 74% was obtained at 24 h for SMX, DCF and TMP, respectively. On the other hand, maximum adsorption of approximately 15% was obtained for all OMPs at 25 mg/L. From Figure 2, it can be seen that the adsorption rate was particularly high within the first ten minutes in all tested OMPs with an initial concentration of 15 and 25 mg/L. The adsorption percentage that was reached in 10 min was approximately 50% of the total adsorption that was obtained after 24 h. As an example, the adsorption of DCF at 10 min was 7%, and after 24 h, it was 15% (Figure 2b). After the first ten minutes, the rate of adsorption was considerably low until it reached equilibrium.

Note that adsorption seems to be dependent on the initial concentration of the pharmaceuticals (Figure 2). Higher adsorptions were found at the initial concentration of 5 mg/L compared to 15 and 25 mg/L for DCF, SMX and TMP, indicating that the adsorption of pharmaceuticals onto activated carbon is dependent on their initial concentration.

2.2. Kinetics

Sorption of the tested pharmaceuticals has proved to be a fast process overall. However, the behavior of each compound was different, presumably due to their physicochemical properties and the initial conditions of the experiments (i.e., the concentrations of the adsorbent and the adsorbate).

The kinetics models were applied to all the tested concentrations of pharmaceuticals and PAC, even though the behavior should be the same regardless of the initial concentration ratios. In this way, a vast data set was covered, and the reliability of the results obtained was assured. The kinetics followed a pseudo-second-order model for the three target compounds at the two tested PAC concentrations (1 and 0.1 g/L). The sorption rate constants (k_1 and k_2), $q_{e,\,calc.}$, $q_{e,\,exp}$. and correlation coefficients (R^2) are shown in Table 1. The correlation coefficients of the adjustments were very close to the unity ($R^2 > 0.98$), with no significant differences between the experimental q_e ($q_{e,\,exp.}$) and calculated values ($q_{e,\,calc.}$), suggesting that the sorption is governed by the number of available active sites [34,35]. The lowest $q_{e,\,exp.}$ values were obtained via SMX in all tested concentrations. The maximum amounts of adsorbed pharmaceuticals onto PAC ($q_{e,\,exp.}$) were the highest at the lowest PAC concentration and vice versa. The values obtained were in the range of 4826–24,083 µg/g for 1 g/L of PAC and 19,398–37,184 µg/g for 0.1 g/L of PAC based on the three tested OMPs. Furthermore, higher initial concentrations (C_0) of tested pharmaceuticals led to higher values of $q_{e,\,exp}$. The results indicate that PAC adsorption capacity in the equilibrium increases when it is found at low concentrations with high concentrations of the absorbate (i.e., pharmaceutical) in the solution.

Table 1. Sorption kinetic parameters of DCF, SMX and TMP in ultra-pure water with 1 g/L and 0.1 g/L of added PAC. C_0 indicates the initial concentration of the pharmaceutical, and $q_{e,\,exp.}$ indicates the values of q_e obtained experimentally.

Compound	PAC (g/L)	C_0 (mg/L)	$q_{e,\,exp.}$ (µg/g)	Pseudo-First Order			Pseudo-Second Order		
				$q_{e,\,calc.}$ (µg/g)	k_1 (1/min)	R^2	$q_{e,\,calc.}$ (µg/g)	k_2 (g/µg·min)	R^2
DCF	1	5	4826	206	1.61×10^{-4}	0.135	5000	4.00×10^{-3}	1.000
	1	15	14,729	3185	2.07×10^{-3}	0.806	14,286	6.13×10^{-6}	1.000
	1	25	22,240	11,163	1.15×10^{-3}	0.851	25,000	1.14×10^{-6}	0.993
	0.1	5	31,442	127,321	6.91×10^{-5}	0.743	33,333	1.13×10^{-6}	0.999
	0.1	15	34,852	29,971	4.61×10^{-4}	0.430	33,333	1.29×10^{-6}	0.996
	0.1	25	34,869	229,192	4.61×10^{-4}	0.877	33,333	6.92×10^{-7}	0.995
SMX	1	5	4999	2085	5.07×10^{-3}	0.987	5000	8.16×10^{-6}	0.999
	1	15	9910	11,527	6.91×10^{-4}	0.902	11,111	8.71×10^{-7}	0.992
	1	25	11,549	23,206	4.61×10^{-4}	0.877	14,286	1.88×10^{-7}	0.979
	0.1	5	19,398	43,813	2.30×10^{-4}	0.868	20,000	4.55×10^{-7}	0.992
	0.1	15	26,490	138,038	9.21×10^{-5}	0.784	25,000	7.41×10^{-8}	0.996
	0.1	25	37,016	233,830	6.91×10^{-5}	0.940	33,333	3.83×10^{-8}	0.984
TMP	1	5	4992	82	2.07×10^{-3}	0.598	5000	4.00×10^{-7}	1.000
	1	15	14,933	606	1.84×10^{-3}	0.543	14,286	4.90×10^{-5}	1.000
	1	25	24,083	3151	1.15×10^{-3}	0.657	25,000	8.00×10^{-6}	1.000
	0.1	5	37,184	25,439	4.61×10^{-4}	0.844	33,333	1.13×10^{-6}	0.997
	0.1	15	33,416	126,765	6.91×10^{-5}	0.561	33,333	1.5×10^{-6}	0.999
	0.1	25	36,425	229,826	6.91×10^{-5}	0.917	33,333	6.43×10^{-7}	0.989

As anticipated in Figure 2, the fastest kinetics (k_2) were obtained with the lowest pharmaceutical concentration (5 mg/L) for all the tested compounds except for TMP at 1 g/L PAC. Depending on the initial concentration, k_2 changes by at least one order of magnitude, indicating that the initial OMP concentration seems to have a significant role in the sorption kinetics.

In parallel with pseudo-first and second-order models, the data were fit into the IPD. Previous studies have reported that the removal of pharmaceuticals via adsorption

onto PAC does not fit IPD because the rate of adsorption is controlled by one or more stages [34,36,37]. Nevertheless, although the model does not fit, it is known that in porous adsorbents such as PAC, intraparticle diffusion plays a major role in the adsorption process [36]. The IPD model may be useful for predicting the reaction pathways and the rate-controlling step in the transport from the water matrix to the active sites [38]. For porous adsorbents such as PAC, the adsorption process is differentiated into four stages, as stated originally by Walter and Weber [39]. The first stage is the transfer of the target pollutant to the solution (bulk transport); the second is the film diffusion, in which the adsorbate is transported from the bulk phase to the external surface of the PAC; the third stage is the diffusion of the adsorbate molecules along the adsorbent surface or through the pores (i.e., intraparticle diffusion), which is defined as the rate-controlling step in the IPD model; and the fourth stage is when the adsorption bond is formed between the OMP and the active site. When the adsorption onto PAC is controlled via intraparticle diffusion, stages 1, 2 and 4 occur very quickly, and the intraparticle diffusion is the only rate-controlling step. As a result, the IPD model adjustment should show a linear relationship between $t^{1/2}$ and q_t with a null intercept ($C = 0$). In the original linear form of the IPD [40], only the second, third and fourth stages are considered because bulk transport does not directly relate to the solid–liquid sorption process.

In this study, the q_t versus $t^{1/2}$ plot showed multi-linearity with three different slopes, indicating that the adsorption process is governed by a multistep mechanism, which is differentiated via the three abovementioned stages [38]. The fitting data for the model are shown in Table 2. First of all, it can be seen that the values of the rate constant (k_{id}) follow the following order: $k_{id1} > k_{id2} > k_{id3}$, for all the samples tested. k_{id} values are also at a higher C_0. The fact that the third stage is the lowest is due to it corresponding to the equilibrium state in which intraparticle diffusion gradually slows down; the OMPs come into contact with the active sites, and the final equilibrium is reached, resulting in the corresponding plots being nearly horizontal lines [41,42]. Regarding constant C, the results show that $C \neq 0$ in all samples tested, and increasing values from C_1 to C_3 were found for DCF and TMP. Constant C is associated with the thickness of the boundary layer, which implies that there is a higher boundary layer effect within the pores (and active sites) of the activated carbon compared to the outer surface. According to Rudzinski and Plazinski [43], negative values of intercept C observed for SMX can be explained by the presence of a "subsurface" region close to the surface of PAC on which the concentration of the adsorbate is different from that in the bulk phase, which affects the rate of the surface reactions (pseudo-second-order kinetics) at the initial times.

Table 2. Intraparticle diffusion model constants and correlation coefficients for DCF, SMX and TMP sorption at different initial concentrations (C_0), together with the respective regression coefficients (R^2). The PAC concentration used for the model is 1 g/L.

Compound	C_0 (mg/L)	Intraparticle Diffusion								
		First Phase			Second Phase			Third Phase		
		k_{p1} (μg/g min$^{1/2}$)	C_1	R^2	k_{p2} (μg/g min$^{1/2}$)	C_2	R^2	k_{p3} (μg/g min$^{1/2}$)	C_3	R^2
DCF	5	0.402	93.03	0.921	0.078	95.45	1.000	−0.006	96.751	0.979
	15	15.657	129.49	0.996	2.322	242.66	0.999	−0.013	295.08	1.000
	25	26.047	109.34	0.976	11.310	192.21	0.962	0.029	443.70	1.000
SMX	5	2.596	50.37	0.985	1.926	54.95	0.962	0.074	97.16	1.000
	15	7.479	20.77	0.977	8.644	−8.99	1.000	0.187	191.09	1.000
	25	8.524	−23.18	0.947	14.061	−97.14	0.991	0.033	229.71	1.000
TMP	5	3.813	78.36	0.889	0.348	96.39	0.995	0.020	99.15	0.781
	15	12.055	211.25	0.958	0.958	285.80	0.998	0.072	296.07	0.938
	25	15.330	337.67	0.982	3.291	420.88	0.999	0.321	470.19	0.933

Although the adsorption onto PAC is governed via a multi-step mechanism, and intraparticle diffusion is not the only rate-limiting stage in the adsorption process, the IPD model was useful for understanding the sorption mechanisms of the three target pharmaceuticals. In general, it can be deduced that once the compound passes through the boundary layer from the bulk phase to the external surface of the PAC, it slowly moves from the macropores to the active sites, decreasing the adsorption rate. The adsorption also seems to be determined by a boundary layer effect that increases its relevance in the latter stages of the adsorption process.

2.3. Sorption Isotherms in Ultra-Pure Water and Competition Effect

Pharmaceutical concentrations tested for isotherm determination were in the range of 5–25 mg/L, whereas PAC concentration was between 0.1 and 1 g/L. The equilibrium time was set at 24 h. PAC concentrations were selected in accordance with the literature [8,29,44]. The pharmaceutical concentrations were the lowest allowed by the analytical method. Due to the high adsorption capacity of the PAC, lower concentrations would be almost completely adsorbed and would not be detectable. The sorption coefficient of the linear sorption, together with the sorption parameters derived from the Langmuir and Freundlich models, and regression coefficients (R^2) are listed in (Table 3, individual solutions). From the analysis of the results obtained, it emerges that regression coefficients for linear sorption (0.783–0.96) were significantly lower than the Langmuir and Freundlich models ($p < 0.05$) for all three tested compounds, which means that the model does not fit the adsorption data very well. On the other hand, no significant differences were found between Langmuir and Freundlich for DCF and TMP, whereas the Freundlich model provided better R^2 coefficients for SMX. This finding is in agreement with previous studies in the literature [36,37,45], where very similar R^2 values were obtained, and no statistical analyses were performed to determine the best-fitting equation. Langmuir and Freundlich isotherms are the most used for describing the adsorption of porous adsorbents in wastewater, but further investigations on isotherm modelling may be needed to best describe the adsorption process.

Considering K_d, q_m and K_F parameters, the results observed in the kinetic studies were confirmed once again, and the pharmaceuticals that were better adsorbed in PAC are as follows: TMP, DCF and SMX. On the other hand, the term 1/n of Freundlich isotherm represents the intensity of adsorption. Because the values found for all compounds are less than 1, it can be assumed that there is a good affinity between the adsorbates and the adsorbent and that chemical adsorption occurs.

Complex mixtures of pharmaceuticals are usually found in urban wastewater [7]. The diversity of the nature and target use of these substances is usually reflected in their physicochemical properties (e.g., hydrophobicity, solubility, charge, molecular weight). When PAC is applied for the removal of pollutants in wastewater, adsorption depends on the interactions between the compound and the adsorbent surface, and the aforesaid pharmaceutical properties may be the key to understanding and predicting the adsorption tendency of the compound. For these reasons, it is of great importance to understand the competitive effect among pharmaceuticals when considering adsorption onto activated carbon. The target compounds are expected to be adsorbed to varying degrees, and the competition for the adsorption sites may vary depending on the initial concentration and physicochemical properties of the compound.

To evaluate the competitive effect of DCF, SMX and TMP, the results of adsorption isotherms of the mixture (Table 3) and kinetic studies (Table 4) are presented. As for individual solutions, no statistical differences among isotherm models were found, except for the significantly lower R^2 of linear isotherm in the case of DCF ($p < 0.05$). Despite the lack of significance, the regression coefficients for the Langmuir isotherm are slightly higher, indicating that monolayer adsorption on the PAC surface is assumed and that the differences in adsorption among pharmaceuticals depend on the affinity of the compound to the PAC surface. Although there were no differences between the maximum adsorption capacity (q_m) among the pharmaceuticals, the Langmuir adsorption constants (K_L) were

significantly lower for SMX ($p = 0.018$). Similarly, K_d and K_F showed significant differences among tested compounds ($p < 0.05$), with higher coefficient values in the following order: TMP > DCF > SMX.

Table 3. Distribution coefficient (K_d), Langmuir and Freundlich isotherm constants obtained in individual solutions of each pharmaceutical (DCF, SMX and TMP) and the mixture of the three pharmaceuticals in ultra-pure water. N.A. (not applicable) indicates that the parameters could not be obtained, as the residual concentration found in the liquid phase was too low to conduct the modelling.

		Linear Sorption		**Langmuir Isotherm**			**Freundlich Sorption**		
Compound	**PAC Conc. (g/L)**	**K_d (mL/g)**	**R^2**	**q_m (µg/g)**	**K_L (L/mg)**	**R^2**	**1/n**	**K_F (mg/g) (mL/mg)$^{1/n}$**	**R^2**
Individual solutions									
DCF	0.1	1777.9	0.895	33,333	0.300	0.963	0.281	12,673.9	0.925
	0.25	1949.2	0.836	33,333	0.429	0.979	0.215	14,368.6	0.953
	0.5	2980.6	0.783	25,000	2.000	0.978	0.271	14,099.6	0.991
	1	7167.1	0.855	20,000	5.000	0.946	0.574	10,802.1	0.999
SMX	0.1	1896.0	0.960	50,000	0.100	0.915	0.439	8918.7	0.959
	0.25	1634.0	0.947	33,333	0.150	0.936	0.392	7972.1	0.967
	0.5	1756.3	0.902	25,000	0.444	0.956	0.380	7667.1	0.985
	1	1417.6	0.937	16,667	0.300	0.912	0.520	3947.0	0.990
TMP	0.1	2618.9	0.833	50,000	0.400	0.951	0.178	23,576.4	0.801
	0.25	3712.3	0.820	50,000	0.667	0.972	0.249	21,407.6	0.961
	0.5	5939.4	0.852	33,333	1.500	0.967	0.393	16,565.9	0.998
	1	19,820.0	0.910	25,000	4.444	0.939	N.A.	N.A.	N.A.
Mixture									
DCF	0.1	1806.2	0.852	33,333	0.375	0.987	0.203	16,008.9	0.955
	0.25	1063.6	0.763	16,667	1.000	1.000	0.124	11,356.0	0.900
	0.5	1348.8	0.785	16,667	1.000	0.995	0.212	9531.0	0.962
	1	1390.1	0.707	12,500	1.000	0.996	0.125	9464.5	0.823
SMX	0.1	423.03	0.935	50,000	0.010	0.031	0.587	1222.7	0.423
	0.25	385.32	0.965	14,286	0.054	0.924	0.670	1012.2	0.950
	0.5	280.47	0.976	10,000	0.053	0.869	0.709	629.0	0.998
	1	162.16	0.868	3333	0.375	0.968	0.137	1783.6	0.652
TMP	0.1	2442.7	0.901	50,000	0.200	0.832	0.257	17,243.7	0.597
	0.25	2036.5	0.733	25,000	2.000	0.999	0.128	19,171.9	0.964
	0.5	2716.2	0.730	25,000	2.000	0.999	0.151	17,870.4	0.955
	1	5636.6	0.843	25,000	2.000	0.995	0.239	14,485.5	1.000

When comparing isotherm coefficients between individual solutions and the mixture, only K_F and K_d were found to be significantly lower in the mixture compared to the individual solution in SMX. In this sense, although no significant differences were found for the other parameters (q_m, K_L) and compounds (DCF, TMP), higher values were found in the individual solutions, indicating that there is some competition effect, especially for SMX.

Kinetics studies were used to evaluate whether the rate and mechanism of adsorption of each compound in the mixture (Table 4) varied in comparison with individual solutions (Table 1). In this regard, the same experimental conditions were applied to compare the results with accuracy. In the mixture, the results show that the compounds followed a pseudo-second order equation (Table 4), with no significant differences between $q_{e,exp}$ and $q_{e,calc}$ ($p > 0.05$). Despite there being no differences between the kinetic coefficients (k_2) for the individual solutions and the mixture, the $q_{e,exp}$ values were overall greater in the individual solutions compared to the mixture ($p = 0.01$). Indeed, considering the removal of the compounds in the liquid phase, removal efficiencies were found to be between 23% and

27% higher in the individual solutions at 5 mg/L of the three tested compounds compared to the mixture (e.g., 62.9% versus 36.9% for DCF).

Table 4. Sorption kinetic parameters for the mixture of DCF, SMX and TMP in ultra-pure water with 0.1 g/L of added PAC.

Compound	C_0 (mg/L)	$q_{e,exp.}$ (µg/g)	Pseudo-First Order			Pseudo-Second Order		
			$q_{e,calc.}$ (µg/g)	k_1 (1/min)	R^2	$q_{e,calc.}$ (µg/g)	k_2 (g/µg·min)	R^2
DCF	5	18,467	136,395	9.21×10^{-5}	0.878	16,667	1.33×10^{-6}	0.991
	15	28,362	40,272	1.84×10^{-4}	0.851	33,333	4.09×10^{-7}	0.993
	25	15,957	242,493	2.30×10^{-5}	0.387	16,667	1.2×10^{-6}	0.990
SMX	5	5716	48,865	6.909×10^{-5}	0.801	10,000	1.81×10^{-7}	0.890
	15	4742	147,809	1.382×10^{-5}	0.633	5000	2.72×10^{-6}	0.991
	25	35,771	237,684	6.909×10^{-5}	0.740	33,333	2.81×10^{-7}	0.997
TMP	5	25,531	32,464	2.30×10^{-4}	0.820	25,000	1.45×10^{-6}	0.999
	15	25,310	134,122	4.61×10^{-5}	0.435	25,000	1.23×10^{-6}	0.990
	25	25,948	239,111	4.61×10^{-5}	0.874	25,000	5.71×10^{-7}	0.941

In general, TMP was the compound that adsorbed best at PAC. TMP is the only tested pharmaceutical that is found mainly in its cationic form at the pH of water and wastewater (pH 6–8) (Figure 3). Regardless of their other physicochemical properties, cationic compounds are proven to be well removed on PAC hybrid systems, due to the electrostatic interactions with the negatively charged surface of most manufactured PACs [5,6]. The charge of ionizable compounds is the conducting parameter that determines their adsorption onto PAC [12]. In water and wastewater, DCF and SMX are present mainly in their anionic form, and the expected removal via PAC is lower. In the absence of positive electrostatic interactions, hydrophobicity (measured logK_{ow}) becomes the critical factor for predicting adsorption. SMX is an anionic compound with very low hydrophobicity (logK_{ow} = 0.79) compared to that of DCF (logK_{ow} = 4.26). Both properties are responsible for the lower adsorption of SMX onto PAC in the tested conditions.

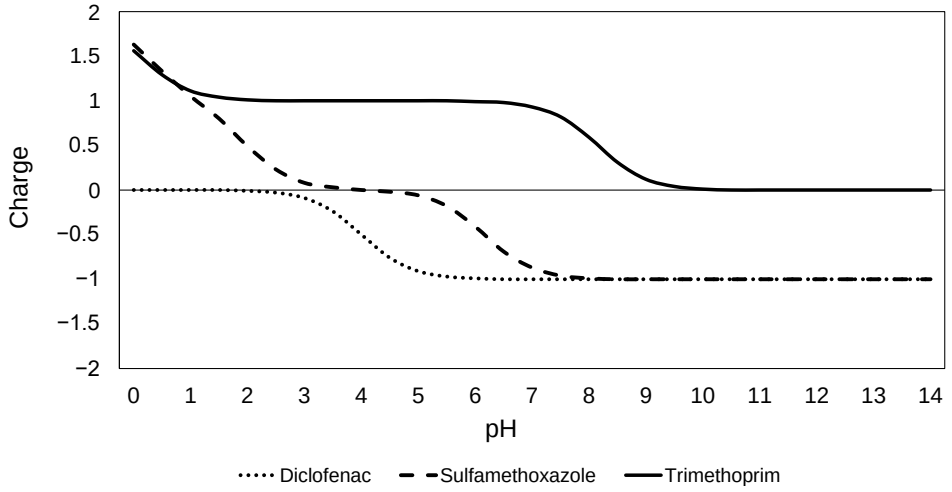


Figure 3. Changes in the ionization state of DCF, SMX and TMP as a function of the pH. J Chem for Office (20.11.0, ChemAxon, https://www.chemaxon.com, accessed on 11 June 2021) was used for calculating the ionization state.

2.4. Influence of the Water Matrix

In wastewater treatment, the water matrix influences the adsorption process as well as the physicochemical properties of the of the adsorbates. In hybrid systems combining

biological treatment with adsorption, PAC can be added in the biological tank (in contact with the mixed liquor) or as a polishing treatment for the secondary effluent [9,32]. Because the constituents and quality of the wastewater change along with the treatment step, it is essential to study the influence of the water matrix on the adsorption of contaminants. One of the most important parameters to consider is the presence of dissolved organic matter (DOM) [46]. DOM is constituted of fractions of different sizes (i.e., building blocks, humic and fulvic acids, biopolymers and low molecular weight organics) which may interfere with the adsorption to varying degrees [15] by blocking the PAC pores or competing with the pollutants of interest for adsorption sites. Indeed, the addition of fresh PAC is required to maintain high removal efficiencies, because the PAC surface becomes saturated over time mainly due to the adsorption of the DOM present in the wastewater [9,46]. In addition, the effect of PAC saturation is more pronounced for anionic compounds, because DOM is negatively charged at the overall pH of wastewater and interferes with the adsorption of anionic compounds through electrostatic repulsion [6]. However, the effect of the presence of DOM is still unclear. Many studies report that DOM has no significant effect or may even have a positive effect on the adsorption of some pharmaceuticals, depending on the experimental conditions [11,14,47].

The influence on the water matrix was studied by performing adsorption batch experiments in ultra-pure water, humic acid (HA) solution, MBR permeate and mixed liquor and comparing the obtained experimental results and isotherm modelling. Although the composition of DOM in the MBR permeate and the mixed liquor was not determined, the total DOC concentration was measured for the HA solution (29.35 mg/L), MBR permeate (4.1 mg/L) and mixed liquor (4.7 mg/L). It should be noted that the DOC concentration in the MBR permeate and that in the mixed liquor are quite similar, despite their different nature. Mixed liquor possesses a high concentration of total suspended solids (6 g/L) compared to MBR permeate (5.4 mg/L). In this case, the solid phase mixed liquor was included in the adsorption experiments, because it can act as an adsorbent and influence the interactions between pharmaceuticals and PAC.

Experimental equilibrium adsorption capacities of DCF, SMX and TMP for each water matrix are depicted in Figure 4. Sorption parameters from isotherm models and regression coefficients for each water matrix are listed in Table 5.

The adsorption mechanisms and, therefore, the isotherm models that describe them may vary from compound to compound, as described in the literature [48]. Similarly, they appear to depend on the water matrix in which adsorption occurs. As mentioned earlier, both the Langmuir and the Freundlich models fitted the results of DCF and TMP in ultra-pure water very well, whereas for SMX, the Freundlich model provided a better fit. Nonetheless, the regression coefficients of the Langmuir model for SMX are very high ($R^2 > 0.956$). As for ultra-pure water, both Langmuir and Freundlich isotherms had very similar regression coefficients in MBR permeate, and there was not a model that fitted the results better for any of the compounds tested. None of the Langmuir parameters (K_L and q_m) differed significantly between the pharmaceuticals. Instead, the Langmuir isotherm clearly fitted the q_e versus C_e plot in the humic acid solution, whereas the Freundlich isotherm had significantly higher R^2 values in the mixed liquor. In the Langmuir isotherm, monolayer adsorption onto the PAC surface is assumed with a fixed number of energetically equivalent sites, whereas the Freundlich isotherm is considered to be an empirical expression for multilayer adsorption with different energy in the active sites [35]. Mixed liquor is expected to represent a much more complex matrix because it was extracted from the biological reactor, where most of the biological and chemical transformations take place for the removal of contaminants. In previous studies, it has been observed that given similar DOC-pharmaceutical concentrations, DOM composition may induce a stronger adsorption competition effect depending on the type of water (i.e., drinking water compared to WWTP effluent) [14]. In this way, the results are not surprising and confirm that adsorption mechanisms change depending on experimental conditions.

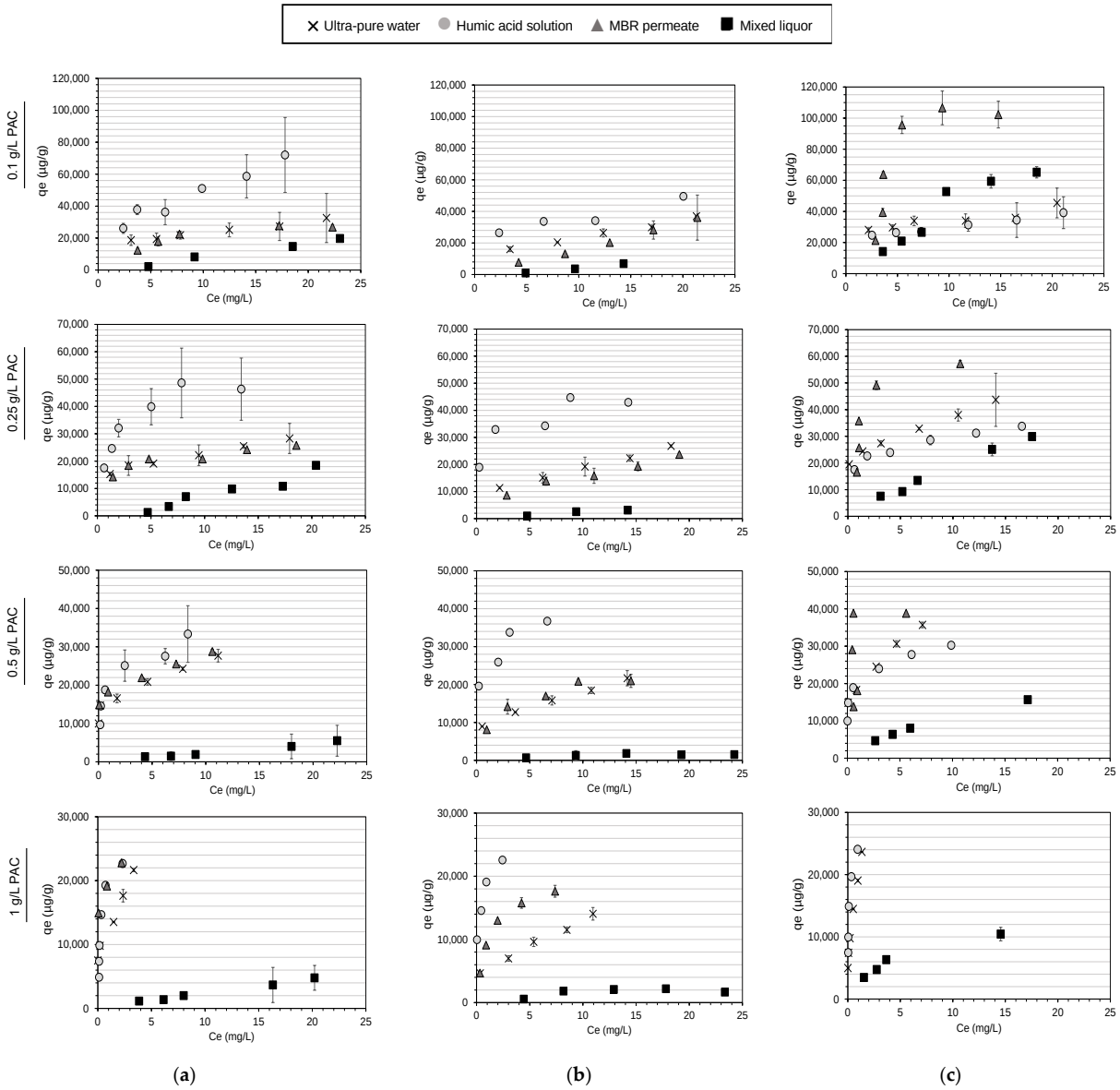


Figure 4. Experimental equilibrium adsorption capacity of (**a**) DCF, (**b**) SMX and (**c**) TMP at four different PAC concentrations (0.1, 0.25, 0.5 and 1 g/L) in ultra-pure water (×), humic acid solution (○), MBR permeate (▲) and mixed liquor from a WWTP (■). Error bars indicate the standard deviation.

Assuming that the Freundlich isotherm had the best fit for all the water matrices, the higher average K_F values were found as follows: HA solution, ultra-pure water, MBR permeate and mixed liquor. Higher K_F values correspond to a higher adsorption capacity of the PAC (q_e) for the same equilibrium concentration (C_e) for all three compounds. As shown in Figure 4, higher PAC loads were obtained in the humic acid solution for DCF and SMX, followed by ultra-pure water and MBR permeate, with very similar results ($p > 0.05$). On the other hand, PAC loads were found to be the lowest in the mixed liquor for all pharmaceuticals. For TMP instead, the best results were obtained in the MBR permeate, followed by ultra-pure water, humic acid solution and mixed liquor. Indeed, for 1 g/L of PAC, the remaining concentrations of TMP in the MBR permeate were too low to perform the isotherm modelling. For 0.1 g/L of PAC, an unexpected increase in the adsorption capacity was achieved at higher TMP concentrations in the mixed liquor, not following the trend in the other PAC concentrations. Although the overall results are not consistent with other studies [11,49], in which the adsorption capacity in wastewater was systematically lower compared to that in ultra-pure water, it is possible that positive interactions between

the humic acids and MBR effluent DOM lead to an increased adsorption capacity of PAC. Moreover, in real wastewater systems, DOM is present at a concentration of three to six orders of magnitude higher than organic micropollutants (mg/L compared to µg/L—ng/L). In our experimentation, the extent of the effect of DOM may be limited or altered because the C_0 of the tested pharmaceuticals ranged from 5 to 25 mg/L. In all water matrices, the highest PAC loadings (q_e) were observed at the lowest PAC concentration (0.1 g/L) and maximum pharmaceutical concentration (25 mg/L) for all the water matrixes and compounds (Figure 4).

Table 5. Distribution coefficient (K_d), Langmuir and Freundlich isotherm constants in different water matrices (humic acid solution, MBR permeate and mixed liquor). Results for humic acid solutions were considered without pre-contact time between the HAs and the pharmaceuticals. N.A. (not applicable) indicates that the parameters could not be obtained, as the residual concentration found in the liquid phase was very low to conduct the modelling.

		Linear Sorption		**Langmuir Isotherm**			**Freundlich Sorption**		
Compound	**PAC Conc. (g/L)**	**K_d (mL/g)**	**R^2**	**q_m (µg/g)**	**K_L (L/mg)**	**R^2**	**1/n**	**K_F (mg/g) (mL/mg)$^{1/n}$**	**R^2**
Humic acid solution									
DCF	0.1	4521.6	0.941	100,000	0.125	0.908	0.4568	18,012.1	0.929
	0.25	4802.4	0.783	50,000	1.000	0.994	0.2799	24,760.4	0.896
	0.5	4600.6	0.768	33,333	1.500	0.984	0.2000	20,607.3	0.781
	1	12,308.0	0.718	100,000	1.429	0.994	N.A.	N.A.	N.A.
SMX	0.1	2856.7	0.878	50,000	0.250	0.919	0.2630	20,426.7	0.863
	0.25	3957.7	0.792	50,000	1.000	0.983	0.1408	29,673.2	0.651
	0.5	6994.4	0.801	33,333	3.000	0.983	0.2731	22,606.7	0.807
	1	11,372.0	0.763	25,000	5.000	0.991	N.A.	N.A.	N.A.
TMP	0.1	2287.9	0.860	50,000	0.286	0.976	0.2116	19,150.8	0.900
	0.25	2600.1	0.791	33,333	0.750	0.992	0.1891	19,424.7	0.958
	0.5	3824.5	0.720	33,333	3.000	0.994	0.1960	19,358.8	0.998
	1	31,430.0	0.740	25,000	10.000	0.998	N.A.	N.A.	N.A.
MBR permeate									
DCF	0.1	1553.7	0.880	33,333	0.150	0.978	0.4160	8206.6	0.865
	0.25	1785.4	0.802	25,000	0.667	0.989	0.2066	14,004.0	0.925
	0.5	3273.4	0.776	50,000	1.000	0.985	0.2785	14,831.4	0.997
	1	12,011.0	0.734	25,000	1.000	0.995	N.A.	N.A.	N.A.
SMX	0.1	1642.8	0.999	1,000,000	0.002	0.028	0.9527	1843.1	0.988
	0.25	1349.2	0.962	33,333	0.100	0.924	0.4976	5154.4	0.978
	0.5	1874.2	0.870	25,000	0.444	0.993	0.2650	10,690.4	0.932
	1	3009.7	0.837	20,000	1.000	0.999	0.2310	11,178.0	0.996
TMP	0.1	9370.2	0.875	250,000	0.057	0.225	0.8102	15,532.7	0.647
	0.25	6616.8	0.690	50,000	1.000	0.974	0.2822	31,351.0	0.754
	0.5	8417.5	0.535	50,000	1.000	0.937	N.A.	N.A.	N.A.
	1	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Mixed liquor									
DCF	0.1	827.9	0.993	−25,000	−0.019	0.466	1.3563	299.7	0.957
	0.25	766.7	0.963	−10,000	−0.033	0.407	1.6076	148.1	0.903
	0.5	235.9	0.995	50,000	0.005	0.038	0.9064	296.5	0.952
	1	234.1	0.998	33,333	0.008	0.268	0.8891	312.6	0.979
SMX	0.1	431.5	0.965	−3333	−0.048	0.907	1.8270	55.0	1.000
	0.25	233.2	0.990	−33,333	−0.006	0.085	1.0983	186.3	0.954
	0.5	84.0	0.892	2000	0.172	0.873	0.4847	384.3	0.707
	1	109.4	0.858	2500	0.118	0.552	0.6615	300.6	0.594
TMP	0.1	3988.7	0.976	1,250,000	0.004	0.015	1.0055	4011.8	0.939
	0.25	1785.7	0.995	125,000	0.020	0.538	0.8440	2659.3	0.980
	0.5	1002.7	0.960	33,333	0.060	0.986	0.6493	2484.4	1.000
	1	822.7	0.868	14,286	0.233	0.996	0.4847	2980.3	0.967

It has been observed that the adsorption of some pharmaceuticals is promoted by the presence of humic acid in soils and sediments, suggesting that the presence of these substances may positively influence the sorption affinity for the adsorbent. Humic substances, which are also commonly found in wastewater, are known to act as carriers of

organic micropollutants such as pharmaceuticals [50]. Due to their mobility and ability to form complexes with organic and inorganic species, commercial HAs may contain trace elements (e.g., ions, heavy metals) that contribute to the adsorption of further organic compounds (i.e., diclofenac) in adsorption experiments [50]. In another study, the formation of ciprofloxacin–HA complexes has been reported as a "false positive adsorption" when testing the sorption capacity of various adsorbents [17]. According to Behera et al. [33], the pharmaceutical–HA complex would be able to adsorb onto the surface of the adsorbent. These authors also suggest that the free pharmaceuticals in the solution could adsorb onto the already adsorbed HA, leading to an increase in adsorption [17]. On the other hand, the high concentrations of HAs in our study (29.35 mg/L) may enhance the sorption of some pharmaceuticals via hydrophobicity. Even if the interaction between DOM and pharmaceuticals is not expected, the presence of HAs may promote the adsorption through the PAC in the solution. The adsorption of dissolved humic substances has been proved to reduce the aggregation of carbon nanotubes, thus increasing the surface area available for adsorption by two orders of magnitude, increasing the change in the hydrophobic interactions between the adsorbent and SMX [47]. This could explain the increased adsorption of DCF and SMX, two anionic compounds for which the electrostatic interactions with the DOM would not be primarily considered. For the aforementioned reasons, the increased adsorption capacity of PAC in the HA solution is not surprising. Although there is no single phenomenon that explains the observed results, the literature data confirm that the presence of humic substances can affect the adsorption of organic compounds such as pharmaceuticals in several ways.

In the case of the MBR permeate, the results show that the presence of DOM had no negative effect on drug adsorption, with no statistical differences from ultra-pure water for DCF and SMX ($p > 0.05$) and with an increase in the adsorption capacity of PAC for TMP ($p < 0.05$). Because the concentration of the pharmaceutical influences the experimental adsorption values (with the highest q_e values at C_0 of 25 mg/L in all water matrices), it may be that DOC is not high enough in the solution to cause a decrease in adsorption compared with ultra-pure water. In any case, the results show that the adsorption of TMP in the MBR permeate was enhanced, probably due to the above-mentioned reasons related to HAs and, in particular, to the fact that TMP is positively charged, which could favor the interactions with negatively charged DOM. PAC added to the secondary effluent of full-scale WWTPs has been proved to provide a better quality effluent (i.e., lower TMP concentration) compared to PAC added in the biological reactor, in contact with the mixed liquor, indicating that the DOM constituents of the MBR permeate have a different effect on the adsorption of TMP onto PAC [18]. Indeed, TMP was not the only compound with lower adsorption in the mixed liquor (Figure 4). Even with the very similar DOC concentration, the differences in the adsorption capacity of PAC between the MBR permeate and mixed liquor indicate that the DOM constituents play a significant role in the adsorption process. Although HAs appeared to favor adsorption, low molecular weight organics have been demonstrated to limit the process due to direct competition for the adsorption sites [35]. However, it should be noted that the experiments conducted aimed to reproduce the adsorption process under real WWTP conditions, and, therefore, the solid fraction of the mixed liquor was included in the adsorption batch experiments. Because some pharmaceuticals are also able to adsorb onto the sludge [27], additional adsorption experiments were performed without the addition of PAC to quantify the adsorption onto the solid phase of the mixed liquor (dried sludge). The results of the experimental q_e and C_e values were highly variable, and no modelling could be performed (data not shown). However, the resulting q_e values were very low compared to PAC adsorption (e.g., the maximum q_e found was 530 μg/g for SMX), and thus, the adsorption onto the mixed liquor can be neglected for the pharmaceuticals under study [27]. However, the presence of additional suspended material (with a concentration of 6 g/L) could limit the ability of the pharmaceuticals to reach the PAC adsorption sites and, thus, physically reduce the adsorption of pharmaceuticals.

2.5. Influence of the Pre-Equilibrium Time between Pharmaceuticals and DOM on Adsorption

The influence on the interaction between DOM and the pharmaceuticals before the adsorption onto PAC was studied by using the HA solution. Humic acids are one of the most common DOM fractions found in wastewater [50], and they were chosen because of their commercial availability and ease of use in the laboratory. Because the objective was to study the interaction between DOM and the pharmaceuticals, DOC concentration does not have to be identical to the one found in the biological tank of the WWTP (4.7 mg/L). In fact, the experiments were performed with the highest possible DOC concentration, in order to produce the largest difference between DOM and the pharmaceutical concentration. The pre-contact time between HAs and OMPs was set at 24 h because it has already been tested as sufficient to evaluate the influence of the interaction between them [11].

The results of the adsorption isotherm parameters and correlation coefficients of the three pharmaceuticals with 24 h of pre-contact time are shown in Table 6, whereas the results of adsorption without a pre-equilibrium time are depicted in Table 5. Langmuir isotherm is the model that better fits the results in the HA solution in both conditions, and no statistical differences were found between them for the maximum adsorption capacity (q_m) and Langmuir coefficient (K_L). Regarding removal efficiencies (data not shown), no statistical differences were found between no pre-contact time and 24 h of pre-contact time with the HA solution, although a slight increment was observed for the condition without pre-contact time (3% for SMX, 7% for TMP and 8% for DCF). As explained earlier, the presence of HA in the solution had a neutral to positive effect for the three pharmaceuticals tested, which may be attributed to the high adsorption of the HAs and the interaction between the HA and the pollutants. However, the pre-contact time had no significant effect on the adsorption. The long shaking times of the adsorption experiments (24 h) were already sufficient to observe the potential beneficial effects of the presence of HA in the solution (e.g., formation of pharmaceutical–HA complexes, increased dispersion of the PAC), without the need for additional pre-contact time. In this way, in a previous study, it was found that the 24 h pre-contact time between DOM and various pharmaceuticals favored adsorption only at short contact times (i.e., 30 min) and had no effect once the equilibrium between the adsorbent and adsorbates was reached (i.e., 72 h) [11].

Table 6. Distribution coefficient (K_d) and Langmuir and Freundlich isotherm parameters, together with the corresponding regression coefficients (R^2) for the adsorption DCF, SMX and TMP onto PAC in a humic acid solution with 24 h pre-contact time between the pharmaceuticals and the humic acids. Not applicable (N.A.) indicates that the parameters could not be obtained, as the residual concentration found in the liquid phase was too low to conduct the modelling.

		Linear Isotherm		**Langmuir Isotherm**			**Freundlich Isotherm**		
Compound	**PAC Conc. (g/L)**	**K_d (mL/g)**	**R^2**	**q_m (µg/g)**	**K_L (L/mg)**	**R^2**	**1/n**	**K_F (mg/g) (mL/mg)$^{1/n}$**	**R^2**
DCF	0.1	2931.5	0.8482	50,000	0.400	0.983	0.2194	23,435.3	0.951
	0.25	3196.9	0.8713	50,000	0.333	0.980	0.3342	15,739.0	0.988
	0.5	2932.1	0.7000	25,000	2.000	0.999	0.0962	20,854.0	0.959
	1	2403.6	0.6190	16,667	6.000	0.990	0.0825	13,418.6	0.614
SMX	0.1	2378.1	0.8972	50,000	0.250	0.985	0.2619	18,030.1	0.953
	0.25	3434.0	0.8685	50,000	0.500	0.981	0.3040	18,300.8	0.970
	0.5	5491.8	0.8108	33,333	3.000	0.988	0.1885	23,086.4	0.948
	1	7530.7	0.7846	20,000	6.250	0.988	N.A.	N.A.	N.A.
TMP	0.1	2340.0	0.8716	50,000	0.250	0.989	0.2932	16,000.9	0.9487
	0.25	2567.3	0.7911	33,333	0.750	0.991	0.2272	17,667.8	0.9735
	0.5	3896.4	0.7282	33,333	3.000	0.996	0.1366	22,092.6	0.9872
	1	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.

3. Materials and Methods

3.1. Adsorbent and Adsorbates

PAC (ACTISORBE 700, Brenntag S.p.A, Italy) was used for all the adsorption experiments. The PAC characteristics were supplied by the manufacturer as follows: iodine number 750 mg/g, methylene blue 12 mL, BET specific surface area 850 m^2/g, bulk density 430 kg/m^3, ash content 10%, humidity 5% and alkaline pH. The surface properties of the selected PAC are in agreement with the literature on adsorption of organic pollutants [18,51–53]. After its purchase, the PAC was not treated in order to emulate real conditions for which the adsorbent is directly added to the wastewater treatment line.

The DCF, SMX and TMP properties are listed in Table 7. J Chem for Office (20.11.0, ChemAxon, https://www.chemaxon.com, accessed on 11 June 2021) was used for calculating the physicochemical properties (logK_{ow}, molecular weight) and the ionization state (Figure 3). The calculation method for logK_{ow} is based on a modified version of the algorithm published by Viswanadhan et al. [54]. In this publication, the K_{ow} is the sum of the assigned values of the individual atomic contributions of a molecule. Molecular weight was based on the data published by IUPAC on the atomic weights of elements [55]. To calculate the ionization state, the software conducts a weighted sum of the net charges of the microspecies comprising the molecule as a function of the pH in aqueous solution. More information about the software functioning is available online.

Diclofenac and sulfamethoxazole (≥98% TLC) were purchased from Sigma-Aldrich (St. Louis, MO, USA), and trimethoprim (≥98% TLC) was purchased from Acros Organics (Thermo Fisher Scientific Inc., Trenton, NJ, USA). To prepare the pharmaceutical solutions, exact amounts of the target compounds were weighed and added to the corresponding water matrix (Section 3.2). To ensure that the compounds were completely dissolved, a maximum of 1% of methanol was added, and the solutions were sonicated in an ultrasonic bath (Sonorex Digital 10P, Bandelin electronic, Berlin, Germany) for 5 min.

Table 7. Physicochemical properties of the selected pharmaceuticals. J Chem for Office (20.11.0, ChemAxon, https://www.chemaxon.com, accessed on 11 June 2021) was used for calculating the physicochemical properties (molecular weight and logK_{ow}). Values for pK_{a1} and pK_{a2} were obtained from the literature [56,57].

Compound	Molecular Formula	Molecular Weight (g/mol)	logK_{ow} [1]	pK_{a1}	pK_{a2}
Diclofenac	$C_{14}H_{10}Cl_2NNaO_2$	318.13	4.26	4.21 [2]	
Sulfamethoxazole	$C_{10}H_{11}N_3O_3S$	253.28	0.79	1.83 [2]	5.57 [2]
Trimethoprim	$C_{14}H_{18}N_4O_3$	290.32	1.28	7.10 ± 0.02 [3]	

[1] Octanol–water partition coefficient. [2] Obtained from [56]. [3] Obtained from [57].

3.2. Water Matrices

Four different water matrices were used to prepare pharmaceutical solutions: ultrapure water (Milli-Q), humic acid (HA) solution and effluent and mixed liquor from a WWTP. The preparation method of each water matrix is described below.

Milli-Q water was obtained from the Millipore Simplicity UV system (Millipore Corporation, Billerica, MA, USA).

Commercially available humic acids (CAS 1415-93-6, Sigma-Aldrich, St. Louis, MO, USA) were used to prepare the HA solution (50 mg/L), with a dissolved organic carbon (DOC) concentration of 29.35 mg/L. The solution was prepared following the method described by [48]. Briefly, to prepare a volume of 100 mL, 5 mL of 1M NH_4OH were added to a 100 mL flask. Then, 0.005 g of HAs were weighed, and the Milli-Q water was added to a maximum of 85 mL. The pH of the solution was then adjusted to 5.34 with 1 M formic acid and prepared to the desired volume (100 mL).

The effluent and mixed liquor were collected from the permeate and the nitrification tank, respectively, of a full-scale MBR located in northern Italy, and frozen at −20 °C until

their use. Both the MBR permeate and mixed liquor were autoclaved at 121 °C to reduce any potential biological activity and subsequently filtered through paper filters (Lab Expert, KEFO d.o.o, Croatia) to remove any particulate matter. Filters from the mixed liquor were air dried for 24 h and scrapped to obtain dry sludge. To ensure that all the glass beakers on which the adsorption experiments were conducted contained the same amount of mixed liquor suspended solids (MLSS), a certain amount (120 mg) of dry sludge was added to each glass baker. The resulting MLSS concentration in the mixed liquor was 6 g/L, a concentration commonly found in real WWTPs.

3.3. Batch Adsorption Experiments

Experiments were conducted in triplicate using 20 mL of pharmaceutical solutions in each glass beaker. The glass beakers were sealed with parafilm to avoid evaporation. All experiments were performed in triplicate using an incubator shaker at 150 rpm and a constant temperature of 25 °C (Innova 4080, New Brunswick Scientific, Edison, NJ, USA), which enabled continuous contact between the compounds and the activated carbon. To avoid photodegradation, all experiments were performed in darkness.

Preliminary experiments were conducted to determine the contact time necessary to reach the equilibrium between the PAC and the target pharmaceutical in ultra-pure water. Three different concentrations of target pollutants were tested (5, 15 and 25 mg/L). The PAC was agitated in the solutions for 10, 20, 30, 40 and 50 min and 1, 2, 4, 6, 12, 18 and 24 h at a constant temperature (25 °C). Two PAC concentrations (0.1 g/L and 1 g/L) were tested in each target compound individually, and 0.1 g/L of PAC was also tested in the mixture of the three pharmaceuticals. The results of the preliminary experiments determined 24 h to be sufficient time to reach the equilibrium for all three compounds and the mixture. Based on the results obtained, the sorption kinetics were determined. Kinetics studies were conducted by applying three different kinetics models: Lagergren pseudo-first-order [58] (1), pseudo-second-order (2) and intraparticle diffusion model (IPD) (3) [40].

$$\frac{dq_e}{dt} = k_1(q_e - q_t) \tag{1}$$

$$\frac{t}{q_t} = \frac{1}{k_2 q_e^2} + \frac{1}{q_e}t \tag{2}$$

$$q_t = k_{id}t^{1/2} + C \tag{3}$$

where q_e and q_t are the quantity of solute adsorbed onto the PAC surface (μg/g) at the equilibrium (q_e) and at time t (q_t); k_1 (1/min), k_2 (μg/g min) and k_{id} (μg/g·min$^{1/2}$) are considered the Lagergren pseudo-first order, pseudo-second order and IPD rate constants, respectively; and intercept C provides information about the thickness of the boundary layer.

The batch sorption experiments were conducted in 20 mL of pharmaceutical solutions. For each water matrix, concentrations of pharmaceuticals ranging from 5 to 25 mg/L were tested to determine the sorption isotherms. PAC was added to the solutions at 0.1, 0.25, 0.5 and 1 g/L in each experiment and placed into agitation for 24 h. Equilibrium adsorption was studied by applying linear (4), Langmuir (5) and Freundlich (6) isotherm models to the experimental data,

$$q_e = K_d C_e \tag{4}$$

$$\begin{matrix} \mathrm{q_e} = \mathrm{K_F C_e^{1/n}} \\ q_e = K_F C_e^{1/n} \end{matrix} \tag{5}$$

$$\frac{1}{q_e} = \frac{1}{q_m} + \frac{1}{K_L q_m C_e} \tag{6}$$

where q_e is the amount of adsorbed compound per mass unit of adsorbent at the equilibrium (μg/g); C_e is the equilibrium concentration of the pharmaceutical (mg/mL); K_d is the distribution coefficient; K_F is the Freundlich adsorption constant ((μg/g) (mL/mg)$^{1/n}$);

1/n is the heterogeneity constant; q_m is the equilibrium sorption capacity, that is, the maximum amount of OMP to be adsorbed by the activated carbon (μg/g); and K_L is the adsorption constant for Langmuir isotherms and is related to the sorption bonding energy (L/mg). Based on the four water matrices previously described, different experiments were conducted. Firstly, the pharmaceuticals were tested individually in each water matrix to compare the effect of the DOM (measured as DOC) in the adsorption process (ultra-pure water, humic acid solution, MBR permeate and mixed liquor). Secondly, sorption experiments were conducted in ultra-pure water with a mixture of the three target compounds (DCF, SMX and TMP) at the previously selected concentrations to evaluate the interaction and competition among the pharmaceuticals. Then, the HA solution was used to study the influence of a pre-equilibrium contact time between the DOM and the pharmaceuticals prior to the adsorption onto PAC. Pharmaceuticals were added to the HA solution 24 h before the addition of PAC to simulate their interactions in the sewer and inside the WWTP. Finally, mixed liquor experiments were performed with the addition of PAC and without PAC to assess the adsorption of the pharmaceuticals to the MLSS (i.e., added dried sludge).

3.4. HPLC Analysis

Prior to the quantitative analysis of the OMP concentration, glass beakers were decanted, and samples were centrifuged at 3500 rpm for 5 min (Hettich EBA 20, Westphalia, Germany) to subsequently be filtered with a 0.45 μm Nylon syringe filter (Filter-Bio, Nantong, China). Blank samples containing the corresponding water matrices were also included in the analysis to act as controls.

The residual pharmaceutical concentration was determined via high-performance liquid chromatography coupled to a photodiode array detection (HPLC-PDA) (Waters 2795 Separation Module and Waters 2996, Waters Corporation, Milford, MA, USA). A Kinetex C18 column was used (Phenomenex, 150 × 4.6 mm, 5 μm particle size, 100 Å pore size). The mobile phase contained eluent A, which was composed of 0.1% of formic acid in Milli-Q water, and solvent B, with 0.1% of formic acid in acetonitrile. The flow rate was 0.5 mL/min for all the experiments. The column temperature was 20 °C. The injection volume for each sample was 20 μL. Peak wavelengths are 276.9 nm for DCF, 269.8 for SMX and 270.8 nm for TMP.

Isocratic methods were used to determine the concentrations of individual target pollutants. For DCF, the volume proportion of eluent A was 35%, and that of eluent B was 65%. For SMX, the proportions were 65% A and 35% B, whereas for TMP, the proportions were 85% A and 15% B. The total elution time was 10 min. The retention time was 6.5 min, 6 min and 5.6 min for DCF, SMX and TMP, respectively.

For the solution containing the mixture of pharmaceuticals, a method with gradient elution was developed. The total run time was 25 min, and the flow was kept constant at 0.5 mL/min. It started with a 1 min step gradient with 85% A and 15% B, which was then maintained as linear for another 5 min. Then, the flow was continued with a 1 min linear gradient with 65% A and 35% B, which was maintained for another 3 min; a 5 min gradient with 35% A and 65% B; and a step gradient of 0.1 min back to 85% A and 15% B, which was maintained for another 4.9 min. The retention time of each compound in the mixture was 6.2 min for TMP, 12.9 min for SMX and 20.2 min for DCF in the gradient elution method.

4. Conclusions

The adsorption of three pharmaceuticals (namely DCF, SMX and TMP) onto PAC was studied through the use of kinetic and isotherm models in different water and wastewater matrices. Sorption of the tested pharmaceuticals was proven to be an overall fast process in ultra-pure water. Kinetics followed a pseudo-second order, suggesting that the sorption rate is governed by the number of available active sites. Additionally, the boundary layer effect seems to decrease the adsorption rate as compounds gradually reach the active sites at the equilibrium. Compared to individual solutions, the rate of the adsorption of the

compounds in a mixture did not differ; however, a greater adsorption capacity of the PAC was observed in the individual solutions.

Adsorption of pharmaceuticals onto the PAC surface is a complex process that greatly depends on physicochemical properties of the investigated compounds and on the matrix where it takes place. Charge, followed by hydrophobicity, determined the rate and the extent of the adsorption in all the tested matrices, with better results obtained via TMP (cationic compound), followed by DCF (anionic, hydrophobic) and SMX (anionic, hydrophilic). The effect of the water matrix varied from compound to compound. Humic acids appeared to positively affect the affinity for the adsorbent in DCF and SMX, presumably by forming pharmaceutical–HA complexes and by reducing the aggregation of PAC. Mixed liquor gave the lowest adsorption capacities of PAC, probably due to its complex nature and the presence of additional suspended solids. The adsorption isotherms also varied among water matrices. Only Langmuir isotherm explained adsorption in humic acid solution and Freundlich isotherm in the mixed liquor, whereas both isotherms fitted the results in ultra-pure water and MBR permeate very well. In this way, DOM and specifically HAs proved to be beneficial for the adsorption of the selected pharmaceuticals. However, the effects of the interaction of these elements prior to the addition of the adsorbent did not have an effect after long contact times (24h). In this way, future work should be focused on the understanding of the potential interactions between the organic components of the wastewater that may favor the adsorption of pharmaceuticals onto PAC.

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Advanced processes for the removal of organic micropollutants from wastewater by the addition of powdered activated carbon to membrane bioreactor

Titolo della tesi (traduzione):

Trattamenti avanzati per la rimozione di microinquinanti organici dalle acque reflue mediante aggiunta di carbone attivo in polvere nel bioreattore a membrana

Tutore: Prof. (Cognome e Nome)

Verlicchi Paola

Settore Scientifico Disciplinare (S.S.D.)

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