Check for updates

Pharmaceuticals' removal by constructed wetlands: a critical evaluation and meta-analysis on performance, risk reduction, and role of physicochemical properties on removal mechanisms

Huma Ilyas, Ilyas Masih and Eric D. van Hullebusch

ABSTRACT

This paper presents a comprehensive and critical analysis of the removal of pharmaceuticals (PhCs), the governing physicochemical properties, and removal mechanisms in constructed wetlands (CWs). The average removal efficiency of the most widely studied 34 PhCs ranges from 21% to 93%, with the exception of one PhC that exhibited negative removal. Moreover, CWs are effective in significantly reducing the environmental risk caused by many PhCs. Based on risk assessment, 12 PhCs were classified under high risk category (oxytetracycline > ofloxacin > sulfamethoxazole > erythromycin > sulfadiazine > gemfibrozil > ibuprofen > acetaminophen > salicylic acid > sulfamethazine > naproxen > clarithromycin), which could be considered for regular monitoring, water quality standard formulation and control purposes. Biodegradation (aerobic and anaerobic) is responsible for the removal of the majority of PhCs, often in conjunction with other mechanisms (e.g., adsorption/sorption, plant uptake, and photodegradation). The physicochemical properties of molecules play a pivotal role in the elimination processes, and could serve as important predictors of removal. The correlation and multiple linear regression analysis suggest that organic carbon sorption coefficient (Log Koc), octanol-water distribution coefficient (Log Dow), and molecular weight form a good predictive linear regression model for the removal efficiency of PhCs ($R^2 = 0.65$, P-value <0.05).

Key words | constructed wetlands, pharmaceuticals, physicochemical properties, removal efficiency, removal mechanisms, transformation products

Huma Ilyas (corresponding author)
Eric D. van Hullebusch
Université de Paris, Institut de physique du globe de Paris, CNRS,
F-75005 Paris,
France
E-mail: *hi.wtmconsult@gmail.com*

Ilyas Masih
IHE Delft, Institute for Water Education,
2611 AX Delft,
The Netherlands

Huma Ilyas
Ilyas Masih
Water Treatment and Management Consultancy, B.V.,
2289 ED Rijswijk,
The Netherlands

INTRODUCTION

Pharmaceuticals (PhCs) are among the emerging organic contaminants (EOCs) that are discharged to water resources and the environment through various sources such as domestic wastewater (excretion), effluent discharge from wastewater treatment plants (WWTPs), hospital and PhCs' industrial waste streams, landfill leachate, and animal excretion (Caliman & Gavrilescu 2009; Michael *et al.* 2013; Luo *et al.* 2014; Barbosa *et al.* 2016). Therefore, PhC pollution can be seen as a worldwide concern for almost every country – no matter how much of the total wastewater produced is treated before discharge into the environment. Although PhCs are found to be in relatively small concentrations (e.g., ng L^{-1} to μg L^{-1}) in water resources, their presence (as individual compounds, transformation

This is an Open Access article distributed under the terms of the Creative Commons Attribution Licence (CC BY 4.0), which permits copying, adaptation and redistribution, provided the original work is properly cited (http://creativecommons.org/licenses/by/4.0/).

doi: 10.2166/wh.2020.213

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

products (TPs), and multitude of compounds) could pose risk for aquatic and terrestrial life. The continuous discharge of PhCs through various sources including WWTPs could make these 'pseudo-persistent' organic chemicals a potential source of risk, especially when present in large concentrations, and the combination of a wide range of compounds that may act synergistically (e.g., Gorito *et al.* 2017). Furthermore, in WWTPs, during biological treatment, the development of antibiotic resistant bacteria (ARB) and/or antibiotic resistance genes (ARGs) due to the sub-therapeutic concentrations of antibiotics is of major concern. Antibiotic resistance is the ability of bacteria and other microorganisms to resist the effects of an antibiotic to which they were once sensitive (Berglund *et al.* 2014; Liu *et al.* 2014; Santos *et al.* 2019). Since these antibiotics, ARB, and ARGs are also not eliminated by conventional WWTPs (Hijosa-Valsero *et al.* 2011a; Rowan 2011; Huang *et al.* 2017), the effluent discharge from WWTPs and the use of activated sludge containing antibiotics and ARB/ARGs makes them one of the major sources of antibiotics and ARB/ARGs in the environment (Finley *et al.* 2013; Rodriguez-Mozaz *et al.* 2015; Santos *et al.* 2019). Several studies have indicated negative impacts of PhCs on aquatic and plant life (e.g., Caliman & Gavrilescu 2009; Carvalho *et al.* 2014).

Various strategies may be employed to reduce the discharge of PhCs into the environment. The efforts on source reduction and use of more degradable compounds with comparable therapeutic effects (green pharmacy) could reduce the quantity of PhCs consumed and discharged into the environment (Ruhoy & Daughton 2008). Other promising strategies focus on improving wastewater treatment technologies and their scale of adoption (Michael *et al.* 2013; Luo *et al.* 2014). The development of treatment trains that are more suited for the removal of PhCs by upgrading existing WWTPs or designing new ones are important areas of research and development. Therefore, many experimental investigations have been carried out in recent years to test technologies for their ability to reduce the concentrations of PhCs in the final effluent. For instance, advanced chemical and biological systems have been assessed: ozonation, ozone/ultraviolet irradiation, ozone/hydrogen peroxide (Ternes *et al.* 2003; Hollender *et al.* 2009; Benitez *et al.* 2011), ultrafiltration, reverse osmosis, granular activated carbon contact (Acero *et al.* 2010; Michael *et al.* 2013), and membrane biological reactors (Radjenovic *et al.* 2009; Lipp *et al.* 2012). Modern WWTPs could be equipped with these technologies for a polishing step, as these technologies are proven to be effective in many cases (Huber *et al.* 2005; Michael *et al.* 2013; Papaevangelou *et al.* 2016). However, their capital and operational costs are very high (Ternes *et al.* 2003; Reif *et al.* 2011), which highlights the need for cost-effective, sustainable, and efficient wastewater treatment technologies.

Constructed wetlands (CWs) are low cost and nature-based treatment technologies that have been extensively investigated for the removal of conventional pollution parameters such as organic matter and nutrients (nitrogen and phosphorus) (e.g., Kadlec & Wallace 2009; Vymazal 2011, 2013; Ilyas & Masih 2017a, 2017b, 2018) as well as PhCs from wastewater. Regarding PhCs, to date, more than 50 individual case studies have been published in peer-reviewed journals, with rapidly growing numbers since the last decade. Among the investigated CWs are free water surface CW (FWSCW), horizontal flow CW (HFCW), vertical flow CW (VFCW), and hybrid CW (HCW). For instance, Matamoros *et al.* (2008b) compared the removal efficiencies of a few EOCs including six PhCs (ibuprofen, naproxen, diclofenac, ketoprofen, clofibric acid, and carbamazepine) between a HFCW and a conventional WWTP. The influent in the CW was secondary wastewater that had trace concentrations of these PhCs. Removal efficiencies were found to be compound-dependent (e.g., ibuprofen and naproxen >70%, and carbamazepine <20%). Seasonal variations in the removal efficiency were observed, with higher efficiencies in the warm season compared with the cold season due to higher biodegradation and photodegradation in summer. Hijosa-Valsero *et al.* (2010a) investigated the performance of seven CWs (e.g., surface and sub-surface flow, planted and unplanted, with and without gravel bed), and a conventional activated sludge treatment plant. The removal efficiencies of six PhCs (ketoprofen, naproxen, ibuprofen, diclofenac, salicylic acid, and carbamazepine) were investigated over a period of nine months. This study asserted most of the findings of Matamoros *et al.* (2008b), such as effect of seasonality, compound specific variation in removal efficiency, and similar or better performance of CWs compared with the conventional WWTP. Additionally,

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

superior performance of planted CWs for some PhCs compared with unplanted ones was demonstrated. Vymazal *et al.* (2017) investigated the presence of 31 PhCs in four HFCWs used to treat rural wastewater in the Czech Republic. Seven out of 31 PhCs were detected in all sampling campaigns in the influent samples (acetaminophen, caffeine, diclofenac, furosemide, hydrochlorothiazide, ibuprofen, and metoprolol) and five were found in at least 75% of the samples (clarithromycin, gabapentin, ketoprofen, tramadol, and warfarin). The removal efficiencies showed a large variation among the studied CWs as well as PhCs' type. The highest removal efficiency was reported for acetaminophen (91%), caffeine (84%), and furosemide (75%), whereas warfarin (31%), ketoprofen (31%), and gabapentin (14%) demonstrated poor removal efficiency. The authors also assessed environmental risk due to the PhCs by estimating risk quotient (RQ) (a ratio between the predicted or measured environmental concentration (PEC or MEC)), and the worst-case predicted no effect concentration (PNEC) (Hernando *et al.* 2006). Ibuprofen, acetaminophen, and clarithromycin were assessed under high risk category (RQ > 1.0).

An in-depth overview of all the reviewed studies on PhCs' removal by CWs, including the few mentioned above, indicates the following major thematic areas of research: (1) identification of PhCs in influent and effluent wastewater, and the removal efficiencies by different treatment technologies; (2) investigation of mechanisms and processes leading to the removal of PhCs; (3) impact of physicochemical properties of PhCs on treatment process efficiencies; (4) relationship of the design and operational factors with removal efficiencies; (5) temporal variations in the performance due to seasonal and aging effects; and (6) environmental risk assessment and risk reduction due to treatment. A large number of published research studies offer an opportunity to summarize and critically reflect on the available knowledge on these thematic areas. However, only a few review studies, with specific focus on PhCs' removal by CWs, have been conducted in order to summarize the available knowledge on some of the above-mentioned themes (Imfeld *et al.* 2009; Carvalho *et al.* 2014; Li *et al.* 2014; Verlicchi & Zambello 2014; Zhang *et al.* 2014; Gorito *et al.* 2017). An excellent scientific description regarding the removal processes in CWs has been provided by Imfeld *et al.* (2009), which was further advanced by Zhang *et al.* (2014) supported by (limited) scientific evidence from available studies on the subject. Li *et al.* (2014) summarized the role of design parameters such as physical configuration, hydraulic mode, and vegetation species in the removal of PhCs. Verlicchi & Zambello (2014) provided a detailed overview of the removal of several PhCs by CWs, with in-depth analysis of performance when CWs are used as primary, secondary, and tertiary treatment purposes. Although Li *et al.* (2014) and Verlicchi & Zambello (2014) shed light on the influence of physicochemical properties of PhCs on their removal efficiencies, they did not advance the knowledge on the correlation of physicochemical properties and removal mechanisms. A comprehensive review on plant–PhCs interactions was conducted by Carvalho *et al.* (2014), indicating the potential of CWs for phytoremediation. Gorito *et al.* (2017) presented the removal of four PhCs (azithromycin, clarithromycin, diclofenac, and erthromycin), which are on the watch list of the European Union (EU) as per EU decision 2015/495, with discussion on associated removal processes and influence of design and operation parameters of CWs. While these studies have significantly advanced the knowledge on various aspects of PhCs' removal by CWs, there is still a need to conduct more research on the studied thematic areas in order to formulate sound and evidence-based general conclusions. Moreover, most of the previous reviews target a limited number of PhCs and are often constrained by a limited number of available studies on certain topics.

This study aims to fill some of the above-mentioned knowledge gaps by building on the previous reviews and a large number of published case studies, including recently published sources (e.g., after 2013, as most of the previous reviews were published before 2014). Therefore, the main objectives of this study are: (1) to conduct a comprehensive assessment of a large number of PhCs in wastewater and their removal by four types of CWs; (2) to critically evaluate and summarize the available evidence on major PhCs' removal mechanisms in CWs; (3) to examine the impact of physicochemical properties of PhCs on their removal mechanisms; and (4) to assess the environmental risk posed by a large number of PhCs, and contribution of CWs in risk reduction.

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

METHODOLOGY

The research papers, review papers, and books were searched from various sources, such as Scopus, Google Scholar, and individual journal websites, related to the performance of different types of CWs for the removal of different categories of PhCs. The snowball sampling method yielded over 100 journal articles, which were further screened and used for the purpose of this research. The screening was carried out to check the quality of published data. Only peer-reviewed journal papers were selected for this research, which helped to ensure the reliability of given data. The selected studies have used generally accepted and reliable analytical methods such as solid phase extraction-gas chromatography-tandem mass spectrometry (SPE-GC-MS/MS); SPE-(ultra) high performance liquid chromatography-diode array detector (SPE-(U)HPLC-DAD); liquid-liquid phase extraction-gas chromatography-micro electron capture detector (LLPE-GC-μECD); and SPE-rapid resolution liquid chromatography-MS/MS (SPE-RRLC-MS/MS). The samples were analyzed soon after collection, as the storage time was less than one or two days in most cases. The selected studies contained the required information on most of the key parameters such as concentration of PhCs in influent and effluent waters, removal efficiency, chemical oxygen demand (COD), biochemical oxygen demand (BOD), hydraulic loading rate (HLR), and hydraulic retention time (HRT).

In this way, a global database was compiled containing information about 260 CWs that were reported in 66 peer-reviewed journal publications with case studies from 19 countries (Supplementary Materials 1: Tables S1–S4). This database contains influent and effluent concentrations, removal efficiencies, and removal rates of 148 PhCs grouped into 33 categories according to their therapeutic classes and 25 TPs (Table 1). The treatment performance of four types of CWs (FWSCW, HFCW, VFCW, and HCW) was evaluated for PhCs' removal. The other parameters, such as treatment scale and type, wastewater type, depth, area, HLR, organic loading rate (OLR), HRT, experiment duration, system age, filter media, temperature, pH, dissolved oxygen (DO), and redox potential were considered for the comparison of four types of CWs. The performance analysis was based on the information compiled from the available studies, as stated above.

A detailed analysis of the reported PhCs was conducted from the studied literature including the designed database, which focused on therapeutic classes, types of PhCs, and impact of their physicochemical properties and contribution of removal mechanisms in CWs. The mechanisms were identified for the selected PhCs as presented in the published case studies. The majority of the studies only attributed removal to certain mechanisms (e.g., biodegradation, adsorption/sorption, plant uptake, and photodegradation). The relative contribution of mechanisms in removal was only quantified in a few experimental studies. Therefore, the analysis on removal mechanisms was based on a critical oversight from both qualitative and quantitative information. The information on the physicochemical properties of PhCs was gathered from various sources (e.g., journal papers, reports, and websites) for molecular formula/structure/weight, water solubility, dissociation constant (pKa), organic carbon sorption coefficient (Log Koc), octanol-water partition coefficient (Log Kow), and distribution coefficient (Log Dow). The available evidence on the role of these properties in the removal of PhCs in CWs was comprehensively and critically analyzed. The linkages between physicochemical properties and removal mechanisms were delineated from this analysis. Moreover, a statistical analysis (Pearson correlation and multiple linear regression) was conducted for removal efficiency and physicochemical properties. The causality of the observed relationship was established through a synthesis of available knowledge and the authors' own insights. Additionally, risk assessment was carried out by estimating RQ. Following the recommendations by Hernando *et al.* (2006) and several applications (Gros *et al.* 2010; Verlicchi *et al.* 2012; Kosma *et al.* 2014; Zhu & Chen 2014; Chen *et al.* 2016b; Matamoros *et al.* 2016, 2017; Auvinen *et al.* 2017b; Vymazal *et al.* 2017), the risk was categorized into four levels: high risk ($RQ > 1.0$), medium risk ($0.1 \leq RQ \leq 1.0$), low risk ($0.01 \leq RQ \leq 0.1$), and no risk ($RQ < 0.01$).

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

Table 1 | The studied PhCs categorized according to their therapeutic classes and their TPs

Categories of pharmaceuticals

No. of categories	Therapeutic classes	PhCs
1	Analgesic/anti-inflammatory drugs	Buprenorphine, Diclofenac, Fenoprofen, Ibuprofen, Ketoprofen, Mefenamic acid, Naproxen, Salicylic acid, Phenylbutazone, Propyphenazone
2	Analgesic	Acetaminophen, Codeine, Dihydrocodeine, Gabapentin, Methadone, Morphine, Nefopam, Orphenadrine, Tramadol
3	Anti-inflammatory drugs	Indomethacin, Prednisolone
4	Antibiotics	Amoxicillin, Ampicillin, Azithromycin, Chlortetracycline, Ciprofloxacin, Clarithromycin, Clindamycin, Difloxacin, Doxycycline, Enrofloxacin, Enoxacin, Erythromycin, Lincomycin, Metronidazole, Monensin, Nifuroxazide, Norfloxacin, Novobiocin, Ofloxacin, Oxytetracycline, Roxithromycin, Spiramycin, Sulfadiazine, Sulfadimethoxine, Sulfamerazine, Sulfamethazine, Sulfamethoxazole, Sulfapyridine, Sulfathiazole, Tetracycline, Tilmicosin, Trimethoprim
5	Antifungals	Clotrimazol, Fluconazole
6	Antivirals	Acyclovir
7	Antiallergic drugs	Cetirizine, Desloratidin, Diphenhydramine, Fexofenadine
8	Antidysenterics	Loperamide
9	Antiasthma	Theophylline
10	Antiepileptic	Lamotrigine, Levetiracetam, Oxcarbazepine, Topiramate
11	Antiulcer	Esomeprazole, Omeprazole, Sulfasalazine
12	Antispasmodic	Phloroglucinol
13	Stimulants/psychoactive drugs	3,4-Methylenedioxy-amphetamine, 3,4-Methylenedioxy-methamphetamine, Caffeine, Cocaine, Ephedrine/pseudoephedrine, Naloxone, Nicotine
14	Antihypertensives	Diltiazem, Dipyridamol, Eprosartan, Hydrochlorothiazide, Irbesartan, Lisinopril, Losartan, Telmisartan, Valsartan, Verapamil
15	Psychiatric drugs	Alprazolam, Amitryptiline, Bupropion, Carbamazepine, Citalopram, Fluoxetine, Hydroxyzine, Levomepromazine, Lorazepam, Maprotilin, Mianserin, Mirtazapin, Oxazepam, Paroxetin, Perphenazine, Sertraline, Venlafaxine, Zoldipem
16	Anti-Alzheimer drugs	Memantin
17	Beta-blockers	Atenolol, Bisoprolol, Metoprolol, Propranolol, Sotalol, Timolol
18	Beta-agonists	Clenbuterol, Salbutamol, Terbutaline
19	Hormone inhibitors	Finasteride
20	Receptor antagonists	Alfuzosin, Cimetidine, Famotidine, Loratadine, Ranitidine
21	Lipid regulators	Atorvastatin, Bezafibrate, Clofibric acid, Fenofibrate, Gemfibrozil, Mevastatin, Pravastatin, Rosuvastatin
22	Antineoplastic	Cyclophosphamide
23	Antiarrhythmic	Propafenone
24	Anti-ischaemic	Pentoxifylline
25	Neuroleptics	Haloperidol
26	Barbiturates	Butalbital, Pentobarbital, Phenobarbital
27	TTT coronary insufficiency	Candesartan, Nadolol
28	Cardiovascular	Ramipril
29	Anticoagulant	Warfarin
30	Antidiabetics	Glibenclamide, Gliclazide, Metformin
31	Diuretics	Furosemide
32	Anesthetic drugs	Ketamine
33	Radiocontrast agents	Diatrizoate, Iomeprol, Iopromide

(*continued*)

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

Table 1 | continued

Transformation products

No. of PhCs	PhCs	TPs
1	Diclofenac	4-Hydroxydiclofenac
2	Ibuprofen	1-Hydroxyibuprofen, 2-Hydroxyibuprofen, Carboxyibuprofen
3	Ketoprofen	3-Ethylbenzophenone, Dihydroketoprofen
4	Naproxen	O-desmethylnaproxen
5	Tramadol	O-desmethyltramadol, N-desmethyltramadol, N,O- didesmethyltramadol
6	Methadone	2-Ethylidene – 1,5-dimethyl – 3,3-diphenylpyrrolidine
7	Sulfamethoxazole	N-acetylsulfamethoxazole
8	Carbamazepine	10,11-Dihydro – 10,11-dihydroxycarbamazepine, 10,11-Dihydro – 10-hydroxycarbamazepine, 2 Hydroxycarbamazepine, 3-Hydroxycarbamazepine, Carbamazepine 10,11-epoxide
9	Citalopram	N-desmethylcitalopram
10	Venlafaxine	O-desmethylvenlafaxine, N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine
11	Cocaine	Benzoylecgonine, Cocaethylene
12	Nicotine	Cotinine
13	Ketamine	Norketamine

RESULTS AND DISCUSSION

Removal of PhCs and TPs by CWs

Figure 1 presents the average removal efficiencies of the examined PhCs and TPs estimated for 113 out of 173 compounds for which three or more data points were available. The results indicate a very high range of variability in the removal efficiencies. The assessment indicates that CWs are capable of removing a large number of PhCs and their metabolites from wastewater. Positive removal was observed for 96 compounds, with average removal efficiencies in the range of 7.0% to 100%. On the other hand, negative removal was estimated for 17 compounds (both PhCs and TPs) in the range of −5.0% to −2,043%. There is no distinct removal pattern among PhCs and TPs – both show large variability in removal. Moreover, high standard deviations were estimated, which showed high variability in the results. The estimated statistics (mean and standard deviation of influent and effluent concentration, removal rate, and removal efficiency) for each of the 113 compounds are presented in Supplementary Materials 2: Table S5.

We choose to illustrate a few more observations from this analysis by an in-depth and critical evaluation of four PhCs that are on the EU watch list. The studies on azithromycin removal by CWs were very limited (only four data points). The observed concentrations were very small (influent range: 0.007–0.01 μg L^{-1}; effluent range: 0.0–0.02 μg L^{-1}). A positive removal was observed in three CWs (removal efficiency range: 14–100%) as reported by Breitholtz *et al.* (2012), Verlicchi *et al.* (2013), and Berglund *et al.* (2014). However, Breitholtz *et al.* (2012) also reported negative removal (−350%) in one of the studied FWSCWs. It is important to note that the high negative removal could be influenced by the quantity of the PhCs present in the influent and effluent. For example, small changes in concentration for the compounds present in very small concentrations may lead to remarkably high percentage changes. In the case of azithromycin, the effluent concentration was slightly increased (influent: 0.008 vs effluent: 0.04 μg L^{-1}) but a very high value of negative removal was estimated. Based on these findings, it is not possible to draw any general conclusions about azithromycin removal by CWs because there is a very limited number of studies available, and their findings are also contradictory.

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

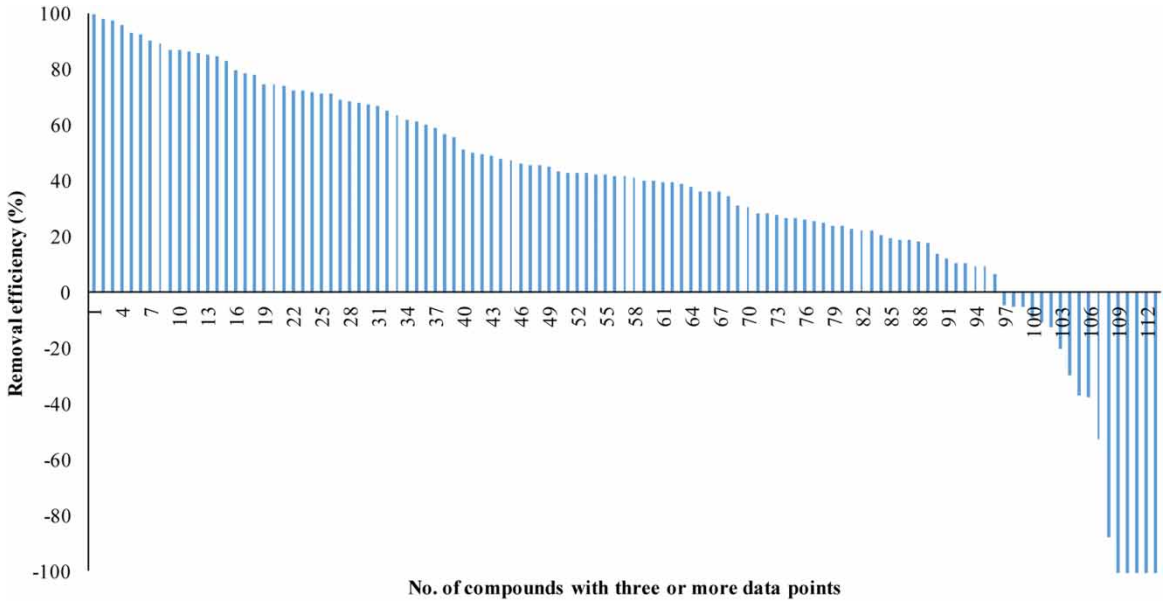


Figure 1 | Removal efficiency of the investigated compounds (both PhCs and TPs). *Note*: The statistics are for 113 compounds with three or more data points. Negative values were capped at −100 to improve the readability of the graph. Actual values (e.g., below −100) can be found in Supplementary Materials 2.

Unfortunately, this is true for a large number of PhCs and TPs. Therefore, more experimental studies are inevitable in order to draw sound evidence-based conclusions on the removal of several PhCs by CWs. In general, the selection of sampling strategy is important for reliable results (Auvinen *et al.* 2017a). For instance, some studies reported that sampling can be started once the concentration of the tracer (potassium bromide-KBr) is stabilized at the effluent of the system to achieve reliable estimation of the removal efficiency of PhCs under steady state conditions (Ávila *et al.* 2010, 2013, 2014b) and sampling should be done on the same day and at the same time (Hijosa-Valsero *et al.* 2010a, 2010b, 2016; Reyes-Contreras *et al.* 2012; Ávila *et al.* 2014a, 2015; Rühmland *et al.* 2015). Furthermore, primary treatment (homogenization tank-HRT: 1 day) might reduce the huge influent variability (Matamoros *et al.* 2016), and sampling at different locations should also be done to assess the reduction capacity of different treatment phases in CWs (Conkle *et al.* 2008; Matamoros *et al.* 2009; Park *et al.* 2018; Wang *et al.* 2019). Moreover, the sample holding time should be lower (sample should not be kept for a long time before analysis) (Matamoros *et al.* 2008a, 2008b, 2012; Hijosa-Valsero *et al.* 2010a, 2010b, 2011a; Reyes-Contreras *et al.* 2012; Zhang *et al.* 2012a, 2018b; Chen *et al.* 2016a; Vymazal *et al.* 2017; Sgroi *et al.* 2018; Nivala *et al.* 2019).

Fortunately, a number of PhCs have been extensively studied for which sound evidence-based conclusions could be drawn. Diclofenac, an analgesic/anti-inflammatory drug which is on the EU watch list, is among the most extensively studied PhCs. It was examined by 37 studies with 127 data points (Table 2) under a wide range of design and operating conditions (e.g., lab, pilot, and full-scale applications; treatment of primary, secondary, and tertiary effluent; different CW types such as FWSCW, HFCW, VFCW, HCW, aerated and non-aerated CWs) (Tables S1–S4). There is a large variation across case studies for the estimated statistics. For instance, the mean and standard deviation for removal efficiency stood at $38 \pm 35\%$. The influent and effluent concentrations were calculated as 17 ± 33 and 9 ± 17 $\mu g\ L^{-1}$, respectively. These values indicate low to moderate removal of diclofenac by most of the studied CWs. On the other hand, clarithromycin was investigated by seven studies with 21 CW systems. Negative removal was observed only in one CW studied by Breitholtz *et al.* (2012); a positive removal was reported for all the other CWs (e.g., Hijosa-Valsero *et al.* 2011a; Breitholtz *et al.* 2012; Verlicchi *et al.* 2013; Vymazal

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

Table 2 | Statistics (mean and standard deviation) of 34 widely studied PhCs

Therapeutic class/ Pharmaceutical	No. of observation based on removal (%)	Influent conc. ($\mu g\ L^{-1}$) mean ± stdev	Effluent conc. ($\mu g\ L^{-1}$) mean ± stdev	Removal rate ($mg\ m^{-2}\ d^{-1}$) mean ± stdev	Removal efficiency (%) mean ± stdev
Analgesic/anti-inflammatory drugs					
Diclofenac	127	17 ± 33	9 ± 17	0.9 ± 2.1	38 ± 35
Ibuprofen	138	30 ± 34	13 ± 20	1.7 ± 2.9	57 ± 30
Ketoprofen	76	20 ± 36	8 ± 17	1.4 ± 3.0	40 ± 40
Naproxen	112	21 ± 34	7 ± 16	1.4 ± 2.6	62 ± 29
Salicylic acid	52	16 ± 10	2.3 ± 1.8	0.7 ± 1.3	79 ± 22
Analgesic					
Acetaminophen	28	17 ± 29	1.4 ± 4.3	0.2 ± 0.9	64 ± 85
Codeine	11	0.4 ± 0.3	0.1 ± 0.2	0.4 ± 0.8	68 ± 23
Tramadol	23	17 ± 47	9 ± 40	0.4 ± 1.2	39 ± 43
Antibiotics					
Clarithromycin	21	0.3 ± 0.2	0.2 ± 0.1	0.2 ± 0.4	39 ± 33
Erythromycin	26	5.7 ± 5.9	2.3 ± 3.1	0.6 ± 0.8	26 ± 63
Lincomycin	20	0.2 ± 0.6	0.05 ± 0.07	0.002 ± 0.006	−441 ± 1,001
Doxycycline	9	0.6 ± 1.2	0.07 ± 0.04	0.009 ± 0.002	69 ± 15
Ofloxacin	17	37 ± 122	8 ± 30	4 ± 12	89 ± 27
Oxytetracycline	10	501 ± 439	21 ± 33	158 ± 194	87 ± 30
Sulfadiazine	30	13 ± 35	0.5 ± 1.7	4 ± 10	51 ± 31
Sulfamethazine	39	42 ± 170	9 ± 43	21 ± 112	43 ± 33
Sulfamethoxazole	51	34 ± 119	6 ± 32	1.9 ± 5.8	43 ± 42
Sulfapyridine	25	1.0 ± 0.6	0.2 ± 0.1	0.3 ± 0.2	83 ± 5
Trimethoprim	45	0.2 ± 0.3	0.4 ± 2.1	−0.2 ± 1.7	48 ± 116
Monensin	12	0.1 ± 0.0	0.01 ± 0.01	0.03 ± 0.01	93 ± 3
Antiallergic drugs					
Fexofenadine	7	0.9 ± 0.9	0.6 ± 0.6	1.1 ± 1.7	21 ± 28
Stimulants/psychoactive drugs					
Caffeine	115	29 ± 23	6 ± 11	2.1 ± 1.9	80 ± 22
Antihypertensives					
Diltiazem	7	0.05 ± 0.02	0.02 ± 0.02	0.06 ± 0.08	67 ± 19
Psychiatric drugs					
Carbamazepine	113	19 ± 60	13 ± 38	0.6 ± 3.7	22 ± 30
Mirtazapin	6	0.04 ± 0.01	0.03 ± 0.02	0.01 ± 0.01	31 ± 29
Venlafaxine	12	0.4 ± 0.2	0.3 ± 0.2	0.03 ± 0.06	36 ± 27
Beta-blockers					
Atenolol	22	2.1 ± 2.6	0.5 ± 0.8	0.3 ± 0.4	72 ± 29
Metoprolol	25	17 ± 37	4 ± 11	0.8 ± 1.7	56 ± 34
Sotalol	12	0.8 ± 0.6	0.7 ± 0.6	0.04 ± 0.04	25 ± 36
Receptor antagonists					
Ranitidine	8	0.6 ± 0.6	0.4 ± 0.4	0.6 ± 0.8	43 ± 41

(*continued*)

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

Table 2 | continued

Therapeutic class/ Pharmaceutical	No. of observation based on removal (%)	Influent conc. (μg L^{-1}) mean ± stdev	Effluent conc. (μg L^{-1}) mean ± stdev	Removal rate (mg m^{-2} d^{-1}) mean ± stdev	Removal efficiency (%) mean ± stdev
Lipid regulators					
Bezafibrate	10	0.5 ± 0.4	0.3 ± 0.2	0.5 ± 0.8	42 ± 27
Clofibric acid	16	15 ± 13	10 ± 8	0.2 ± 0.2	45 ± 24
Gemfibrozil	17	67 ± 48	42 ± 35	4.1 ± 3.2	46 ± 28
Diuretics					
Furosemide	10	12 ± 22	2.3 ± 3.6	0.03 ± 0.01	72 ± 26

et al. 2017; Petrie *et al.* 2018). The statistics on removal efficiency for clarithromycin (39 ± 33%) are somewhat similar to those of diclofenac. However, the influent and effluent concentrations of clarithromycin (<0.5 μg L^{-1}) are much lower than for diclofenac (Table 2). The reported data on erythromycin depicted stark differences, which prohibit any generalization. For example, positive removal was documented by Rühmland *et al.* (2015) and Chen *et al.* (2016a) but negative removal was observed by Hijosa-Valsero *et al.* (2011a) and Nuel *et al.* (2018). Another noteworthy observation from these data is the difference among the influent concentrations in the case study regions. For example, a case study from China by Chen *et al.* (2016a) reported influent concentration of 12 μg L^{-1}, while a few studies from Europe (e.g., Hijosa-Valsero *et al.* 2011a; Verlicchi *et al.* 2013; Nuel *et al.* 2018) reported much lower values (e.g., <2.0 μg L^{-1}).

The above-mentioned results highlight extremely high compound specific variations. Moreover, several factors play a role in removal efficiencies. The results reveal that the recent studies have examined a higher number of PhCs and TPs, which is a promising trend to comprehensively investigate the occurrence and removal of these compounds. However, the number of data points for several compounds is still limited. Additionally, contradictory results on the removal of numerous PhCs have been reported as well. This prohibits generalization of individual case study results for these PhCs. Therefore, a comprehensive assessment is not possible for every compound. However, we identified 34 PhCs that were studied by several authors for a comprehensive assessment and critical review of the available knowledge. Therefore, the following sections present results and discussion on these selected PhCs.

Removal of widely studied PhCs by CWs

The following insights can be drawn from the analysis presented in Table 2. A very high range of variability in the influent and effluent concentrations, and removal efficiencies exist among the studied PhCs. Despite large variability, CWs prove to be a promising treatment technology for a large number of PhCs. For the 34 selected PhCs, CWs demonstrate a moderate to high potential for successful treatment (e.g., average removal efficiency >50%) in the case of monensin (93%), ofloxacin (89%), oxytetracycline (87%), sulfapyridine (83%), caffeine (80%), salicylic acid (79%), atenolol (72%), furosemide (72%), doxycycline (69%), codeine (68%), diltiazem (67%), acetaminophen (64%), naproxen (62%), ibuprofen (57%), metoprolol (56%), and sulfadiazine (51%). The PhCs with least removal efficiency (average removal efficiency <25%) are carbamazepine (22%) and fexofenadine (21%). In contrast, lincomycin shows a negative removal (on average), although with very high standard deviation. This indicates a high level of uncertainty in making sound conclusions about this and other such cases (e.g., acetaminophen, erythromycin, and trimethoprim). In fact, the two available studies on lincomycin reveal a stark contrast. Chen *et al.* (2016a) reported a positive removal efficiency in the range of 9.0–81%. On the other hand, Hijosa-Valsero *et al.* (2011a) reported a negative removal efficiency ranging from −283% to −4,067%.

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

These variations stress the need for better understanding of factors behind the observed variability.

It is pertinent to note that the performance of CWs is influenced by a wide range of design and operational factors. The impact of these factors on the performance of CWs was comprehensively examined by the authors in another publication (Ilyas & van Hullebusch 2019). The studied factors, such as area, depth, OLR, HLR, HRT, DO, pH, and temperature, play an important role in the removal of PhCs by CWs. However, the impacts of these factors are variable for different PhCs, which makes it very difficult to draw specific conclusions. For instance, high HRT facilitates removal of some PhCs but also indicates no effect or negative correlation in the case of some PhCs. The type of CW was considered an important factor for the removal of PhCs, with HCW being the most efficient followed by VFCW, HFCW, and FWSCW (Ilyas & van Hullebusch 2020). Additionally, in this research, the removal efficiency of widely studied PhCs was analyzed when CWs were used for primary, secondary, or tertiary treatment (Supplementary Materials 3: Table S6). The results indicate no clear pattern of high or low performance in the case of primary, secondary, or tertiary treatment. For example, in some cases, higher removal efficiencies are achieved when CWs are used as tertiary treatment compared to primary treatment and vice versa. Verlicchi & Zambello (2014) compared the performance of different types of CWs used as primary, secondary, and tertiary treatment. This study also indicated a very high variability in removal efficiency under the studied systems, and it is difficult to establish which level of treatment is better in performance and risk reduction.

Environmental risk assessment for the selected PhCs

Ecological risk was assessed for 27 PhCs for which the PNEC estimates were available from the literature, such as from a comprehensive study by Verlicchi *et al.* (2012). The PNECs for a certain PhC are reported based on experimental and modeling studies related to several organisms, such as fish, *Daphnia*, algae, invertebrates, and bacteria (e.g., Verlicchi *et al.* 2012). We adopted the approach of Verlicchi *et al.* (2012) and used the lowest estimate of PNEC in our calculations of RQ. For instance, PNEC estimates for erythromycin were available from the study by Sanderson *et al.* (2003), cited in Verlicchi *et al.* (2012), for fish (61–900 $\mu g\ L^{-1}$), *Daphnia* (7.8 $\mu g\ L^{-1}$), algae (0.02–4.3 $\mu g\ L^{-1}$), and invertebrates (15 $\mu g\ L^{-1}$). In this case, the lowest value of 0.02 $\mu g\ L^{-1}$ was used as the PNEC for our assessment.

Then, RQ was calculated using the lowest PNEC value and the MEC of influent and effluent of PhCs. These calculations were performed for the selected PhCs based on all the available data points. The mean RQ were estimated from this analysis and discussed in detail in this section. Since mean could be biased towards high values, median and various other percentiles were also estimated. The RQ was also estimated based on extremes (minimum and maximum values). The resulting statistics are given in Supplementary Materials 4: Table S7. The mean RQ estimates are given by Figure 2 and Table 3. Based on effluent RQ assessment, 12 out of 27 PhCs could be grouped under the high risk category. These are in order from high to low risk as: oxytetracycline > ofloxacin > sulfamethoxazole > erythromycin > sulfadiazine > gemfibrozil > ibuprofen > acetaminophen > salicylic acid > sulfamethazine > naproxen > clarithromycin. Most of these PhCs are antibiotics, analgesic and anti-inflammatory drugs. Similar to our findings, Vymazal *et al.* (2017) reported ibuprofen, acetaminophen, and clarithromycin under the high risk category. Chen *et al.* (2016b) reported that ibuprofen had a high to medium risk, and diclofenac had a medium risk. The study by Matamoros *et al.* (2017) indicated that ibuprofen had a medium risk in the effluent. Based on our study with data from several countries, we see the need for including several PhCs (e.g., those that emerged under high risk category in our assessment in regulatory monitoring, water quality standard formulation, and control purposes. For instance, the EU watch list of four PhCs (azithromycin, clarithromycin, erythromycin, and diclofenac) (Barbosa *et al.* 2016; Gorito *et al.* 2017) could be enhanced by considering these PhCs.

Our results also reveal that, in general, the estimated RQs based on effluent concentrations are significantly lower than those based on influent values (Figure 2 and Table 3), thus indicating the effective role of CWs in reducing the ecological risk posed by PhCs. These observations are similar to the studies by Zhu & Chen (2014) and Matamoros *et al.* (2016, 2017). Conversely, CWs may trigger higher ecological risk for certain PhCs and TPs whose concentrations increase in effluent water; however, such cases of risk assessment are not yet reported in the published

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

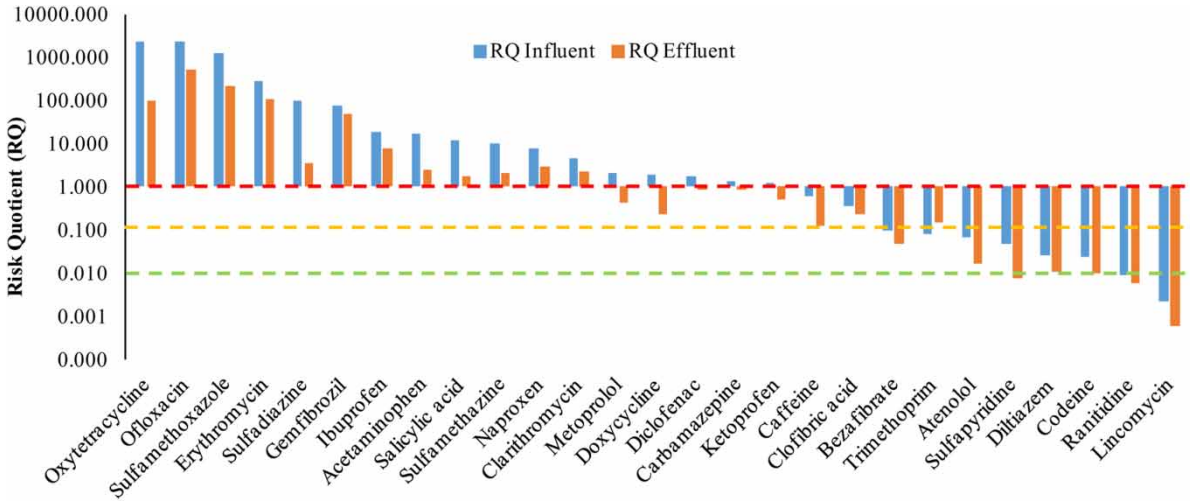


Figure 2 | Risk quotient (RQ) of the 27 selected PhCs based on influent and effluent concentration in CWs. *Note*: Risk is categorized into four levels: high risk (RQ > 1.0; above red line), medium risk (0.1 ≤ RQ ≤ 1.0; between red and orange line), low risk (0.01 ≤ RQ ≤ 0.1; between orange and green line), and no risk (RQ < 0.01; below green line) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.). Please refer to the online version of this paper to see this figure in color: http://dx.doi.org/10.2166/wh.2020.213.

literature. Moreover, while CWs do, indeed, contribute to reduce the ecological risk of several PhCs, they are not fully eliminated in most of the cases.

A critical evaluation of our estimates and a review of the available studies on risk assessment indicate a careful interpretation and application of the estimated ecological risk. Thus, a thorough understanding of the given context and governing factors is recommended. First, the choice of PNEC estimates plays a central role in resultant RQs and associated classification into risk categories. It is recognized that the toxicity data are significantly affected by many factors such as the lifecycle assessment stage of the organism, characteristics of the surrounding environment, and the experimental conditions (Soares *et al.* 2008). Additionally, the approach of using the lowest PNEC value is very stringent, although safest from an ecological protection point of view. It implies higher possibilities of categorizing a PhC under a high risk class compared to when other approaches are used (e.g., PNEC based on an indicator species). For instance, *Daphnia magna* has been used as an indicator species to estimate PNEC (Matamoros *et al.* 2016). The PNEC values of 74.0, 2.5, and 76.3 μg L^{-1} for carbamazepine were reported for *Desmodesmus subspicatus* (algae), *Ceriodaphnia dubia*, and *D. magna* (invertebrates), respectively (Auvinen *et al.* 2017b). Obviously, RQs' assessment based on *C. dubia* will be much higher than estimated using *D. magna* in this case. Moreover, different PNECs were reported for a PhC for a certain organism. For instance, in the case of diclofenac, a few experimental studies on *D. magna* reported PNEC estimates in the range of 22.4–68.0 μg L^{-1} (Verlicchi *et al.* 2012). Second, it must be recognized that the overall risk due to the presence of multiple PhCs and TPs may be higher than that of an individual compound (Cleuvers 2003; Yang *et al.* 2008; Zhu & Chen 2014; Matamoros *et al.* 2017). Third, a large variability in the RQ estimates demands an in-depth study for a specific environmental context. Fourth, the choice of MEC statistics, for example, using parametric (e.g., mean) and non-parametric (e.g., median or other percentiles/quartiles), may also influence the risk categorization (Table S7). Our analysis on this aspect revealed that using median statistics resulted in seven PhCs under high risk category (gemfibrozil, oxytetracycline, erythromycin, sulfamethoxazole, ibuprofen, clarithromycin, and salicylic acid) instead of 12 rated under high risk when mean RQ values were used for the classification. This indicates that the mean is a more stringent measure than the median, and could be a preferable statistic from a better environmental protection point of view. The choice of mean values aligns with the logic of using the lowest PNEC value in order to aim for better environmental and ecological protection. On the other hand, the risk

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

Table 3 | Risk assessment of the 27 selected PhCs based on influent and effluent concentration in CWs

Therapeutic class/ Pharmaceutical	PNEC ($\mu g\ L^{-1}$)	(MEC) influent conc. ($\mu g\ L^{-1}$)	(MEC) effluent conc. ($\mu g\ L^{-1}$)	Influent RQ	Effluent RQ	Risk rank* influent/ effluent	References for PNEC values
Analgesic/anti-inflammatory drugs							
Diclofenac	9.7	17	8.7	**1.8**	0.9	High/Medium	Verlicchi *et al.* (2012)
Ibuprofen	1.65	30	13	**18**	**7.9**	High/High	Verlicchi *et al.* (2012)
Ketoprofen	15.6	19	7.6	**1.2**	0.5	High/Medium	Verlicchi *et al.* (2012)
Naproxen	2.62	21	7.5	**7.9**	**2.9**	High/High	Verlicchi *et al.* (2012)
Salicylic acid	1.28	16	2.3	**12**	**1.8**	High/High	Verlicchi *et al.* (2012)
Analgesic							
Acetaminophen	1.0	16	2.5	**16**	**2.5**	High/High	Verlicchi *et al.* (2012)
Codeine	16	0.4	0.2	0.02	0.009	Low/No	Verlicchi *et al.* (2012)
Antibiotics							
Clarithromycin	0.07	0.3	0.2	**4.4**	**2.2**	High/High	Verlicchi *et al.* (2012)
Erythromycin	0.02	5.7	2.2	**287**	**109**	High/High	Verlicchi *et al.* (2012)
Lincomycin	82	0.2	0.05	0.002	0.001	No/No	Verlicchi *et al.* (2012)
Doxycycline	0.3	0.6	0.07	**1.9**	0.2	High/Medium	Verlicchi *et al.* (2012)
Ofloxacin	0.016	37	8.1	**2,319**	**504**	High/High	Verlicchi *et al.* (2012)
Oxytetracycline	0.207	501	21	**2,421**	**101**	High/High	Verlicchi *et al.* (2012)
Sulfadiazine	0.135	14	0.5	**100**	**3.4**	High/High	Verlicchi *et al.* (2012)
Sulfamethazine	4.0	42	8.6	**10**	**2.1**	High/High	Gros *et al.* (2010)
Sulfamethoxazole	0.027	34	5.6	**1,247**	**209**	High/High	Verlicchi *et al.* (2012)
Sulfapyridine	21.61	1.0	0.2	0.05	0.007	Low/No	Verlicchi *et al.* (2012)
Trimethoprim	2.6	0.2	0.4	0.08	0.2	Low/Medium	Verlicchi *et al.* (2012)
Stimulants/psychoactive drugs							
Caffeine	46	28	5.9	0.6	0.1	Medium/Medium	Kosma *et al.* (2014)
Antihypertensives							
Diltiazem	1.9	0.05	0.02	0.03	0.01	Low/Low	Verlicchi *et al.* (2012)
Psychiatric drugs							
Carbamazepine	13.8	19	12	**1.3**	0.9	High/Medium	Verlicchi *et al.* (2012)
Beta-blockers							
Atenolol	30	2.1	0.5	0.07	0.02	Low/Low	Verlicchi *et al.* (2012)
Metoprolol	8.0	17	3.4	**2.1**	0.4	High/Medium	Verlicchi *et al.* (2012)
Receptor antagonists							
Ranitidine	63	0.6	0.4	0.009	0.006	No/No	Verlicchi *et al.* (2012)
Lipid regulators							
Bezafibrate	5.3	0.5	0.3	0.09	0.05	Low/Low	Verlicchi *et al.* (2012)
Clofibric acid	40.2	14	9.3	0.4	0.2	Medium/Medium	Verlicchi *et al.* (2012)
Gemfibrozil	0.9	67	42	**74**	**47**	High/High	Verlicchi *et al.* (2012)

Note: Predicted no effect concentration (PNEC); Measured environmental concentration (MEC); PNEC values are taken from the referred studies; Bold values indicate a high risk category; Risk rank is based on our results (*); Risk is categorized into four levels: high risk (RQ > 1.0), medium risk ($0.1 \leq RQ \leq 1.0$), low risk ($0.01 \leq RQ \leq 0.1$), and no risk (RQ < 0.01).

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

categorization based on the 25th percentile (P25) shows only a few PhCs under the high risk category, and may result in severe underestimation of risk. However, the risk categorization based on the 75th percentile (P75) is more stringent than the mean, and could also be used as a risk classification threshold, then a more stringent approach can be adopted. The extreme value analysis was not recommended for the risk classification because of significant underestimation in the case of using minimum RQ value or significant overestimation in the case of maximum RQ value. Finally, while aiming at achieving the best ecosystem protection can be recommended in theory, several trade-offs may apply in practice, which require sound scientific evidence to make an informed decision on the target levels of PhCs in a specific aquatic environment.

Role of physicochemical properties of PhCs and removal mechanisms in CWs

Based on the available evidence, synthesis on the role of physicochemical properties and removal mechanisms for 34 PhCs was conducted. For a few PhCs, experimental studies were available to quantify the relative contribution of various mechanisms. This work is summarized in Figure 3 (hydroponic microcosms and media adsorption experiments), Figure 4 (CWs), and Supplementary Materials 5: Tables S8 and S9. Correlation and multiple linear regression analyses were performed to examine the linkages between removal efficiency and physicochemical properties, which are discussed in this section (details are given in Table 4 and Supplementary Materials 6: Tables S10–S14). The summary of removal mechanisms reported in the literature for the PhCs is presented in Table 5. The physicochemical properties are compiled in Table 6. The main observations and insights drawn from these results are discussed below.

The experimental studies reveal various possible removal mechanisms of PhCs: biodegradation (aerobic and anaerobic), adsorption, sorption, plant uptake, biological transformation, reductive transformation, fermentation, precipitation, hydrolysis, and photodegradation. Although all these mechanisms do not come into play for every PhC, there is often more than one mechanism responsible

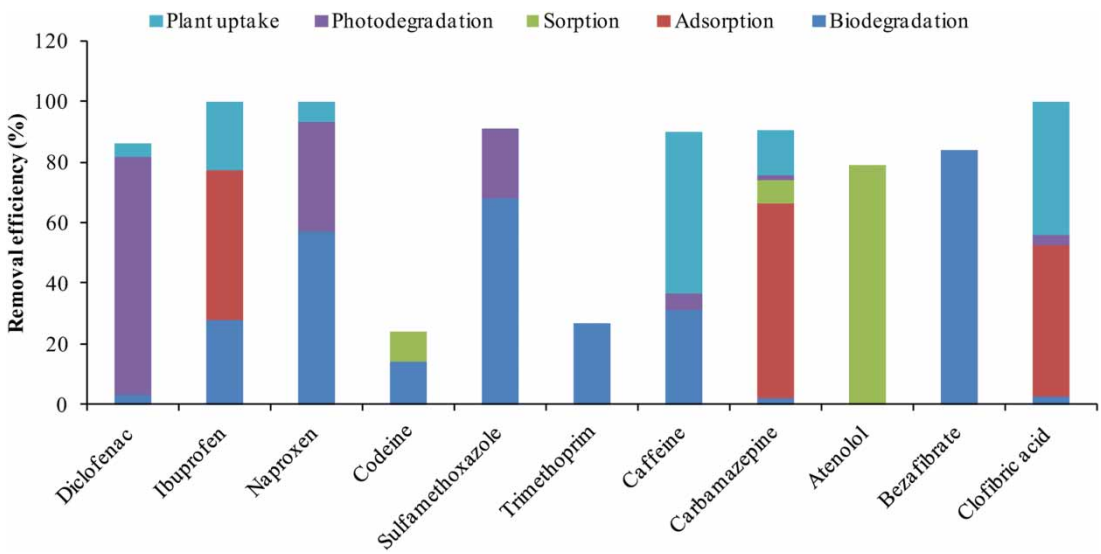


Figure 3 | Relative contribution of removal mechanisms for PhCs in hydroponic microcosms and media adsorption experiments. *Note*: The studies examined the contribution of one or more removal mechanisms. When the sum of the reported contribution by different mechanisms exceeded 100%, we standardized the contribution from each mechanism to 100% by adding removal of all the studied mechanisms and dividing it by the total. For example, in the case of ibuprofen, the contribution by biodegradation, adsorption, and plant uptake was 30%, 53%, and 24.6%, respectively. The total removal is 107.6%. However, out of 100%, the contribution of biodegradation, adsorption, and plant uptake was 27.9%, 49.3%, and 22.9%, respectively. Adsorption is the adhesion of dissolved solid molecules (adsorbate) to a surface of the substrate (adsorbent). It is a surface phenomenon. Absorption is a process in which a fluid (absorbate) permeates a solid (absorbent), thus involving the whole volume of the material. In the case of sorption both processes take place. Data are taken from Dordio *et al.* (2009a, 2009b); Matamoros *et al.* (2012); Zhang *et al.* (2012c, 2013a, 2013b, 2013c); Sharif *et al.* (2014); Choi *et al.* (2016); Zhang *et al.* (2016); Li *et al.* (2017); Zhang *et al.* (2018a); Petrie *et al.* (2018); and Park *et al.* (2018).

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

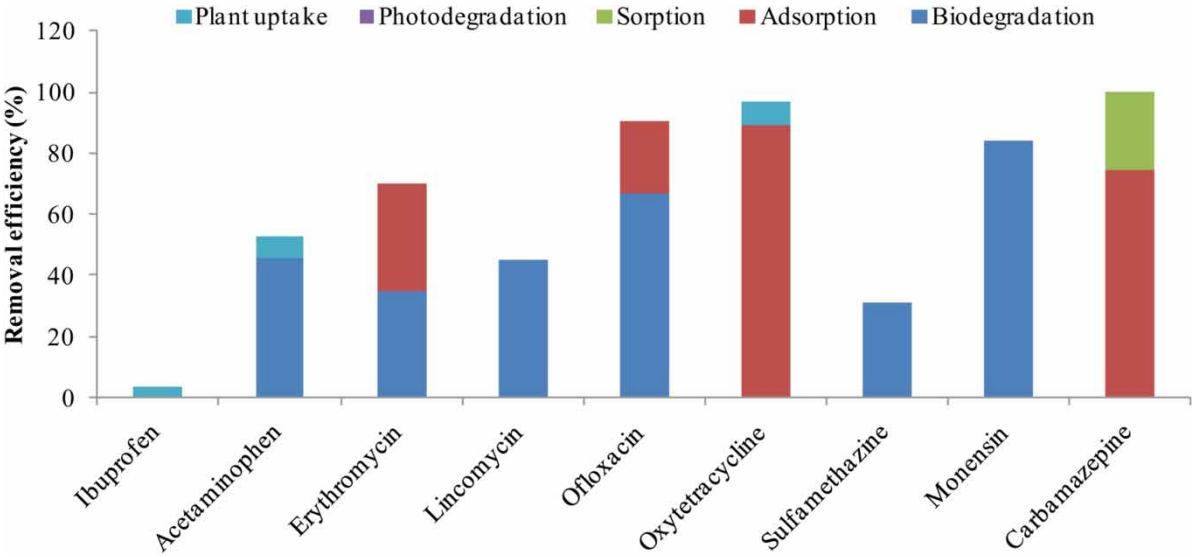


Figure 4 | Relative contribution of removal mechanisms for PhCs in CWs. Note: Data is taken from: Dordio *et al.* (2010); Dordio & Carvalho (2013); Carranza-Diaz *et al.* (2014); Chen *et al.* (2016a); Koottatep *et al.* (2017); Li *et al.* (2017); Zhang *et al.* (2017a); Zhang *et al.* (2017b); and Park *et al.* (2018).

Table 4 | Results of the Pearson correlation analysis

Parameter	Removal efficiency (%)	Log Koc	Log Dow	Log Kow	Molecular weight (g mol^{-1})	Water solubility (mg L^{-1})	pKa
Removal efficiency (%)	1.000						
Log Koc	**−0.697**	1.000					
Log Dow	**−0.420**	0.126	1.000				
Log Kow	−0.342	0.247	**0.568**	1.000			
Molecular weight (g mol^{-1})	−0.384	0.135	0.247	0.218	1.000		
Water solubility (mg L^{-1})	0.225	−0.125	**−0.512**	**−0.713**	−0.162	1.000	
pKa	−0.065	−0.116	0.167	−0.311	0.130	−0.023	1.000

Note: Organic carbon sorption coefficient (Log Koc); Octanol-water partition coefficient (Log Kow); Distribution coefficient (Log Dow); Dissociation constant (pKa); Bold values indicate a significant correlation at 95% confidence level; The number of data points per pair was 17.

for the removal of a PhC. This indicates the need of compound specific examination for removal mechanisms. Additionally, it is important to note that certain types of CWs (e.g., FWSCW, HFCW, and VFCW) provide certain environmental conditions to facilitate the specific mechanisms to take place. For instance, FWSCW provides a suitable environment for photodegradation, while VFCW and HFCW are known for the presence of microbial communities that can be directly involved in the biodegradation of PhCs.

Moreover, physicochemical properties play a pivotal role in the removal processes which are governed by molecular weight/structure, solubility in water, Log Koc, Log Kow, Log Dow, cationic or anionic nature (pKa/charge), and the presence of certain elements (e.g., chlorine, well known for its recalcitrance against biodegradation). Due to a large array of removal mechanisms and physicochemical properties, it is very difficult to draw general conclusions for all the PhCs on the responsible removal mechanisms, physicochemical properties, and other governing factors.

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

Table 5 | Removal mechanisms of 34 selected PhCs in CWs

Therapeutic class/ Pharmaceutical	Possible removal mechanism	References	Dominant removal mechanism*
Analgesic/anti-inflammatory drugs			
Diclofenac	Biodegradation (anaerobic)	Ávila *et al.* (2010, 2014a); Hijosa-Valsero *et al.* (2010b); Chen *et al.* (2016b); Kahl *et al.* (2017); He *et al.* (2018); Zhang *et al.* (2018b); Nivala *et al.* (2019)	Photodegradation; Biodegradation (aerobic)**
	Biodegradation (aerobic)	Hijosa-Valsero *et al.* (2010a, 2010b, 2011b); Ávila *et al.* (2013, 2014a); Kahl *et al.* (2017)	
	Photodegradation	Matamoros *et al.* (2008a); Matamoros & Salvadó (2012); Ávila *et al.* (2014b, 2015); Rühmland *et al.* (2015); Chen *et al.* (2016b); Francini *et al.* (2018); Zhang *et al.* (2018b)	
	Plant uptake	Hijosa-Valsero *et al.* (2010a); Zhang *et al.* (2011, 2012c)	
Ibuprofen	Biodegradation (aerobic)	Matamoros *et al.* (2007, 2008b); Hijosa-Valsero *et al.* (2010a, 2011c); Ávila *et al.* (2010, 2013, 2014a, 2014b, 2015); Matamoros & Salvadó (2012); Li *et al.* (2014); Zhu & Chen (2014); Chen *et al.* (2016b); Vymazal *et al.* (2017); Březinova *et al.* (2018); Zhang *et al.* (2018b); Nivala *et al.* (2019)	Biodegradation (aerobic)
	Sorption	Dordio *et al.* (2010); Dordio & Carvalho (2013)	
	Adsorption	Auvinen *et al.* (2017b)	
	Photodegradation	Reyes-Contreras *et al.* (2012); Zhang *et al.* (2014)	
	Plant uptake	Hijosa-Valsero *et al.* (2010a); Li *et al.* (2016b)	
Ketoprofen	Biodegradation	Hijosa-Valsero *et al.* (2010a); Zhang *et al.* (2012a); Chen *et al.* (2016b); Francini *et al.* (2018); Zhang *et al.* (2018b)	Photodegradation
	Photodegradation	Matamoros *et al.* (2008a); Matamoros & Salvadó (2012); Reyes-Contreras *et al.* (2012); Francini *et al.* (2018); Zhang *et al.* (2018b)	
Naproxen	Biodegradation (aerobic)	Matamoros *et al.* (2007, 2009); Hijosa-Valsero *et al.* (2010a); Matamoros & Salvadó (2012); Zhang *et al.* (2012b); Chen *et al.* (2016b); He *et al.* (2018); Zhang *et al.* (2018b); Nivala *et al.* (2019)	Biodegradation (aerobic)**; Photodegradation
	Biodegradation (anaerobic)	Matamoros *et al.* (2009); Ávila *et al.* (2010); Li *et al.* (2014); He *et al.* (2018); Nivala *et al.* (2019)	
	Photodegradation	Matamoros *et al.* (2008a); Reyes-Contreras *et al.* (2012); Hijosa-Valsero *et al.* (2016); Zhang *et al.* (2018b)	
	Plant uptake	Hijosa-Valsero *et al.* (2010a); Zhang *et al.* (2013b); He *et al.* (2018)	
Salicylic acid	Biodegradation	Hijosa-Valsero *et al.* (2010a, 2011b); Reyes-Contreras *et al.* (2012); Zhang *et al.* (2012a)	Biodegradation (aerobic)**
	Plant uptake	Hijosa-Valsero *et al.* (2016)	
Analgesic			
Acetaminophen	Biodegradation (aerobic)	Ávila *et al.* (2013, 2015); Koottatep *et al.* (2017); Li *et al.* (2017); Vystavna *et al.* (2017)	Biodegradation (aerobic)**
	Biodegradation (anaerobic)	Chen *et al.* (2016b)	
	Photodegradation	Ávila *et al.* (2015); Li *et al.* (2017)	

(*continued*)

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

Table 5 | continued

Therapeutic class/ Pharmaceutical	Possible removal mechanism	References	Dominant removal mechanism*
	Adsorption	Ávila *et al.* (2015); Koottatep *et al.* (2017)	
	Sorption	Chen *et al.* (2016b)	
	Plant uptake	Li *et al.* (2017)	
Codeine	Biodegradation (aerobic)	Rühmland *et al.* (2015); Petrie *et al.* (2018)	Sorption; Biodegradation (aerobic)
	Sorption	Petrie *et al.* (2018)	
Tramadol	Biological transformation	Rühmland *et al.* (2015); Chen *et al.* (2016b); Petrie *et al.* (2018)	Biological transformation
Antibiotics			
Clarithromycin	Biodegradation	Hijosa-Valsero *et al.* (2011a); Berglund *et al.* (2014)	Photodegradation; Sorption
	Sorption	Hijosa-Valsero *et al.* (2011a); Berglund *et al.* (2014)	
	Photodegradation	Hijosa-Valsero *et al.* (2011a); Berglund *et al.* (2014)	
Erythromycin	Biodegradation (aerobic)	Rühmland *et al.* (2015); Chen *et al.* (2016a)	Biodegradation (aerobic); Adsorption
	Adsorption	Chen *et al.* (2016a)	
	Plant uptake	Hijosa-Valsero *et al.* (2011a)	
Lincomycin	Biodegradation	Chen *et al.* (2016a)	Biodegradation (aerobic)**
	Sorption	Chen *et al.* (2016a)	
Doxycycline	Biodegradation	Hijosa-Valsero *et al.* (2011a); Ávila *et al.* (2014b)	Biodegradation (aerobic)**; Adsorption
	Adsorption/retention processes	Hijosa-Valsero *et al.* (2011a); Berglund *et al.* (2014)	
Ofloxacin	Adsorption	Chen *et al.* (2016a)	Biodegradation (anaerobic)**; Adsorption
	Biodegradation	Chen *et al.* (2016a); Yan *et al.* (2016)	
Oxytetracycline	Adsorption	Dordio & Carvalho (2013); Berglund *et al.* (2014); Huang *et al.* (2017)	Adsorption; Plant uptake
	Plant uptake	Dordio & Carvalho (2013); Huang *et al.* (2017)	
	Biodegradation (aerobic)	Dordio & Carvalho (2013); Huang *et al.* (2017)	
Sulfadiazine	Biodegradation	Xian *et al.* (2010)	Biodegradation (anaerobic)**
	Fermentation	Dan *et al.* (2013)	
Sulfamethazine	Adsorption	Liu *et al.* (2014); Chen *et al.* (2016a); Choi *et al.* (2016)	Biodegradation (aerobic)**; Plant uptake
	Biodegradation	Xian *et al.* (2010); Liu *et al.* (2014); Chen *et al.* (2016a); Choi *et al.* (2016)	
	Fermentation	Dan *et al.* (2013)	
	Plant uptake	Xian *et al.* (2010)	

(*continued*)

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

Table 5 | continued

Therapeutic class/ Pharmaceutical	Possible removal mechanism	References	Dominant removal mechanism*
Sulfamethoxazole	Adsorption	Choi *et al.* (2016); Liang *et al.* (2018)	Biodegradation (aerobic; anaerobic)**
	Sorption	Zhu & Chen (2014)	
	Biodegradation (aerobic)	Conkle *et al.* (2008); Choi *et al.* (2016); Sgroi *et al.* (2018); Button *et al.* (2019)	
	Biodegradation (anaerobic)	Hijosa-Valsero *et al.* (2011a); Dan *et al.* (2013); Rühmland *et al.* (2015); Liang *et al.* (2018); Sgroi *et al.* (2018)	
	Photodegradation	Hijosa-Valsero *et al.* (2011a)	
	Plant uptake	Xian *et al.* (2010); Hijosa-Valsero *et al.* (2011a)	
Sulfapyridine	Biodegradation (aerobic)	Conkle *et al.* (2008)	Biodegradation (anaerobic)**
	Biodegradation (anaerobic)	Dan *et al.* (2013)	
Trimethoprim	Biodegradation (aerobic)	Hijosa-Valsero *et al.* (2011a); Rühmland *et al.* (2015)	Biodegradation (anaerobic)**
	Biodegradation (anaerobic)	Dan *et al.* (2013)	
Monensin	Biodegradation	Chen *et al.* (2016a)	Biodegradation (aerobic)**
Antiallergic drugs			
Fexofenadine	NA	NA	Adsorption/retention processes**
Stimulants/psychoactive drugs			
Caffeine	Biodegradation (aerobic)	Matamoros & Bayona (2006); Hijosa-Valsero *et al.* (2010b); Zhang *et al.* (2014); Chen *et al.* (2016b); Li *et al.* (2017); Vymazal *et al.* (2017); Vystavna *et al.* (2017); He *et al.* (2018)	Biodegradation (aerobic)**; Plant uptake
	Biodegradation (anaerobic)	Hijosa-Valsero *et al.* (2010a); Carranza-Diaz *et al.* (2014); He *et al.* (2018)	
	Adsorption onto carbon-rich surfaces of the gravel bed	Matamoros & Bayona (2006); Dettenmaier *et al.* (2009); Wang *et al.* (2014); Li *et al.* (2017)	
	Plant uptake	Hijosa-Valsero *et al.* (2010a); Zhang *et al.* (2013a); Zhu & Chen (2014); Chen *et al.* (2016b); Li *et al.* (2017); Petrie *et al.* (2018)	
Antihypertensives			
Diltiazem	Plant uptake	Petrie *et al.* (2018)	Plant uptake
	Sorption	Petrie *et al.* (2018)	
Psychiatric drugs			
Carbamazepine	Adsorption onto the available organic surfaces	Matamoros *et al.* (2005, 2008b); Hijosa-Valsero *et al.* (2011b); Carranza-Diaz *et al.* (2014); Sharif *et al.* (2014); Vystavna *et al.* (2017); Park *et al.* (2018)	Adsorption; Sorption; Plant uptake
	Sorption	Dordio *et al.* (2010); Dordio & Carvalho (2013); Park *et al.* (2018)	
	Biodegradation (aerobic)	Hijosa-Valsero *et al.* (2010a)	
	Reductive transformation	Kahl *et al.* (2017); Nivala *et al.* (2019)	

(*continued*)

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

Table 5 | continued

Therapeutic class/ Pharmaceutical	Possible removal mechanism	References	Dominant removal mechanism*
	Plant uptake	Hijosa-Valsero *et al.* (2010a, 2016); Macci *et al.* (2015); Yan *et al.* (2016); Petrie *et al.* (2018); He *et al.* (2018)	
Mirtazapin	Biodegradation	Breitholtz *et al.* (2012)	Biodegradation (aerobic)**; Plant uptake
	Plant uptake	Petrie *et al.* (2018)	
Venlafaxine	Precipitation	Breitholtz *et al.* (2012); Vystavna *et al.* (2017)	Plant uptake; Precipitation
	Biological transformation	Rühmland *et al.* (2015); Petrie *et al.* (2018)	
	Plant uptake	Petrie *et al.* (2018)	
Beta-blockers			
Atenolol	Biodegradation (aerobic)	Conkle *et al.* (2008); Rühmland *et al.* (2015)	Sorption
	Biodegradation (anaerobic)	Chen *et al.* (2016b)	
	Adsorption	Auvinen *et al.* (2017b); Park *et al.* (2018)	
	Sorption	Petrie *et al.* (2018); Park *et al.* (2018)	
	Photodegradation	Salgado *et al.* (2013)	
	Plant uptake	Francini *et al.* (2018)	
Metoprolol	Biodegradation (aerobic)	Conkle *et al.* (2008); Rühmland *et al.* (2015); Chen *et al.* (2016b); He *et al.* (2018)	Biodegradation (aerobic)
Sotalol	NA	NA	Biodegradation (aerobic)**
Receptor antagonists			
Ranitidine	Biodegradation	Breitholtz *et al.* (2012)	Sorption
	Sorption	Petrie *et al.* (2018)	
Lipid regulators			
Bezafibrate	Biodegradation (aerobic)	Rühmland *et al.* (2015)	Biodegradation (anaerobic)**
	Biodegradation (anaerobic)	Petrie *et al.* (2018)	
Clofibric acid	Plant uptake	Dordio *et al.* (2010)	Plant uptake
Gemfibrozil	Biodegradation (aerobic)	Conkle *et al.* (2008); Yi *et al.* (2017); Zhang *et al.* (2018b)	Biodegradation (aerobic)
Diuretics			
Furosemide	Hydrolysis	Chen *et al.* (2016b); Vymazal *et al.* (2017)	Hydrolysis; Biodegradation (aerobic)**
	Photolysis	Chen *et al.* (2016b)	

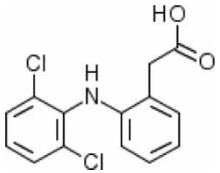
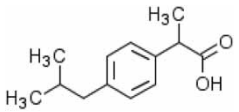
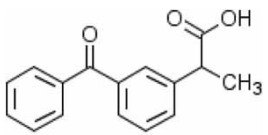
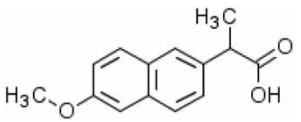
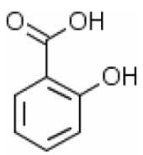
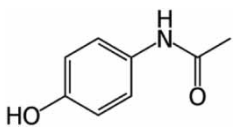
Note: Authors' own insight based on physicochemical properties, removal mechanisms, and limited evidence in the literature (*). Authors' own insight based on physicochemical properties and removal mechanisms (**).

Thus, a compound specific examination is inevitable. Nevertheless, a few generic observations can be made from an overall analysis of the available evidence, which could be used as a preliminary screening of possible removal efficiencies and governing factors. The main insights are noted below.

The Log Kow is the ratio of the concentration of unionized compound between octanol and water, and has been assumed as the standard measure of hydrophobicity of organic compounds (Burken & Schnoor 1998; Reinhold *et al.* 2010). The hydrophobicity of non-ionic organic compounds is invariable under different pH conditions but the

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

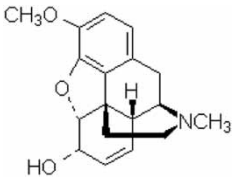
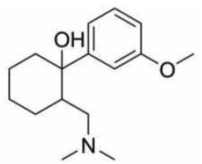
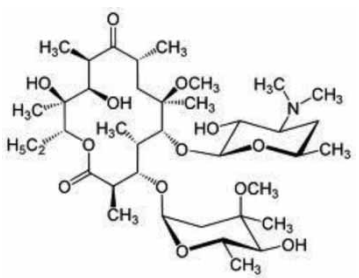
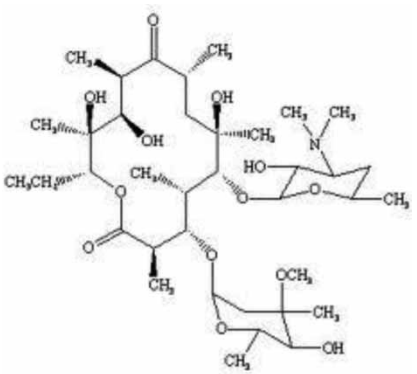
Table 6 | Physicochemical properties of 34 selected PhCs

Therapeutic classes/ PhCs/Molecular weight (g mol^{-1})	Molecular formula	Molecular structure	Water solubility at 25 °C (mg L^{-1})	Log Kow	Log Koc	Log Dow	Henry's law constant (atm m^3 mol^{-1})	pKa/charge at pH 7	Reference
Analgesic/anti-inflammatory drugs									
Diclofenac/296.15	$C_{14}H_{11}Cl_2NO_2$		4.52	4.51	2.921	0.96	4.73×10^{-12}	4.15/negative	Hijosa-Valsero *et al.* (2010a); Zhang *et al.* (2012b, 2012c); Verlicchi *et al.* (2012, 2013); He *et al.* (2018); Petrie *et al.* (2018); Zhang *et al.* (2018b);
Ibuprofen/206.29	$C_{13}H_{18}O_2$		41.05	3.97	2.596	1.25	1.52×10^{-7}	4.91/negative	Hijosa-Valsero *et al.* (2010a); Verlicchi *et al.* (2012, 2013); He *et al.* (2018); Park *et al.* (2018); Petrie *et al.* 2018); Zhang *et al.* (2018b); Wang *et al.* (2019)
Ketoprofen/254.29	$C_{16}H_{14}O_3$		120.4	3.12	2.459	0.45	2.12×10^{-11}	4.45/negative	Reyes-Contreras *et al.* (2012); Verlicchi *et al.* (2012, 2013); Hijosa-Valsero *et al.* (2016); Petrie *et al.* (2018); Zhang *et al.* (2018b)
Naproxen/230.27	$C_{14}H_{14}O_3$		144.9	3.18	2.543	0.30	3.39×10^{-10}	4.15/negative	Verlicchi *et al.* (2012, 2013); Hijosa-Valsero *et al.* (2016); He *et al.* (2018); Petrie *et al.* (2018); Zhang *et al.* (2018b)
Salicylic acid/138.12	$C_7H_6O_3$		3.80×10^3	2.26	1.379	1.79	1.42×10^{-8}	2.97/negative	Verlicchi *et al.* (2012, 2013); Hijosa-Valsero *et al.* (2011b, 2016)
Analgesic									
Acetaminophen[a]/ 151.17	$C_8H_9NO_2$		3.04×10^4	0.46	–	0.90	6.42×10^{-13}	9.38/neutral	Verlicchi *et al.* (2012, 2013); Chen *et al.* (2016b); Petrie *et al.* (2018)

(*continued*)

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

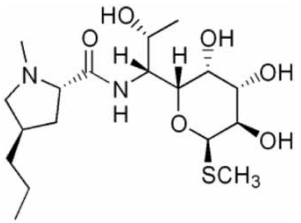
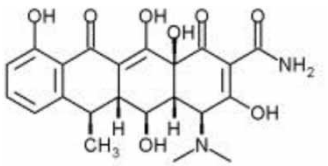
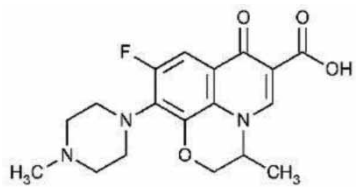
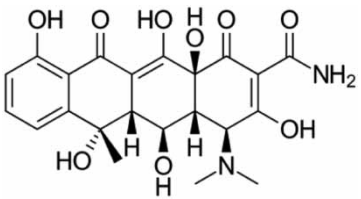
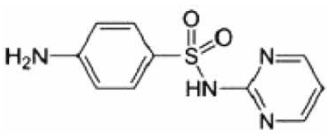
Table 6 | continued

Therapeutic classes/ PhCs/Molecular weight (g mol^{-1})	Molecular formula	Molecular structure	Water solubility at 25 °C (mg L^{-1})	Log Kow	Log Koc	Log Dow	Henry's law constant (atm m^3 mol^{-1})	pKa/charge at pH 7	Reference
Codeine/299.37	$C_{18}H_{21}NO_3$		1.21×10^4	1.28	2.845	−0.23	7.58×10^{-14}	8.21/positive	Verlicchi *et al.* (2012, 2013); Petrie *et al.* (2018)
Tramadol[b]/263.38	$C_{16}H_{25}NO_2$		1.15×10^3	3.01	–	0.72	1.54×10^{-11}	9.61/positive	Verlicchi *et al.* (2012); Rühmland *et al.* (2015); Chen *et al.* (2016b); Petrie *et al.* (2018)
Antibiotics									
Clarithromycin/ 747.97	$C_{38}H_{69}NO_{13}$		0.342	3.16	2.174	2.31	1.73×10^{-29}	8.99/positive	Verlicchi *et al.* (2012, 2013); Chen *et al.* (2016b); Petrie *et al.* (2018)
Erythromycin/733.93	$C_{37}H_{67}NO_{13}$		0.517	3.06	2.754	–	5.42×10^{-29}	8.9/positive	Verlicchi *et al.* (2012, 2013); Chen *et al.* (2016b); Yi *et al.* (2017)

(*continued*)

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

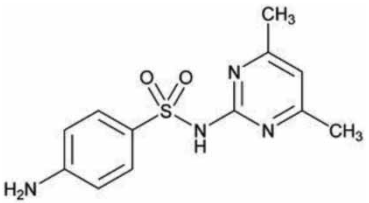
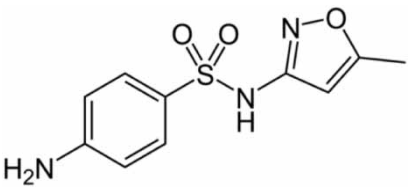
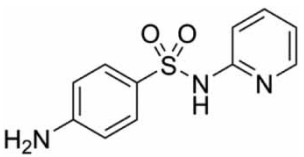
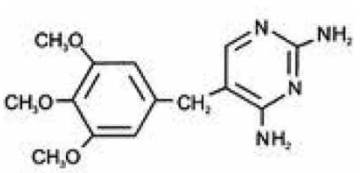
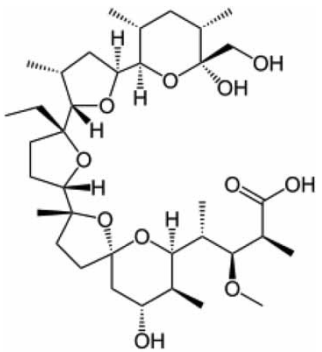
Table 6 | continued

Therapeutic classes/ PhCs/Molecular weight (g mol^{-1})	Molecular formula	Molecular structure	Water solubility at 25 °C (mg L^{-1})	Log Kow	Log Koc	Log Dow	Henry's law constant (atm m^3 mol^{-1})	pKa/charge at pH 7	Reference
Lincomycin[c]/406.54	$C_{18}H_{34}N_2O_6S$		92.19	0.72	–	–	–	8.78/positive; neutral	*; Verlicchi *et al.* (2012); Yi *et al.* (2017)
Doxycycline/444.44	$C_{22}H_{24}N_2O_8$		312.9	−0.02	1.693	–	–	pK1 = 3.5; pK2 = 7.7; pK3 = 9.5/ negative	Verlicchi *et al.* (2012, 2013)
Ofloxacin/361.37	$C_{18}H_{20}FN_3O_4$		2.83×10^4	−0.39	1.086	–	–	5.97/neutral; negative	**; Verlicchi *et al.* (2012, 2013)
Oxytetracycline[d]/ 460.43	$C_{22}H_{24}N_2O_9$		1.4×10^3	1.22	1.867	–	–	pK1 = 3.3; pK2 = 7.3; pK3 = 9.1/ negative	Verlicchi *et al.* (2012, 2013); Choi *et al.* (2016); Huang *et al.* (2017)
Sulfadiazine/250.28	$C_{10}H_{10}N_4O_2S$		2.81×10^4	−0.09	1.871	−0.23 to −1.5	–	pK1 = 6.4; pK2 = 2.1/ neutral; negative	Verlicchi *et al.* (2012, 2013); Dan *et al.* (2013)

(*continued*)

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

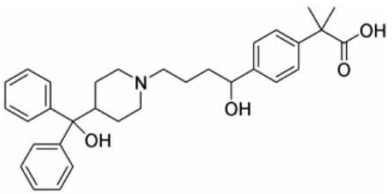
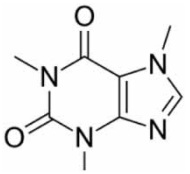
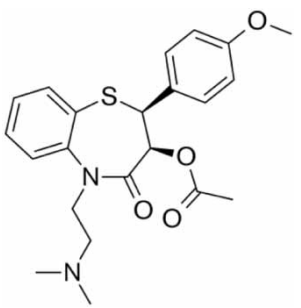
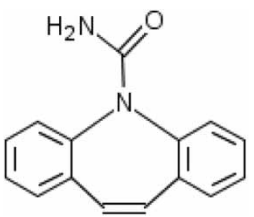
Table 6 | continued

Therapeutic classes/ PhCs/Molecular weight (g mol^{-1})	Molecular formula	Molecular structure	Water solubility at 25 °C (mg L^{-1})	Log Kow	Log Koc	Log Dow	Henry's law constant (atm m^3 mol^{-1})	pKa/charge at pH 7	Reference
Sulfamethazine/ 278.33	$C_{12}H_{14}N_4O_2S$		1.12×10^4	0.89	2.282	0.79–0.16	3.05×10^{-13}	pK1 = 7.6; pK2 = 2.3/ neutral; negative	Verlicchi *et al.* (2012, 2013); Dan *et al.* (2013); Chen *et al.* (2016b)
Sulfamethoxazole/ 253.28	$C_{10}H_{11}N_3O_3S$		3.94×10^3	0.89	2.412	−0.03	9.56×10^{-13}	pK1 = 5.7; pK2 = 1.8/ neutral; negative	Verlicchi *et al.* (2012, 2013); Chen *et al.* (2016b); Petrie *et al.* (2018)
Sulfapyridine[e]/249.29	$C_{11}H_{11}N_3O_2S$		1.20×10^4	0.53	–	−0.08 to −0.16	–	8.43/neutral; negative	*; Verlicchi *et al.* (2012); Dan *et al.* (2013)
Trimethoprim/290.32	$C_{14}H_{18}N_4O_3$		2.33×10^3	0.91	2.857	1.13	2.39×10^{-14}	7.12/neutral; positive	Verlicchi *et al.* (2012, 2013); Petrie *et al.* (2018); Yi *et al.* (2017); Sgroi *et al.* (2018)
Monensin[f]/670.87	$C_{36}H_{62}O_{11}$		3.0×10^{-3}	5.43	–	–	–	6.6/negative	*; **

(*continued*)

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

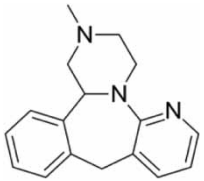
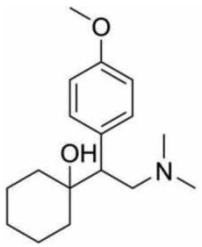
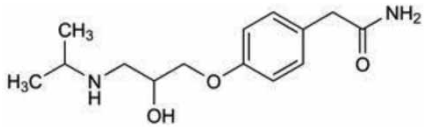
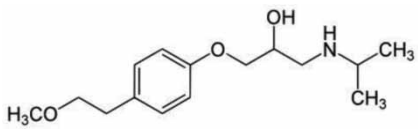
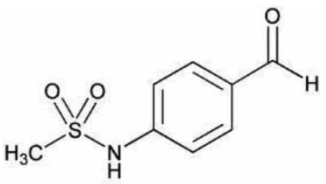
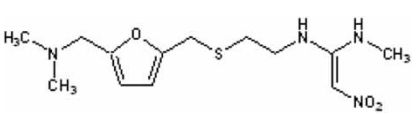
Table 6 | continued

Therapeutic classes/ PhCs/Molecular weight (g mol^{-1})	Molecular formula	Molecular structure	Water solubility at 25 °C (mg L^{-1})	Log Kow	Log Koc	Log Dow	Henry's law constant (atm m^3 mol^{-1})	pKa/charge at pH 7	Reference
Antiallergic drugs									
Fexofenadine[g]/501.67	$C_{32}H_{39}NO_4$		2.4×10^{-2}	2.81	–	2.93	1.19×10^{-18}	pK1 = 8.8; pK2 = 4.3/ neutral	**; Breitholtz *et al.* (2012); Petrie *et al.* (2018)
Stimulants/psychoactive drugs									
Caffeine[h]/194.19	$C_8H_{10}N_4O_2$		2.16×10^4	−0.07	1.00	−0.55	3.58×10^{-11}	10.4/positive	**; Hijosa-Valsero *et al.* (2011b); Chen *et al.* (2016b); Yi *et al.* (2017); He *et al.* (2018); Petrie *et al.* (2018); Sgroi *et al.* (2018); Wang *et al.* (2019)
Antihypertensives									
Diltiazem[i]/414.52	$C_{22}H_{26}N_2O_4S$		12.3	2.79	–	1.97	8.61×10^{-17}	8.94/positive	Breitholtz *et al.* (2012); Verlicchi *et al.* (2012); Petrie *et al.* (2018)
Psychiatric drugs									
Carbamazepine/ 236.28	$C_{15}H_{12}N_2O$		17.7	2.45	3.59	2.77	1.08×10^{-10}	13.9/neutral	Zhang *et al.* (2012b); Verlicchi *et al.* (2012, 2013); Carranza-Diaz *et al.* (2014); Hijosa-Valsero *et al.* (2016); He *et al.* (2018); Park *et al.* (2018); Petrie *et al.* (2018); Wang *et al.* (2019)

(*continued*)

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

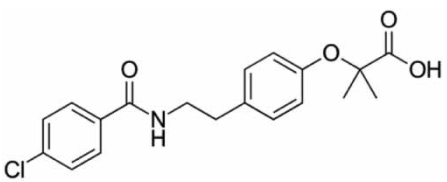
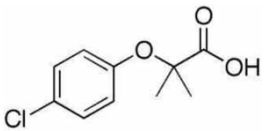
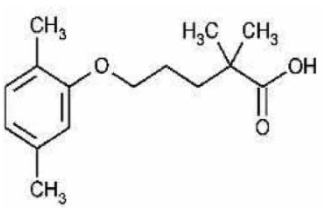
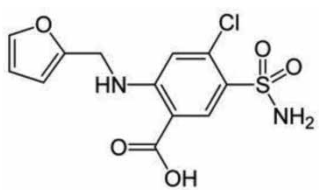
Table 6 | continued

Therapeutic classes/ PhCs/Molecular weight (g mol^{-1})	Molecular formula	Molecular structure	Water solubility at 25 °C (mg L^{-1})	Log Kow	Log Koc	Log Dow	Henry's law constant (atm m^3 mol^{-1})	pKa/charge at pH 7	Reference
Mirtazapin[j]/265.35	$C_{17}H_{19}N_3$		1,100	3.00	–	3.15	–	8.10/positive	**; Breitholtz *et al.* (2012); Giulia *et al.* (2016); Petrie *et al.* (2018)
Venlafaxine[b]/277.41	$C_{17}H_{27}NO_2$		266.7	3.28	–	1.32	2.87×10^{-11}	9.3/positive	Breitholtz *et al.* (2012); Rühmland *et al.* (2015); Giulia *et al.* (2016); Vystavna *et al.* (2017); Petrie *et al.* (2018)
Beta-blockers									
Atenolol/266.34	$C_{14}H_{22}N_2O_3$		685.2	0.16	1.825	−1.71	1.37×10^{-18}	9.6/positive	**; Verlicchi *et al.* (2012, 2013); Yi *et al.* (2017); Park *et al.* (2018); Petrie *et al.* (2018)
Metoprolol/267.37	$C_{15}H_{25}NO_3$		4.77×10^3	1.88	2.057	−0.38	1.40×10^{-13}	9.6/positive	Verlicchi *et al.* (2012, 2013); Chen *et al.* (2016b); He *et al.* (2018); Petrie *et al.* (2018)
Sotalol/272.36	$C_{12}H_{20}N_2O_3S$		5.51×10^3	0.24	1.351	–	–	pK1 = 8.2; pK2 = 9.8/ positive	*; Verlicchi *et al.* (2012, 2013)
Receptor antagonists									
Ranitidine[k]/314.41	$C_{13}H_{22}N_4O_3S$		2.47×10^4	0.27	3.839	−1.56	3.42×10^{-15}	2.4/positive	Breitholtz *et al.* (2012); Verlicchi *et al.* (2012, 2013); Petrie *et al.* (2018)

(*continued*)

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

Table 6 | continued

Therapeutic classes/ PhCs/Molecular weight (g mol^{-1})	Molecular formula	Molecular structure	Water solubility at 25 °C (mg L^{-1})	Log Kow	Log Koc	Log Dow	Henry's law constant (atm m^3 mol^{-1})	pKa/charge at pH 7	Reference
Lipid regulators									
Bezafibrate/361.83	$C_{19}H_{20}ClNO_4$		1.224	4.25	2.617	0.46	2.12×10^{-15}	3.6/negative	Breitholtz *et al.* (2012); Verlicchi *et al.* (2012, 2013); Chen *et al.* (2016b); Petrie *et al.* (2018)
Clofibric acid/214.65	$C_{10}H_{11}ClO_3$		582.5	2.57	1.64	–	–	3.18/negative	Hijosa-Valsero *et al.* (2010a); Verlicchi *et al.* (2012, 2013); Yi *et al.* (2017)
Gemfibrozil/250.33	$C_{15}H_{22}O_3$		4.964	4.77	2.636	–	1.2×10^{-8}	4.8/negative	**; Verlicchi *et al.* (2013); Yi *et al.* (2017); Zhang *et al.* (2018b); Wang *et al.* (2019)
Diuretics									
Furosemide/330.7	$C_{12}H_{11}ClN_2O_5S$		149.3	2.03	2.043	–	3.94×10^{-16}	3.9/negative	Hijosa-Valsero *et al.* (2010a); Chen *et al.* (2016b); Verlicchi *et al.* (2012, 2013)

Note: https://www.drugfuture.com/chemdata/ (*); https://www.ncbi.nlm.nih.gov/pccompound (**). Chemical structures are taken from websites: https://en.wikipedia.org/wiki/Paracetamol (a); https://twitter.com/davidjuurlink/status/921768739540013056 (b); https://en.wikipedia.org/wiki/Lincomycin (c); https://en.wikipedia.org/wiki/Oxytetracycline (d); https://en.wikipedia.org/wiki/Sulfapyridine (e); https://en.wikipedia.org/wiki/Monensin (f); https://commons.wikimedia.org/wiki/File:Fexofenadine_Structure.png (g); https://en.wikipedia.org/wiki/Caffeine (h); https://en.wikipedia.org/wiki/Diltiazem (i); https://en.wikipedia.org/wiki/Mirtazapine (j); https://www.drugfuture.com/chemdata/ranitidine.html (k).

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

hydrophobicity of ionic organic compounds varies due to ionization of the compound at a certain pH. In that case, Log Dow is appropriate to represent the hydrophobicity of ionic organic compounds (Lee *et al.* 2011). Log Dow is the distribution ratio of the concentration of ionizable organic compound between octanol and buffer phase. The concentration in octanol is the total concentration of an ionizable organic compound which is assumed to be dominated by the non-dissociated form. The concentration in the buffer phase is considered as the fraction in dissociated and non-dissociated forms, which depends on the pH and pKa of the organic compound (ECETOC Technical report 123 Log Dow). Log Dow is nearly the same as Log Kow but the modification in ionizable functional groups may affect their removal by biological treatment processes (Zhang *et al.* 2012b). Nevertheless, the Log Kow and Log Dow, which are significantly correlated (Table 4), indicate the hydrophobicity of organic compounds, and thus are important parameters to understand the behavior of PhCs in environmental media.

It is widely considered that organic compounds with moderate hydrophobicity ($1.0 < \text{Log Kow} < 3.5$; Log Dow < 2.5) and low molecular weight (MW < 500 g mol^{-1}) have adequate properties to move through cell membranes, and thus are easily taken up by plant roots and translocated into shoots (Briggs *et al.* 1983; Dietz & Schnoor 2001; Alvarez *et al.* 2004; Pilon-Smits 2005; Le-Minh *et al.* 2010; Yan *et al.* 2016). Hydrophobic compounds (Log Kow > 3.5) bind so strongly to the surface of roots and soils that they cannot be translocated easily within the plant, and the hydrophilic compounds (Log Kow < 1.0), which are quite water soluble, are not sufficiently sorbed to roots nor actively transported through plant membranes (Dietz & Schnoor 2001). Plant uptake is an important mechanism, although dominant only for a few PhCs such as clofibric acid, diltiazem, and venlafaxine. These PhCs also indicate low to moderate removal possibilities. Furthermore, it is revealed that cationic compounds which can partition into the lipophilic cell structure of negatively charged biomembranes of the plant roots show their uptake by the plant (Petrie *et al.* 2018). Negatively charged compounds cannot be taken up by the plants because the charge repulsion with the negatively charged biomembrane restricts their uptake by the plant root (Matamoros *et al.* 2012; Petrie *et al.* 2018). It has been indicated that neutral compounds which are hydrophilic in nature (Log Kow < 1.5) may still be taken up by rooted vascular plants via hydrogen bonding with water molecules into the transpiration stream (Dietz & Schnoor 2001). It has been suggested that hydrophobic compounds (Log Kow > 3.5) are most likely removed by phytostabilization and/or rhizosphere bioremediation (biodegradation) due to their long residence time in the root zone (Dietz & Schnoor 2001).

Biodegradation is the major removal mechanism in most of the studied PhCs (19 out of 34 selected PhCs) (Table 5). This means that the treatment systems targeting multiple PhCs must ensure environmental conditions conducive for biodegradation. Next to this, it can be recognized that the readily biodegradable compounds often demonstrate the highest removal efficiencies (e.g., acetaminophen, ibuprofen, caffeine, monensin, and salicylic acid) (Tables 2 and 5). However, the biodegradability of a PhC cannot be determined only by its physicochemical properties, since a large number of PhCs have Log Kow $<$ 3.5 and their removal is attributed to biodegradation. Therefore, experimental studies are essential to establish biodegradability of every PhC. Moreover, biodegradation as a dominant process does not guarantee higher removal possibilities in all the cases (e.g., bezafibrate, gemfibrozil, mirtazapin, sotalol, and trimethroprim) (Tables 2 and 5). This reveals the complexity of the biodegradation process itself (how much a compound is biodegradable) but also the role of other processes in CWs and physicochemical properties of PhCs.

Furthermore, for the compounds which are most hydrophilic (Log Kow < 1.0), the most water soluble (WS $> 1{,}000$ mg L^{-1}), and have the lowest molecular weight (MW < 100 g mol^{-1}), adsorption cannot be considered as a dominant removal mechanism because more time is required for the sorption/sedimentation of those compounds (Vystavna *et al.* 2017). It is generally considered that for the organic compounds which are most hydrophobic (Log Kow > 4; Log Dow > 2.5), and have high molecular weight (MW > 500 g mol^{-1}), adsorption processes are more common (Briggs *et al.* 1983; Alvarez *et al.* 2004; Le-Minh *et al.* 2010; Dan *et al.* 2013; Yan *et al.* 2016). When adsorption/sorption is a dominant removal mechanism, the removal efficiencies are either moderate (e.g.,

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

atenolol and codeine) or low (e.g., fexofenadine, ranitidine, and carbamazepine) even in the CWs that can provide good media for adsorption/sorption (Tables 2 and 5). It has been observed that adsorption/sorption potential of a CW may decrease due to creation of biofilms around the filter media that may prohibit access to adsorption/sorption surfaces (Dordio *et al.* 2009a, 2010).

The Log Koc is the ratio of the mass of a compound that is adsorbed in the soil per unit mass of organic carbon in the soil. Log Koc values are useful in predicting the mobility of organic soil contaminants; the higher Log Koc values correlate to less mobile organic compounds, while lower Log Koc values correlate to more mobile organic compounds (Piwoni & Keeley 1990). It has been suggested that non-polar organic compounds are sorbed by soils as a function of their hydrophobicity (Log Kow) and the organic carbon content of the soil (Piwoni & Keeley 1990). This can be seen by a positive correlation of Log Koc with Log Kow (although non-significant) (Table 4), which can be further supported by the negative correlation (although non-significant) of Log Koc and water solubility (Table 4). The Log Koc is a good indicator of the sorption potential and mobility of the PhCs, which can influence their fate in CWs. We found a significant negative correlation of Log Koc with removal efficiency (r: −0.697) (Table 4), which could explain about 49% of the variance in the available data (R^2: 0.49) (Table S10). This indicates the possibility of using Log Koc as a screening parameter, even though its proportionate contribution in overall removal may be limited. Similarly, Log Dow shows a significant negative correlation with removal efficiency (r: −0.420) (Table 4), although this could only explain about 18% variance in the available data (R^2: 0.18) (Table S11). A multiple linear regression of removal efficiency with these two physicochemical properties was found as a significant predictor (R^2: 0.60; *P*-value <0.05) (Table S13).

In particular, the PhCs that have chlorine in their molecular structure (e.g., bezafibrate, clofibric acid, diclofenac, and furosemide) are considered recalcitrant to biodegradation. Most of these PhCs are very difficult to remove by CWs, and thus show low removal efficiencies (<50%) with the exception of furosemide (72%) (Tables 2 and 6). As mentioned above, molecular structure/weight plays an important role in the removal processes, although molecular weight did not show a statistically significant correlation with removal efficiency (r: −0.384 and R^2: 0.15) (Tables 4 and S12). Nevertheless, when molecular weight was included in the multiple linear regression with Log Koc and Log Dow, the result was the best possible model for predicting removal efficiency (R^2: 0.65; *P*-value <0.05) (Table S14), compared to when other physicochemical properties (water solubility, Log Kow, and pKa) were included in regression with Log Koc and Log Dow. A statistically significant model was also possible with four physicochemical properties but was not able to explain more variance compared with the best model. Therefore, we preferred a model with three variables, which was derived using the data of all types of examined CWs. The novel relationship developed in this study is given below and details on statistics are presented in Table S14.

$$RE = 96.16 - 14.18\,Log\,Koc - 3.72\,Log\,Dow - 0.03\,MW \quad (1)$$

where: *RE* is removal efficiency in % and *MW* is molecular weight in $g\,mol^{-1}$; *Log Koc* and *Log Dow* are already defined in this paper.

The other processes were found to be dominant only in very few PhCs such as photodegradation in the case of diclofenac, clarithromycin, and ketoprofen, and hydrolysis of furosemide. These processes also demonstrate low to moderate removal efficiencies of these PhCs (Tables 2 and 5).

The above insights clearly indicate the removal mechanisms in CWs and physicochemical properties of PhCs are simultaneously interacting in a complex manner, and resulting impacts on the removal of PhCs are highly variable in nature. The above-mentioned observations are supported in this paper by an in-depth analysis and discussion on 34 PhCs besides adding more insights. In the following sections, synthesis on 12 selected PhCs is presented, which shows the highest environmental risk (as mentioned in the previous section) including two of the four PhCs on the EU watch list (clarithromycin and erythromycin). Additionally, diclofenac (EU watch list) is also added in this section. Azithromycin is not discussed because sufficient data are not available for this PhC. A description

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

of the rest of the 21 PhCs is given in Supplementary Materials 7.

Analgesic/anti-inflammatory drugs

Diclofenac

The removal efficiency of diclofenac was moderate in HCW (56 ± 32%) and VFCW (50 ± 17%), and comparatively lower in FWSCW (42 ± 24%) and HFCW (39 ± 24%). It is suggested that the presence of chlorine in its structure (Table 6) makes it highly recalcitrant to biodegradation (Kimura *et al.* 2005). It is a hydrophobic compound (Log Kow = 4.51) with moderate molecular weight (296.15 g mol^{-1}) and anionic in nature under neutral conditions (pH = 7) (Table 6), which suggests the removal by adsorption onto soil particles following complex formation with metal ions, but its low distribution coefficient (Log Dow = 0.96) (Table 6) might restrict this removal pathway. However, its removal by adsorption has not been tested in adsorption experiments as well as it is not reported in CWs. Nevertheless, its low removal by plant uptake in hydroponic microcosm (4.4 ± 2.7%) explains that it is not a possible removal pathway (Zhang *et al.* 2012c, 2013b) (Figure 3 and Table S8). This was confirmed by Zhang *et al.* (2012c), who calculated the bioaccumulation factor (BAF) and reported that its BAF in the shoots was less than half (0.17–0.51) compared with BAF in the roots (0.40–1.36). This can be attributed to both its high hydrophobicity and relatively low water solubility (4.52 mg L^{-1} at 25 °C) (Table 6). It has been suggested that organic compounds with Log Kow > 3.5 have a high potential for retention in the plant roots (Dietz & Schnoor 2001). Therefore, the difference in the removal efficiency of planted and unplanted HFCW (50 ± 24% and 32 ± 16%, respectively) (Hijosa-Valsero *et al.* 2010a; Zhang *et al.* 2011, 2012a, 2018b; Carranza-Diaz *et al.* 2014; He *et al.* 2018) (Table S2), and planted and unplanted HCW (38% and 25%, respectively) (Hijosa-Valsero *et al.* 2010a) (Table S4) might be due to indirect positive effects of plants' presence such as degradation by enzymatic exudates as well as an increase in the amount of oxygen released by the plant roots in the rhizosphere which can support high microbial activity (biodegradation). However, in hydroponic microcosms it has been revealed that the contribution of biodegradation to its removal was low (3.0%) (Zhang *et al.* 2013b) (Figure 3 and Table S8). Its high removal by photodegradation was achieved in hydroponic microcosms (79 ± 2%) (Zhang *et al.* 2012c, 2013b) (Figure 3 and Table S8) and it was confirmed in the unplanted HCW system with a free water surface (FWS) on top of the horizontal flow filter (HFF) which provides the most appropriate environment for photodegradation (Reyes-Contreras *et al.* 2012). Its higher removal efficiency in unplanted HCW (29%) compared with planted HCW (1.7%) during summer was attributed to photodegradation (Reyes-Contreras *et al.* 2012).

Ibuprofen

The removal efficiency of ibuprofen was much higher in VFCW (79 ± 24%) but moderate in HCW (62 ± 29%), FWSCW (57 ± 28%), and HFCW (53 ± 27%). Its removal by plant uptake is expected to be low since it is hydrophobic (Log Kow = 3.97) and anionic, although slightly water soluble (41.05 mg L^{-1} at 25 °C) (Calderón-Preciado *et al.* 2011; Matamoros *et al.* 2012) (Table 6). This can be explained by its low plant uptake (0.4–5.0%) in the planted CWs (Figure 4 and Table S9) (Zhang *et al.* 2017a, 2017b). Therefore, the removal efficiency differences between the planted and unplanted hydroponic microcosms (78% and 30%, respectively) (Matamoros *et al.* 2012) (Figure 3 and Table S8), planted and unplanted HFCW (68 ± 25% and 41 ± 26%, respectively) (Dordio *et al.* 2010; Hijosa-Valsero *et al.* 2010a; Zhang *et al.* 2011, 2012a, 2018b; Reyes-Contreras *et al.* 2012; Carranza-Diaz *et al.* 2014; Li *et al.* 2016a, 2016b; He *et al.* 2018) (Table S2), and planted and unplanted HCW (64 ± 9% and 51 ± 11%, respectively) (Hijosa-Valsero *et al.* 2010a, 2011b; Reyes-Contreras *et al.* 2012) (Table S4) might be due to indirect effects of plants' presence such as enhancement in biodegradation (Matamoros *et al.* 2012). This can be seen by the high contribution of biodegradation to its removal in hydroponic microcosms (30%) (Matamoros *et al.* 2012) (Figure 3 and Table S8). Nevertheless, its detection in the plant leaves (*Typha angustifolia*) with an even distribution in the lamina and sheath tissues reveals the phytoextraction process for its removal as well. It had been taken up by the plant roots, which is translocated from the

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

roots to the leaves and accumulated in leaf tissues. For instance, its root uptake was partially transformed to carboxyibuprofen, 2-hydroxyibuprofen, and 1-hydroxyibuprofen in the sheath (1,375, 236, and 302 $\mu g\ kg^{-1}$, respectively) and in the lamina (1,051, 694, and 179 $\mu g\ kg^{-1}$, respectively). The accumulation of its metabolites in the plant leaves indicates its phytotransformation in the plant tissues (Li *et al.* 2016b). Although it has Log Kow < 4 and Log Dow < 2.5, its high sorption coefficient (Log Koc = 2.60) (Table 6) and anionic form under neutral pH conditions favors its adsorption onto soil particles following complexation with metal ions such as Ca^{2+}, Mg^{2+}, Fe^{3+}, or Al^{3+} (Berglund *et al.* 2014). This explains its removal by adsorption onto light expanded clay aggregates (LECA) (protonated under the same pH conditions) during adsorption experiments in aqueous solutions (93%) (Dordio *et al.* 2009a) (Figure 3 and Table S8). However, the positive charge of substrate surfaces might alter over time due to the development of negatively charged biofilms on substrate surfaces which might lead to its lower retention (Dordio *et al.* 2009a, 2010). This could be the reason for its low removal in adsorption experiments using different substrate media (13%) (Zhang *et al.* 2018a) (Figure 3 and Table S8) as well as in CWs by adsorption (0.5 ± 0.1%) (Zhang *et al.* 2017a, 2017b) (Figure 4 and Table S9).

Naproxen

The removal efficiency of naproxen was higher in VFCW (75 ± 17%) but moderate in HCW (64 ± 24%), HFCW (63 ± 26%), and FWSCW (50 ± 22%). Its slight water solubility (144.9 mg L^{-1} at 25 °C), moderate hydrophobicity (Log Kow = 3.18; Log Dow = 0.30), and anionic form (Table 6) might decrease its removal by plant uptake and its retention in the plant roots as well as adsorption to the substrate media. This can be explained by its low uptake by the plants in hydroponic microcosms (6.5 ± 1.3%) (Zhang *et al.* 2013b, 2013c) (Figure 3 and Table S8). Therefore, the higher removal efficiency in planted compared with unplanted HFCW (74 ± 26% and 50 ± 19%, respectively) (Hijosa-Valsero *et al.* 2010a; Zhang *et al.* 2011, 2012a, 2018b; Reyes-Contreras *et al.* 2012; Carranza-Diaz *et al.* 2014; Hijosa-Valsero *et al.* 2016; He *et al.* 2018) (Table S2) might be due the enhancement in biodegradation in the presence of plants, which can be seen by its higher removal through biodegradation (58 ± 1%) in hydroponic microcosms (Zhang *et al.* 2013b, 2013c) (Figure 3 and Table S8). Furthermore, its considerable removal by photodegradation (37 ± 12%) was achieved in hydroponic microcosms (Matamoros *et al.* 2012; Zhang *et al.* 2013b, 2013c) and its higher removal efficiency in the unplanted HCW (FWS on top of HFF) compared with planted HCW during summer was attributed to photodegradation (71 ± 4% and 59 ± 10%, respectively) (Reyes-Contreras *et al.* 2012; Hijosa-Valsero *et al.* 2016).

Salicylic acid

The removal efficiency of salicylic acid was higher in VFCW (98%) compared with HCW (86 ± 17%), HFCW (79 ± 21%), and FWSCW (76 ± 19%). The high water solubility (3.81 g L^{-1} at 25 °C), hydrophilic nature (Log Kow = 2.26; Log Dow = 1.79), and low molecular weight (138.12 g mol^{-1}) (Table 6) might decrease its retention in the plant roots as well as to the adsorption media but favors its uptake by the plants. Hijosa-Valsero *et al.* (2016) reported that in CWs its uptake by the roots was 0.2 $\mu g\ g^{-1}$, but in hydroponic systems, its higher concentration was observed in plants (2.5 $\mu g\ g^{-1}$) due to uptake by the roots compared with adsorption on the roots (<0.1 $\mu g\ g^{-1}$) in CWs as well as hydroponic systems. However, it has been reported that it is a phytohormone involved in plant growth, disease resistance, and response to environmental stresses and can be naturally found at concentrations of about 1.0 $\mu g\ g^{-1}$ fresh weight in vegetal tissues (Hayat *et al.* 2010). In addition, exogenous salicylic acid and its methylated forms can be rapidly absorbed and translocated by plants (Hayat *et al.* 2010). Some studies reported that its removal efficiency was not significantly different in planted and unplanted HFCW (81 ± 12% and 77 ± 17%, respectively) (Hijosa-Valsero *et al.* 2010a, 2016; Zhang *et al.* 2012a) (Table S2), and planted and unplanted HCW (88 ± 5% and 87 ± 8%, respectively) (Hijosa-Valsero *et al.* 2010a, 2016; Reyes-Contreras *et al.* 2012; Zhang *et al.* 2012a) (Table S4). Since it is anionic under neutral pH condition, the repulsion with the negatively charged biomembranes might restrict its removal by plant uptake. However, Hijosa-Valsero *et al.* (2011b) reported that it was not removed in unplanted

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

HCW but removed in planted HCW (29–97%) (Table S4). This removal by the planted system could be due to degradation by enzymatic exudates as well as biodegradation.

Analgesic

Acetaminophen

The removal efficiency of acetaminophen was higher in FWSCW (99%) and VFCW (97 ± 1%) compared with HCW (83 ± 25%) and HFCW (70 ± 24%). The high water solubility (30.4 g L^{-1} at 25 °C), high hydrophilicity (Log Kow = 0.46; Log Dow = 0.90), and low molecular weight (151.17 g mol^{-1}) (Table 6) suggest that adsorption is not its main removal mechanism in CWs (Vystavna *et al.* 2017). This can be explained by its low removal through media adsorption (laterite soil) (0.1 μg g^{-1}) at HRT of 6.0 days in VFCW (Koottatep *et al.* 2017) (Figure 4 and Table S9). It is neutral at pH = 7, as well as hydrophilic in nature, thus uptake by the plant might be through hydrogen bonding with water molecules (Dietz & Schnoor 2001). The removal by plant uptake was investigated by Li *et al.* (2017) and they reported that plants contributed to the removal of acetaminophen in FWSCW. For instance, its removal efficiency in the systems with and without plants was 98% and 84%, respectively. However, Koottatep *et al.* (2017) reported its negligible removal (0.04%) by plant uptake (Figure 4 and Table S9), which indicates that the removal difference between the planted and unplanted FWSCW might be due to the enhancement in biodegradation (Li *et al.* 2017), which is evident from the major contribution of biodegradation pathways (46%) to its removal in CWs (Koottatep *et al.* 2017; Li *et al.* 2017) (Figure 4 and Table S9). Furthermore, Koottatep *et al.* (2017) suggested that by-product transformation contributed up to 15% of its total removal (Table S9).

Antibiotics

Clarithromycin

The removal efficiency of clarithromycin was low and almost similar in VFCW (49 ± 57%), HCW (46 ± 9%), HFCW (45 ± 20%), and FWSCW (41 ± 21%). Although it is slightly hydrophobic (Log Kow = 3.16; Log Dow = 2.31) and cationic under neutral pH conditions, its removal by plant uptake cannot be considered due to its very high molecular weight (747.97 g mol^{-1}) and very low water solubility (0.342 mg L^{-1} at 25 °C) (Table 6). Therefore, no difference was observed in the removal efficiency of planted and unplanted HFCW (32% in both) (Hijosa-Valsero *et al.* 2011a) (Table S2). Its removal efficiency in unplanted HCW (FWS on top of HFF) was higher (52%) compared with planted HCW (40%) (Hijosa-Valsero *et al.* 2011a) (Table S4). The removal can be ascribed to photodegradation, since in FWS this is considered the main removal mechanism for PhCs' removal. The adsorption to the substrate and retention in the plant roots can be considered the dominant removal mechanisms considering its low water solubility and high molecular weight. Furthermore, it is present in the cationic form and has moderate sorption capacity (Log Koc = 2.17) (Table 6), which favors its removal by sorption due to electrostatic interactions with the predominantly negatively charged biofilm on the substrate (Zhang *et al.* 2014).

Erythromycin

The removal efficiency of erythromycin was higher in VFCW (89 ± 4%) and FWSCW (85 ± 16%) compared with HFCW (61 ± 25%). Its very high molecular weight (733.93 g mol^{-1}) and very low water solubility (0.517 mg L^{-1} at 25 °C) (Table 6) suggest that adsorption to the substrate and retention in the plant roots can be considered the dominant removal mechanisms. This is evident by the high contribution of adsorption (35%) to its total removal efficiency of 82% in HFCW (Chen *et al.* 2016a) (Figure 4). Since it is present in the cationic form with high sorption capacity (Log Koc = 2.75) (Table 6), its electrostatic interactions with the biofilm on the substrate recommend that sorption is a possible removal mechanism (Zhang *et al.* 2014). The slight hydrophobicity (Log Kow = 3.06) (Table 6) favors its uptake by the plant, but due to very low water solubility this process was not possible. However, in HFCW its removal (63%) was only achieved in the planted system indicating that its removal is favored by the presence of plants due to the improvement in

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

biodegradation (Hijosa-Valsero *et al.* 2011a) (Table S2). This is evidenced by the eminent contribution of biodegradation pathways (35%) to its total removal efficiency of 82% in HFCW (Chen *et al.* 2016a) (Figure 4 and Table S9).

Ofloxacin

The removal efficiency of ofloxacin was higher in HFCW (98 ± 4%) and VFCW (87 ± 10%). However, its removal was not achieved in FWSCW. Its moderate molecular weight (361.37 g mol^{-1}) and anionic form (Table 6) favor its adsorption to the substrate media. This can be seen by its complete removal (100%) in HFCW, 24% of which was removed by adsorption onto zeolite (Chen *et al.* 2016a) (Figure 4 and Table S9). Microporous structures in zeolite can provide a high surface area for chemical sorption and microbial attachment, while bridging hydroxyls (Si-OH) are catalytically active for various chemical reactions (Chen *et al.* 2016a). It is highly water soluble (28.3 g L^{-1} at 25 °C) and anionic or neutral at pH = 7, but due to less lipophilic characteristics (Log Kow = −0.39) (Table 6), the lower ability to partition into lipophilic cell structure hinders its removal by plant uptake in CWs. This can be seen by its low uptake by the plant (*Callitriche palustris*) (13 μg kg^{-1}) (Nuel *et al.* 2018) and low concentration in the plant leaves (*Cyperus alternifolius*) (7.4 ± 0.1 μg kg^{-1}) (Yan *et al.* 2016). However, its higher removal by planted HFCW and VFCW (Tables S2 and S3) indicates its removal by biodegradation. This is obvious by the major contribution of biodegradation pathways (67%) for its total removal efficiency (100%) in HFCW (Chen *et al.* 2016a) (Figure 4 and Table S9).

Oxytetracycline

The removal efficiency of oxytetracycline was higher and almost the same in FWSCW (97%) and VFCW (96 ± 4%). Its removal by adsorption to the substrate media can be considered due to its moderate molecular weight (460.43 g mol^{-1}), moderate sorption capacity (Log Koc = 1.87), and anionic form (Table 6), which favor adsorption onto soil particles following complex formation with metal ions (Berglund *et al.* 2014; Huang *et al.* 2017). Huang *et al.* (2017) reported that its removal was affected by substrate type. The brick particles-based media showed stronger removal capacities compared with oyster shell, which can be attributed to the larger porosity and average micropore size, and high percentage of crystalline iron oxide in brick particle (Fe_2O_3, 32%). Furthermore, its adsorption to LECA (89%) has been observed in unplanted VFCW (Dordio & Carvalho 2013) (Figure 4 and Table S9). Its uptake by the plants can be attributed to its high water solubility (1.4 g L^{-1} at 25 °C) and moderate hydrophilicity (Log Kow = 1.22) (Table 6), which is obvious by its higher removal efficiency in the planted VFCW (97%) compared with unplanted VFCW (89%) (Dordio & Carvalho 2013) (Figure 4 and Table S9). However, the enhancement in removal in the presence of plants might be due to the improvement in biodegradation (Dordio & Carvalho 2013).

Sulfadiazine

The removal efficiency of sulfadiazine was moderate in FWSCW (61 ± 35%) and VFCW (52 ± 22%) but low in HFCW (46 ± 30%). Adsorption to the substrate cannot be considered its main removal mechanism in CWs due to its high water solubility (28.14 g L^{-1} at 25 °C) and very low hydrophobicity (Log Kow = −0.09), although its molecular weight is moderate (250.28 g mol^{-1}) (Table 6). This can be seen by the non-significant difference in the removal efficiency between HFCW and FWSCW in winter (19 ± 2% and 19 ± 5%, respectively) which represented full substrate system and half substrate system, respectively (Dan *et al.* 2013) (Tables S1 and S2). Similarly, although its sorption capacity is moderate (Log Koc = 1.87), due to its neutral or anionic nature under neutral pH conditions (Table 6), its binding to biomass through cation exchange with anionic sites is also likely to be minimal (Dan *et al.* 2013). However, it is highly water soluble, but its less lipophilic character (very low Log Kow) obstructs its removal by plant uptake in CWs. Nevertheless, Xian *et al.* (2010) reported that planted FWSCW performed better than the unplanted FWSCW (99% and 91%, respectively) (Table S1), which might be due to enhanced biodegradation. This can be explained by its higher removal efficiency in HFCW (72 ± 7%) compared with FWSCW (55 ± 3%) during summer (high temperature enhanced biodegradation) (Dan *et al.*

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

2013) (Tables S1 and S2), since substrates provide a surface area suitable for the growth of microorganisms and the formation of biofilm (Dan *et al.* 2013).

Sulfamethazine

The removal efficiency of sulfamethazine was moderate in HCW (74%) and FWSCW (53 ± 48%) but lower in HFCW (45 ± 27%) and VFCW (28 ± 27%). The high water solubility (11.24 g L^{-1} at 25 °C) and high hydrophilicity (Log Kow = 0.89; Log Dow = 0.79) do not favor its adsorption to the substrate in CWs, although its molecular weight is moderate (278.33 g mol^{-1}) (Table 6). Similarly, although its sorption capacity is moderate (Log Koc = 2.28), due to its neutral or anionic nature (Table 6), its binding to biomass (sorption) is also likely to be negligible (Dan *et al.* 2013). This is evident by its removal in HFCW using different substrate materials (oyster shell, zeolite, medical stone, and ceramic), and it was below the limit of detection in substrate media (Chen *et al.* 2016a) (Figure 4 and Table S9). Analogous to that, Liu *et al.* (2014), reported its low concentration in the soil (0.8–27 μg kg^{-1}) and oyster shell (1.2–10 μg kg^{-1}) of CWs. However, high water solubility, low Log Kow, and neutral form favor its removal by plant uptake and biodegradation. This is made explicit by the major contribution of biodegradation pathways (31%) to its total removal efficiency of 52% in HFCW (Chen *et al.* 2016a) (Figure 4 and Table S9) and slight difference in removal efficiency (~4.5%) in planted and unplanted FWSCW (>99% and 95%, respectively) (Xian *et al.* 2010) (Table S1).

Sulfamethoxazole

The removal efficiency of sulfamethoxazole was moderate in HCW (61 ± 31%) and FWSCW (54 ± 29%) and VFCW (54 ± 29%) but lower in HFCW (43 ± 24%). Adsorption to the substrate cannot be considered its removal mechanism due to its high water solubility (3.94 g L^{-1} at 25 °C) and high hydrophilicity (Log Kow = 0.89), although its molecular weight is moderate (253.28 g mol^{-1}) (Table 6). Additionally, due to its neutral or anionic form (Table 6), its binding to biomass is likely to be minimal, although it has moderate sorption capacity (Log Koc = 2.41) (Dan *et al.* 2013). This can be seen by non-significant difference in its removal efficiency between hydroponic system and FWSCW (planted and gravel bed) (38% and 35%, respectively) (Hijosa-Valsero *et al.* 2011a). Similarly, Zhu & Chen (2014) reported its slight sorption to the sludge (19–43 μg kg^{-1}) in HCW. Its high water solubility, hydrophilic character, and neutral form (Table 6) suggest its uptake by the plants in CWs. This is made explicit by its better removal efficiency in the planted compared with the unplanted FWSCW (92% and 73%, respectively) (Xian *et al.* 2010) (Table S1), and planted compared with unplanted HFCW (71% and 46%, respectively) (Hijosa-Valsero *et al.* 2011a) (Table S2). However, in planted and unplanted VFCW, its complete removal (100%) was achieved (Button *et al.* 2019) (Table S3) and in planted and unplanted HCW its removal efficiency was 58% and 61%, respectively (Hijosa-Valsero *et al.* 2011a) (Table S4), which indicates that in planted CWs direct uptake by the plants is minimal due to its low Log Kow, but the plants also support biodegradation (Choi *et al.* 2016; Liang *et al.* 2018). This is evident by the major contribution of biodegradation pathways (68%) to its total removal of 71% in hydroponic systems (Choi *et al.* 2016) (Figure 3 and Table S8). In unplanted CWs, the removal may be because the substrates provide a surface area suitable for the growth of microorganisms and the formation of biofilm for biodegradation (Dan *et al.* 2013; Choi *et al.* 2016). This is obvious by its higher removal in biotic systems (73%) compared with abiotic systems (67%) during a soil adsorption experiment under biotic and abiotic conditions (Choi *et al.* 2016). Furthermore, Choi *et al.* (2016) investigated the possibility of photodegradation and observed 23% of its removal by this process in a photodegradation experiment (Figure 3 and Table S8). Thus, a slightly higher increase in the removal efficiency by unplanted HCW (FWS on top of HFF) compared with planted HCW indicates that photodegradation might contribute to its removal (Hijosa-Valsero *et al.* 2011a).

Lipid regulators

Gemfibrozil

The removal efficiency of gemfibrozil was higher in HCW (95%), moderate in HFCW (58 ± 23%) but low in VFCW

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

(45 ± 9%) and FWSCW (12 ± 2%). Its high hydrophobicity (Log Kow = 4.77), low water solubility (4.964 mg L^{-1} at 25 °C), moderate molecular weight (250.33 g mol^{-1}), high sorption coefficient (Log Koc = 2.636), and anionic form under neutral conditions (pH = 7) (Table 6) favors its adsorption onto soil particles following complexation with metal ions. However, its adsorption to substrate as one of its removal pathways has not been reported by any of the reviewed studies which investigated its removal (Tables S1–S4). Furthermore, its low to moderate removal in most of the cases indicates its lower retention due to the development of negatively charged biofilms on substrate surfaces over time (Dordio *et al.* 2009a, 2010), which might obstruct its binding to biomass. Similarly, due to its anionic nature, uptake by the plants cannot be considered one of its dominant removal mechanisms in CWs. This might be the reason that Nuel *et al.* (2018) did not observe its uptake by any of the studied plants in FWSCW (*Salix alba*, *Callitriche palustris*, *Carex caryophyllea*, *Juncus effusus*, *Iris pseudacorus*). However, its higher removal efficiency was observed in planted compared with unplanted HFCW (58 ± 18% and 49 ± 13%, respectively) (Table S2) and planted and unplanted VFCW (50 ± 11% and 40 ± 3%, respectively) (Table S3) by Zhang *et al.* (2018b). The higher removal in planted systems might be due to the positive effects of plants' presence such as biodegradation. Several studies attributed its removal to biodegradation (Table 4), which can be seen by its higher removal efficiency in summer compared with winter (42 ± 25% and 32 ± 15%, respectively) due to the enhancement in biodegradation in the warm season (Zhang *et al.* 2018b).

CONCLUSIONS

CWs have been investigated for the treatment of wastewater for traditional parameters as well as the removal of PhCs. The large number of published studies provided the foundation of this comprehensive assessment, which is based on critical review of the literature and statistical analysis of data gathered from peer-reviewed studies. Thus, a novel database was compiled in this study, which included influent and effluent concentrations, removal efficiency, and removal rate of PhCs from the information of 260 CWs that were reported in 66 peer-reviewed journal publications with case studies from 19 countries for the removal of 148 PhCs grouped into 33 categories according to their therapeutic classes and 25 TPs. Additionally, the environmental risk posed by a number of PhCs and the contribution of CWs to their risk reduction was evaluated. Finally, the role of physicochemical properties of PhCs was examined, and the available evidence from experimental studies on the major removal mechanisms was comprehensively and critically assessed and summarized. The following specific conclusions were inferred from this research.

A very high range of variability in the influent and effluent concentrations, and removal efficiencies exist among the studied PhCs across the case study regions around the world. While CWs could effectively remove most of the PhCs and their metabolites, some cases of negative removal also occur. However, despite large variability, CWs have demonstrated their capability to effectively and efficiently remove a large number of PhCs from wastewater (e.g., 96 out of 113 compounds or 85% of the sample show a positive removal efficiency). An in-depth analysis of the 34 most widely studied PhCs indicated a moderate to high potential of CWs for the removal of monensin, ofloxacin, oxytetracycline, sulfapyridine, caffeine, salicylic acid, atenolol, furosemide, doxycycline, codeine, diltiazem, acetaminophen, naproxen, ibuprofen, metoprolol, and sulfadiazine.

There is an encouraging trend in studies related to ecological risk assessment posed by PhCs, which should be continued to enhance the available knowledge. The available evidence revealed that CWs could considerably reduce the environmental risk posed by PhCs. However, the risk is not fully eliminated by CWs, although significantly reduced in most cases. Based on this analysis, and on data from several countries, a number of PhCs could be classified under the high risk category: oxytetracycline, ofloxacin, sulfamethoxazole, erythromycin, sulfadiazine, gemfibrozil, ibuprofen, acetaminophen, salicylic acid, sulfamethazine, naproxen, and clarithromycin. These high risk PhCs could be considered for regulatory monitoring, water quality standard formulation, and control purposes. For instance, the EU watch list of four PhCs (azithromycin, clarithromycin, erythromycin, and diclofenac) could be enhanced by considering these PhCs. Since this analysis is based on several countries across the world, these

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

assessments could also inform the WHO's global guidelines on PhCs. However, it is recognized that in-depth studies are essential for a specific water and environmental context to establish risk and consequent monitoring and management actions.

The most widely reported mechanism for PhCs' removal in CWs is biodegradation (aerobic and anaerobic). The other notable mechanisms are adsorption/sorption, plant uptake (planted CWs), and photodegradation (FWSCW). Most readily biodegradable PhCs and the ones removed via several mechanisms are likely to demonstrate the highest removal efficiencies. In contrast, most of the PhCs reveal moderate to low removal efficiency when one of their most dominant removal mechanisms is adsorption, photodegradation, or plant uptake. The role of physicochemical properties of PhCs is pivotal in the removal processes. Among the studied properties, Log Koc, Log Dow, and molecular weight could (together) explain about 65% of the variance in the removal efficiency. Thus, these three factors could be seen as important predictors of removal efficiency of PhCs, and therefore, could contribute to a screening process for potential removal of PhCs by CWs. Finally, an optimal design of CWs and other wastewater treatment technologies must be underpinned by the evidence-based scientific knowledge on the compound-specific variability in removal efficiency, complexity of governing physicochemical properties and removal mechanisms of the targeted PhCs in a specific environmental context.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this paper is available online at https://dx.doi.org/10.2166/wh.2020.213.

REFERENCES

Acero, J. L., Benitez, F. J., Real, F. J. & Roldan, G. 2010 Kinetics of aqueous chlorination of some pharmaceuticals and their elimination from water matrices. *Water Research* **44** (14), 4158–4170.

Alvarez, D. A., Petty, J. D., Huckins, J. N., Jones-Lepp, T. L., Getting, D. T., Goddard, J. P. & Manahan, S. E. 2004 Development of a passive, in situ, integrative sampler for hydrophilic organic contaminants in aquatic environments. *Environmental Toxicology and Chemistry* **23** (7), 1640–1648.

Auvinen, H., Havran, I., Hubau, L., Vanseveren, L., Gebhardt, W., Linnemann, V., Oirschot, D. V., Laing, G. D. & Rousseau, D. P. L. 2017a Removal of pharmaceuticals by a pilot aerated sub-surface flow constructed wetland treating municipal and hospital wastewater. *Ecological Engineering* **100**, 157–164.

Auvinen, H., Gebhardt, W., Linnemann, V., Laing, G. D. & Rousseau, D. P. L. 2017b Laboratory- and full-scale studies on the removal of pharmaceuticals in an aerated constructed wetland: effects of aeration and hydraulic retention time on the removal efficiency and assessment of the aquatic risk. *Water Science and Technology* **76** (6), 1457–1465.

Ávila, C., Pedescoll, A., Matamoros, V., Bayona, J. M. & García, J. 2010 Capacity of a horizontal subsurface flow constructed wetland system for the removal of emerging pollutants: an injection experiment. *Chemosphere* **81**, 1137–1142.

Ávila, C., Reyes, C., Bayona, J. M. & García, J. 2013 Emerging organic contaminant removal depending on primary treatment and operational strategy in horizontal subsurface flow constructed wetlands: influence of redox. *Water Research* **47**, 315–325.

Ávila, C., Nivala, J., Olsson, L., Kassa, K., Headley, T., Mueller, R. A., Bayona, J. M. & García, J. 2014a Emerging organic contaminants in vertical subsurface flow constructed wetlands: influence of media size, loading frequency and use of active aeration. *Science of the Total Environment* **494–495**, 211–217.

Ávila, C., Matamoros, V., Reyes-Contreras, C., Piña, B., Casado, M., Mita, L., Rivetti, C., Barata, C., García, J. & Bayona, J. M. 2014b Attenuation of emerging contaminants in a hybrid constructed wetland system under different hydraulic loading rates and their associated toxicological effects in wastewater. *Science of the Total Environment* **470–471**, 1272–1280.

Ávila, C., Bayona, J. M., Martín, I., Salas, J. J. & García, J. 2015 Emerging organic contaminant removal in a full-scale hybrid constructed wetland system for wastewater treatment and reuse. *Ecological Engineering* **80**, 108–116.

Barbosa, M. O., Moreira, N. F. F., Ribeiro, A. R., Pereira, M. F. R. & Silva, A. M. T. 2016 Occurrence and removal of organic micropollutants: an overview of the watch list of EU Decision 2015/495. *Water Research* **94**, 257–279.

Benitez, F. J., Acero, J. L., Real, F. J., Roldan, G. & Casas, F. 2011 Comparison of different chemical oxidation treatments for the removal of selected pharmaceuticals in water matrices. *Chemical Engineering Journal* **168** (3), 1149–1156.

Berglund, B., Khan, G. A., Weisner, S. E. B., Ehde, P. M., Fick, J. & Lindgren, P.-E. 2014 Efficient removal of antibiotics in surface-flow constructed wetlands, with no observed impact on antibiotic resistance genes. *Science of the Total Environment* **476–477**, 29–37.

Breitholtz, M., Näslund, M., Stråe, D., Borg, H., Grabic, R. & Fick, J. 2012 An evaluation of free water surface wetlands as tertiary sewage water treatment of micro-pollutants. *Ecotoxicology and Environmental Safety* **78**, 63–71.

Březinova, T. D., Vymazal, J., Koželuh, M. & Kule, L. 2018 Occurrence and removal of ibuprofen and its metabolites in

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

full-scale constructed wetlands treating municipal wastewater. *Ecological Engineering* **120**, 1–5.

Briggs, G. G., Bromilow, R. H. & Evans, A. A. 1983 Relationships between lipophilicity and root uptake and translocation of non-ionized chemicals by barley. *Pesticide Science* **13**, 495–500.

Burken, J. G. & Schnoor, J. L. 1998 Predictive relationships for uptake of organic contaminants by hybrid polar trees. *Environmental Science and Technology* **32**, 3379–3385.

Button, M., Cosway, K., Sui, J. & Weber, K. 2019 Impacts and fate of triclosan and sulfamethoxazole in intensified re-circulating vertical flow constructed wetlands. *Science of the Total Environment* **649**, 1017–1028.

Calderón-Preciado, D., Matamoros, V. & Bayona, J. M. 2011 Occurrence and potential crop uptake of emerging contaminants and related compounds in an agricultural irrigation network. *Science of the Total Environment* **412–413**, 14–19.

Caliman, F. A. & Gavrilescu, M. 2009 Pharmaceuticals, personal care products and endocrine disrupting agents in the environment-a review. *Clean* **37** (4–5), 277–303.

Carranza-Diaz, O., Schultze-Nobre, L., Moeder, M., Nivala, J., Kuschk, P. & Koeser, H. 2014 Removal of selected organic micropollutants in planted and unplanted pilot-scale horizontal flow constructed wetlands under conditions of high organic load. *Ecological Engineering* **71**, 234–245.

Carvalho, P. N., Basto, M. C. P., Almeida, C. M. R. & Brix, H. 2014 A review of plant–pharmaceutical interactions: from uptake and effects in crop plants to phytoremediation in constructed wetlands. *Environmental Science and Pollution Research* **21** (20), 11729–11763.

Chen, J., Wei, X.-D., Liu, Y.-S., Ying, G.-G., Liu, S.-S., He, L.-Y., Su, H.-C., Hu, L.-X., Chen, F.-R. & Yang, Y.-Q. 2016a Removal of antibiotics and antibiotic resistance genes from domestic sewage by constructed wetlands: optimization of wetland substrates and hydraulic loading. *Science of the Total Environment* **565**, 240–248.

Chen, Y., Vymazal, J., Březinová, T., Koželuh, M., Kule, L., Huang, J. & Chen, Z. 2016b Occurrence, removal and environmental risk assessment of pharmaceuticals and personal care products in rural wastewater treatment wetlands. *Science of the Total Environment* **566–567**, 1660–1669.

Choi, Y.-J., Kim, L.-H. & Zoh, K.-D. 2016 Removal characteristics and mechanism of antibiotics using constructed wetlands. *Ecological Engineering* **91**, 85–92.

Cleuvers, M. 2003 Aquatic ecotoxicity of pharmaceuticals including the assessment of combination effects. *Toxicology Letters* **142**, 185–194.

Conkle, J., White, J. R. & Metcalfe, C. D. 2008 Reduction of pharmaceutically active compounds by a lagoon wetland wastewater treatment system in Southeast Louisiana. *Chemosphere* **73** (11), 1741–1748.

Dan, A., Yang, Y., Dai, Y.-n., Chen, C.-x., Wang, S.-y. & Tao, R. 2013 Removal and factors influencing removal of sulfonamides and trimethoprim from domestic sewage in constructed wetlands. *Bioresource Technology* **146**, 363–370.

Dettenmaier, E. M., Doucette, W. J. & Bugbee, B. 2009 Chemical hydrophobicity and uptake by plant roots. *Environmental Science and Technology* **43**, 324–329.

Dietz, A. C. & Schnoor, J. L. 2001 Advances in phytoremediation. *Environmental Health Perspectives* **109**, 163–168.

Dordio, A. & Carvalho, A. J. P. 2013 Constructed wetlands with light expanded clay aggregates for agricultural wastewater treatment. *Science of the Total Environment* **463–464**, 454–461.

Dordio, A. V., Candeias, A. J. E., Pinto, A. P., da Costa, C. T. & Carvalho, A. J. P. 2009a Preliminary media screening for application in the removal of clofibric acid, carbamazepine and ibuprofen by SSF-constructed wetlands. *Ecological Engineering* **35**, 290–302.

Dordio, A. V., Duarte, C., Barreiros, M., Carvalho, A. J. P., Pinto, A. P. & da Costa, C. T. 2009b Toxicity and removal efficiency of pharmaceutical metabolite clofibric acid by Typha spp. - potential use for phytoremediation? *Bioresource Technology* **100**, 1156–1161.

Dordio, A. V., Carvalho, A. J. P., Teixeira, D. M., Dias, C. B. & Pinto, A. P. 2010 Removal of pharmaceuticals in microcosm constructed wetlands using Typha Spp. and LECA. *Bioresource Technology* **101**, 886–892.

European Centre for Ecotoxicology and Toxicology of Chemical (ECETOC). Technical report, 123, Log Dow. Available from: http://www.ecetoc.org/report/estimated-partitioning-property-data/computational-methods/logdow/ (accessed 26/06/2019).

Finley, R. L., Collignon, P., Larsson, D. G., McEwen, S. A., Li, X. Z., Gaze, W. H., Reid-Smith, R., Timinouni, M., Graham, D. W. & Topp, E. 2013 The scourge of antibiotic resistance: the important role of the environment. *Clinical Infectious Diseases* **57** (5), 704–710.

Francini, A., Mariotti, L., Gregorio, S. D., Sebastiani, L. & Andreucci, A. 2018 Removal of micro-pollutants from urban wastewater by constructed wetlands with *Phragmites australis* and *Salix matsudana*. *Environmental Science and Pollution Research* **25** (36), 36474–36484.

Giulia, C., Maura, V., Giuseppe, E., Gilles, H. G., Yuriy, A. A., Laurence, P. & Marina, S. 2016 A fast chromatographic method for estimating lipophilicity and ionization in nonpolar membrane-like environment. *Molecular Pharmaceutics* **13** (3), 1100–1110.

Gorito, A. M., Ribeiro, A. R., Almeida, C. M. R. & Silva, A. M. T. 2017 A review on the application of constructed wetlands for the removal of priority substances and contaminants of emerging concern listed in recently launched EU legislation. *Environmental Pollution* **227**, 428–443.

Gros, M., Petrovic, M., Ginebreda, A. & Barceló, D. 2010 Removal of pharmaceuticals during wastewater treatment and environmental risk assessment using hazard indexes. *Environment International* **36**, 15–26.

Hayat, Q., Hayat, S., Irfan, M. & Ahmad, A. 2010 Effect of exogenous salicylic acid under changing environment: a review. *Environmental and Experimental Botany* **68** (1), 14–25.

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

He, Y., Sutton, N. B., Lei, Y., Rijnaarts, H. H. M. & Langenhoff, A. A. M. 2018 Fate and distribution of pharmaceutically active compounds in mesocosm constructed wetlands. *Journal of Hazardous Materials* **357**, 198–206.

Hernando, M. D., Mezcua, M., Fernández-Alba, A. R. & Barceló, D. 2006 Environmental risk assessment of pharmaceutical residues in wastewater effluents, surface waters and sediments. *Talanta* **69** (2), 334–342.

Hijosa-Valsero, M., Matamoros, V., Sidrach-Cardona, R., Martin-Villacorta, J., Becares, E. & Bayona, J. M. 2010a Comprehensive assessment of the design configuration of constructed wetlands for the removal of pharmaceuticals and personal care products from urban wastewaters. *Water Research* **44**, 3669–3678.

Hijosa-Valsero, M., Matamoros, V., Martin-Villacorta, J., Becares, E. & Bayona, J. M. 2010b Assessment of full-scale natural systems for the removal of PPCPs from wastewater in small communities. *Water Research* **44**, 1429–1439.

Hijosa-Valsero, M., Fink, G., Schlüsener, M. P., Sidrach-Cardona, R., Martín-Villacorta, J., Ternes, T. & Bécares, E. 2011a Removal of antibiotics from urban wastewater by constructed wetland optimization. *Chemosphere* **83**, 713–719.

Hijosa-Valsero, M., Matamoros, V., Pedescoll, A., Martín-Villacorta, J., Bécares, E., García, J. & Bayona, J. M. 2011b Evaluation of primary treatment and loading regimes in the removal of pharmaceuticals and personal care products from urban wastewaters by subsurface-flow constructed wetlands. *International Journal of Environmental Analytical Chemistry* **91** (7–8), 632–653.

Hijosa-Valsero, M., Sidrach-Cardona, R., Martín-Villacorta, J., Valsero-Blanco, M. C., Bayona, J. M. & Bécares, E. 2011c Statistical modelling of organic matter and emerging pollutants removal in constructed wetlands. *Bioresource Technology* **102**, 4981–4988.

Hijosa-Valsero, M., Reyes-Contreras, C., Domínguez, C., Bécares, E. & Bayona, J. M. 2016 Behaviour of pharmaceuticals and personal care products in constructed wetland compartments: influent, effluent, pore water, substrate and plant roots. *Chemosphere* **145**, 508–517. Available from: https://www.sciencedirect.com/science/journal/00456535/145/supp/C.

Hollender, J., Zimmermann, S. G., Koepke, S., Krauss, M., McArdell, C. S., Ort, C., Singer, H., von Gunten, U. & Siegrist, H. 2009 Elimination of organic micropollutants in a municipal wastewater treatment plant upgraded with a full-scale post-ozonation followed by sand filtration. *Environmental Science and Technology* **43** (20), 7862–7869.

Huang, X., Zheng, J., Liu, C., Liu, L., Liu, Y. & Fan, H. 2017 Removal of antibiotics and resistance genes from swine wastewater using vertical flow constructed wetlands: effect of hydraulic flow direction and substrate type. *Chemical Engineering Journal* **308**, 692–699.

Huber, M. M., Göbel, A., Joss, A., Hermann, N., Loffler, D., McArdell, C. S., Ried, A., Siegrist, H., Ternes, T. A. & von Gunten, U. 2005 Oxidation of pharmaceuticals during ozonation of municipal wastewater effluents: a pilot study. *Environmental Science and Technology* **39**, 4290–4299.

Ilyas, H. & Masih, I. 2017a The performance of the intensified constructed wetlands for organic matter and nitrogen removal: a review. *Journal of Environmental Management* **198** (1), 372–383.

Ilyas, H. & Masih, I. 2017b Intensification of constructed wetlands for land area reduction: a review. *Environmental Science and Pollution Research* **24** (13), 12081–12091.

Ilyas, H. & Masih, I. 2018 The effects of different aeration strategies on the performance of constructed wetlands for phosphorus removal. *Environmental Science and Pollution Research* **25** (6), 5318–5335.

Ilyas, H. & van Hullebusch, E. D. 2019 Role of design and operational factors in the removal of pharmaceuticals by constructed wetlands. *Water* **11** (11), 2356, 1–24.

Ilyas, H. & van Hullebusch, E. D. 2020 Performance comparison of different types of constructed wetlands for the removal of pharmaceuticals and their transformation products: a review. *Environmental Science and Pollution Research*. https://doi.org/10.1007/s11356-020-08165-w.

Imfeld, G., Braeckevelt, M., Kuschk, P. & Richnow, H. H. 2009 Monitoring and assessing processes of organic chemicals removal in constructed wetlands, a review. *Chemosphere* **74**, 349–362.

Kadlec, R. H. & Wallace, S. D. 2009 *Treatment Wetlands*, 2nd edn. CRC Press, Boca Raton, FL, USA.

Kahl, S., Nivala, J., Afferden, M. V., Müller, R. A. & Reemtsma, T. 2017 Effect of design and operational conditions on the performance of subsurface flow treatment wetlands: emerging organic contaminants as indicators. *Water Research* **125**, 490–500.

Kimura, K., Hara, H. & Watanabe, Y. 2005 Removal of pharmaceutical compounds by submerged membrane bioreactors (MBRs). *Desalination* **178**, 135–140.

Koottatep, T., Phong, V. H. N., Chapagain, S. K., Panuvatvanich, A., Polprasert, C. & Ahn, K.-H. 2017 Potential of laterite soil coupling Fenton reaction in acetaminophen (ACT) removal in constructed wetlands. *Water, Air, and Soil Pollution* **228**, 283.

Kosma, C. I., Lambropoulou, D. A. & Albanis, T. A. 2014 Investigation of PPCPs in wastewater treatment plants in Greece: occurrence, removal and environmental risk assessment. *Science of the Total Environment* **466–467**, 421–438.

Lee, S., Kang, S., Lim, J., Huh, Y. J., Kim, K. & Cho, J. 2011 Evaluating controllability of pharmaceuticals and metabolites in biologically engineered processes, using corresponding octanol-water distribution coefficient. *Ecological Engineering* **37**, 1595–1600.

Le-Minh, N., Khan, S. J., Drewes, J. E. & Stuetz, R. M. 2010 Fate of antibiotics during municipal water recycling treatment processes. *Water Research* **44** (15), 4295–4323.

Li, Y., Zhu, G., Ng, W. J. & Tan, S. K. 2014 A review on removing pharmaceutical contaminants from wastewater by

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

constructed wetlands: design, performance and mechanism. *Science of the Total Environment* **468–469**, 908–932.

Li, Y., Wu, B., Zhu, G., Liu, Y., Ng, W. J., Appan, A. & Tan, S. K. 2016a High-throughput pyrosequencing analysis of bacteria relevant to cometabolic and metabolic degradation of ibuprofen in horizontal subsurface flow constructed wetlands. *Science of the Total Environment* **562**, 604–613.

Li, Y., Zhang, J., Zhu, G., Liu, Y., Wu, B., Ng, W. J., Appan, A. & Tan, S. K. 2016b Phytoextraction, phytotransformation and rhizodegradation of ibuprofen associated with *Typha angustifolia* in a horizontal subsurface flow constructed wetland. *Water Research* **102**, 294–304.

Li, J., Zhou, Q. & Campos, L. C. 2017 Removal of selected emerging PPCP compounds using greater duckweed (*Spirodela polyrhiza*) based lab-scale free water constructed wetland. *Water Research* **126**, 252–261.

Liang, Y., Zhu, H., Bañuelos, G., Shutes, B., Yan, B. & Cheng, X. 2018 Removal of sulfamethoxazole from salt-laden wastewater in constructed wetlands affected by plant species, salinity levels and co-existing contaminants. *Chemical Engineering Journal* **341**, 462–470.

Lipp, P., Gross, H. G. & Tiehm, A. 2012 Improved elimination of organic micropollutants by a process combination of membrane bioreactor (MBR) and powdered activated carbon (PAC). *Desalination and Water Treatment* **42** (1–3), 65–72.

Liu, L., Liu, Y.-H., Wang, Z., Liu, C.-X., Huang, X. & Zhu, G.-F. 2014 Behavior of tetracycline and sulfamethazine with corresponding resistance genes from swine wastewater in pilot-scale constructed wetlands. *Journal of Hazardous Materials* **278**, 304–310.

Luo, Y., Guo, W., Ngo, H. H., Nghiem, L. D., Hai, F. I., Zhang, J., Liang, S. & Wang, X. C. 2014 A review on the occurrence of micropollutants in the aquatic environment and their fate and removal during wastewater treatment. *Science of the Total Environment* **473–474**, 619–641.

Macci, C., Peruzzi, E., Doni, S., Iannelli, R. & Masciandaro, G. 2015 Ornamental plants for micro-pollutant removal in wetland systems. *Environmental Science and Pollution Research* **22** (4), 2406–2415.

Matamoros, V. & Bayona, J. M. 2006 Elimination of pharmaceuticals and personal care products in subsurface flow constructed wetlands. *Environmental Science and Technology* **40**, 5811–5816.

Matamoros, V. & Salvadó, V. 2012 Evaluation of the seasonal performance of a water reclamation pond-constructed wetland system for removing emerging contaminants. *Chemosphere* **86** (2), 111–117.

Matamoros, V., García, J. & Bayona, J. M. 2005 Behavior of selected pharmaceuticals in subsurface flow constructed wetlands: a pilot-scale study. *Environmental Science and Technology* **39**, 5449–5454.

Matamoros, V., Arias, C., Brix, H. & Bayona, J. M. 2007 Removal of pharmaceuticals and personal care products (PPCPs) from urban wastewater in a pilot vertical flow constructed wetland and a sand filter. *Environmental Science and Technology* **41**, 8171–8177.

Matamoros, V., García, J. & Bayona, J. M. 2008a Organic micropollutant removal in a full-scale surface flow constructed wetland fed with secondary effluent. *Water Research* **42** (3), 653–660.

Matamoros, V., Caselles-Osorio, A., García, J. & Bayona, J. M. 2008b Behaviour of pharmaceutical products and biodegradation intermediates in horizontal subsurface flow constructed wetland. A microcosm experiment. *Science of the Total Environment* **394**, 171–176.

Matamoros, V., Hijosa, M. & Bayona, J. M. 2009 Assessment of the pharmaceutical active compounds removal in wastewater treatment systems at enantiomeric level. Ibuprofen and naproxen. *Chemosphere* **75**, 200–205.

Matamoros, V., Nguyen, L. X., Arias, C. A., Salvadó, V. & Brix, H. 2012 Evaluation of aquatic plants for removing polar microcontaminants: a microcosm experiment. *Chemosphere* **88**, 1257–1264.

Matamoros, V., Rodríguez, Y. & Albaigés, J. 2016 A comparative assessment of intensive and extensive wastewater treatment technologies for removing emerging contaminants in small communities. *Water Research* **88**, 777–785.

Matamoros, V., Rodríguez, Y. & Bayona, J. M. 2017 Mitigation of emerging contaminants by full-scale horizontal flow constructed wetlands fed with secondary treated wastewater. *Ecological Engineering* **99**, 222–227.

Michael, I., Rizzo, L., McArdell, C. S., Manaia, C. M., Merlin, C., Schwartz, T., Dagot, C. & Fatta-Kassinos, D. 2013 Urban wastewater treatment plants as hotspots for the release of antibiotics in the environment: a review. *Water Research* **47**, 957–995.

Nivala, J., Kahl, S., Boog, J., Afferden, M., Reemtsma, T. & Müller, R. A. 2019 Dynamics of emerging organic contaminant removal in conventional and intensified subsurface flow treatment wetlands. *Science of the Total Environment* **649**, 1144–1156.

Nuel, M., Laurent, J., Bois, P., Heintz, D. & Wanko, A. 2018 Seasonal and ageing effect on the behaviour of 86 drugs in a full-scale surface treatment wetland: removal efficiencies and distribution in plants and sediments. *Science of the Total Environment* **615**, 1099–1109.

Papaevangelou, V. A., Gikas, G. D., Tsihrintzis, V. A., Antonopoulou, M. & Konstantinou, I. K. 2016 Removal of endocrine disrupting chemicals in HSF and VF pilot-scale constructed wetlands. *Chemical Engineering Journal* **294**, 146–156.

Park, J., Cho, K. H., Lee, E., Lee, S. & Cho, J. 2018 Sorption of pharmaceuticals to soil organic matter in a constructed wetland by electrostatic interaction. *Science of the Total Environment* **635**, 1345–1350.

Petrie, B., Rood, S., Smith, B. D., Proctor, K., Youdan, J., Barden, R. & Kasprzyk-Hordern, B. 2018 Biotic phase micropollutant distribution in horizontal sub-surface flow constructed wetlands. *Science of the Total Environment* **630**, 648–657.

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

Pilon-Smits, E. 2005 Phytoremediation. *Annual Review of Plant Biology* **56**, 15–39.

Piwoni, M. D. & Keeley, J. W. 1990 *Ground Water Issue. Basic Concepts of Contaminant Sorption at Hazardous Waste Sites*. EPA/540/4-90/053 (NTIS 91-191007). U.S. Environmental Protection Agency, Washington, DC, USA.

Radjenovic, J., Petrovic, M. & Barceló, D. 2009 Fate and distribution of pharmaceuticals in wastewater and sewage sludge of the conventional activated sludge (CAS) and advanced membrane bioreactor (MBR) treatment. *Water Research* **43**, 831–841.

Reif, R., Besancon, A., Le Corre, K., Jefferson, B., Lema, J. M. & Omil, F. 2011 Comparison of PPCPs removal on a parallel-operated MBR and AS system and evaluation of effluent post-treatment on vertical flow reed beds. *Water Science and Technology* **63** (10), 2411–2417.

Reinhold, D., Vishwanathan, S., Park, J. J., Oh, D. & Saunders, F. M. 2010 Assessment of plant-driven removal of emerging organic pollutants by duckweed. *Chemosphere* **80**, 687–692.

Reyes-Contreras, C., Hijosa-Valsero, M., Sidrach-Cardona, R., Bayona, J. M. & Bécares, E. 2012 Temporal evolution in PPCP removal from urban wastewater by constructed wetlands of different configuration: a medium-term study. *Chemosphere* **88**, 161–167.

Rodriguez-Mozaz, S., Chamorro, S., Marti, E., Huerta, B., Gros, M., Sanchez-Melsio, A., Borrego, C. M., Barcelo, D. & Balcazar, J. L. 2015 Occurrence of antibiotics and antibiotic resistance genes in hospital and urban wastewaters and their impact on the receiving river. *Water Research* **69**, 234–242.

Rowan, N. J. 2011 Defining established and emerging microbial risks in the aquatic environment: current knowledge, implications, and outlooks. *International Journal of Microbiology* 2011, 462832.

Rühmland, S., Wick, A., Ternes, T. A. & Barjenbruch, M. 2015 Fate of pharmaceuticals in a subsurface flow constructed wetland and two ponds. *Ecological Engineering* **80**, 125–139.

Ruhoy, I. S. & Daughton, C. G. 2008 Beyond the medicine cabinet: an analysis of where and why medications accumulate. *Environmental International* **34**, 1157–1169.

Salgado, R., Pereira, V. J., Carvalho, G., Soeiro, R., Gaffney, V. & Almeida, C. 2013 Photodegradation kinetics and transformation products of ketoprofen, diclofenac and atenolol in pure water and treated wastewater. *Journal of Hazardous Materials* **244–245**, 516–527.

Sanderson, H., Johnson, D. J., Wilson, C. J., Brain, R. A. & Solomon, K. R. 2003 Probabilistic hazard assessment of environmentally occurring pharmaceuticals toxicity to fish, daphnids and algae by ECOSAR screening. *Toxicology Letters* **144** (3), 383–395.

Santos, F., Almeida, C. M. R., Ribeiro, I. & Mucha, A. P. 2019 Potential of constructed wetland for the removal of antibiotics and antibiotic resistant bacteria from livestock wastewater. *Ecological Engineering* **129**, 45–53.

Sgroi, M., Pelissari, C., Roccaro, P., Sezerino, P. H., García, J., Vagliasindi, F. G. A. & Ávila, C. 2018 Removal of organic carbon, nitrogen, emerging contaminants and fluorescing organic matter in different constructed wetland configurations. *Chemical Engineering Journal* **332**, 619–627.

Sharif, F., Westerhoff, P. & Herckes, P. 2014 Impact of hydraulic and carbon loading rates of constructed wetlands on contaminants of emerging concern (CECs) removal. *Environmental Pollution* **185**, 107–115.

Soares, A., Guieysse, B., Jefferson, B., Cartmell, E. & Lester, J. N. 2008 Nonylphenol in the environment: a critical review on occurrence, fate, toxicity and treatment in wastewaters. *Environment International* **34** (7), 1033–1049.

Ternes, T. A., Stüber, J., Herrmann, N., McDowell, D., Ried, A., Kampmann, M. & Teiser, B. 2003 Ozonation: a tool for removal of pharmaceuticals, contrast media and musk fragrances from wastewater? *Water Research* **37** (8), 1976–1982.

Verlicchi, P. & Zambello, E. 2014 How efficient are constructed wetlands in removing pharmaceuticals from untreated and treated urban wastewaters? a review. *Science of the Total Environment* **470–471**, 1281–1306.

Verlicchi, P., Al Aukidy, M. & Zambello, E. 2012 Occurrence of pharmaceutical compounds in urban wastewater: removal, mass load and environmental risk after a secondary treatment–a review. *Science of the Total Environment* **429**, 123–155.

Verlicchi, P., Galletti, A., Petrovic, M., Barceló, D., Al Aukidy, M. & Zambello, E. 2013 Removal of selected pharmaceuticals from domestic wastewater in an activated sludge system followed by a horizontal subsurface flow bed-analysis of their respective contributions. *Science of the Total Environment* **454–455**, 411–425.

Vymazal, J. 2011 Long-term performance of constructed wetlands with horizontal sub-surface flow: ten case studies from the Czech Republic. *Ecological Engineering* **37** (1), 54–63.

Vymazal, J. 2013 The use of hybrid constructed wetlands for wastewater treatment with special attention to nitrogen removal: a review of a recent development. *Water Research* **47** (14), 4795–4811.

Vymazal, J., Březinová, T. D., Koželuh, M. & Kule, L. 2017 Occurrence and removal of pharmaceuticals in four full-scale constructed wetlands in the Czech Republic – the first year of monitoring. *Ecological Engineering* **98**, 354–364.

Vystavna, Y., Frkova, Z., Marchand, L., Vergeles, Y. & Stolberg, F. 2017 Removal efficiency of pharmaceuticals in a full scale constructed wetland in East Ukraine. *Ecological Engineering* **108**, 50–58.

Wang, C., Zheng, S.-s., Wang, P.-f. & Qian, J. 2014 Effects of vegetations on the removal of contaminants in aquatic environments: a review. *Journal of Hydrodynamics, Series B* **26** (4), 497–511.

Wang, Y., Yin, T., Kelly, B. C. & Gin, K. Y.-H. 2019 Bioaccumulation behaviour of pharmaceuticals and personal care products in a constructed wetland. *Chemosphere* **222**, 275–285.

Xian, Q., Hu, L., Chen, H., Chang, Z. & Zou, H. 2010 Removal of nutrients and veterinary antibiotics from swine wastewater

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest

by a constructed macrophyte floating bed system. *Journal of Environmental Management* **91**, 2657–2661.

Yan, Q., Feng, G., Gao, X., Sun, C., Guo, J.-S. & Zhu, Z. 2016 Removal of pharmaceutically active compounds (PhACs) and toxicological response of *Cyperus alternifolius* exposed to PhACs in microcosm constructed wetlands. *Journal of Hazardous Materials* **301**, 566–575.

Yang, L., Ying, G., Su, H., Stauber, J. L., Adams, M. S. & Binet, M. T. 2008 Growth inhibiting effects of 12 antibacterial agents and their mixtures on the freshwater microalga *Pseudokirchneriella subcapitata*. *Environmental Toxicology and Chemistry* **27**, 1201–1208.

Yi, X., Tran, N. H., Yin, T., He, Y. & Gin, K. Y.-H. 2017 Removal of selected PPCPs, EDCs, and antibiotic resistance genes in landfill leachate by a full-scale constructed wetlands system. *Water Research* **121**, 46–60.

Zhang, D. Q., Tan, S. K., Gersberg, R. M., Sadreddini, S., Zhu, J. & Tuan, N. A. 2011 Removal of pharmaceutical compounds in tropical constructed wetlands. *Ecological Engineering* **37**, 460–464.

Zhang, D. Q., Gersberg, R. M., Hua, T., Zhu, J., Tuan, N. A. & Tan, S. K. 2012a Pharmaceutical removal in tropical subsurface flow constructed wetlands at varying hydraulic loading rates. *Chemosphere* **87**, 273–277.

Zhang, D. Q., Gersberg, R. M., Zhu, J., Hua, T., Jinadasa, K. B. S. N. & Tan, S. K. 2012b Batch versus continuous feeding strategies for pharmaceutical removal by subsurface flow constructed wetland. *Environmental Pollution* **167**, 124–131.

Zhang, D. Q., Hua, T., Gersberg, R. M., Zhu, J., Ng, W. J. & Tan, S. K. 2012c Fate of diclofenac in wetland mesocosms planted with *Scirpus validus*. *Ecological Engineering* **49**, 59–64.

Zhang, D. Q., Hua, T., Gersberg, R. M., Zhu, J., Ng, W. J. & Tan, S. K. 2013a Fate of caffeine in mesocosms wetland planted with *Scirpus validus*. *Chemosphere* **90**, 1568–1572.

Zhang, D. Q., Gersberg, R. M., Hua, T., Zhu, J. F., Goyal, M. K., Ng, W. J. & Tan, S. K. 2013b Fate of pharmaceutical compounds in hydroponic mesocosms planted with *Scirpus validus*. *Environmental Pollution.* **181**, 98–106.

Zhang, D. Q., Hua, T., Gersberg, R. M., Zhu, J. F., Ng, W. J. & Tan, S. K. 2013c Carbamazepine and naproxen: fate in wetland mesocosms planted with *Scirpus validus*. *Chemosphere* **91**, 14–21.

Zhang, D., Gersberg, R. M., Ng, W. J. & Tan, S. K. 2014 Removal of pharmaceuticals and personal care products in aquatic plant-based systems: a review. *Environmental Pollution* **184**, 620–639.

Zhang, D. Q., Luo, J., Lee, Z. M. P., Maspolim, Y., Gersberg, R. M., Liu, Y., Tan, S. K. & Ng, W. J. 2016 Characterization of bacterial communities in wetland mesocosms receiving pharmaceutical-enriched wastewater. *Ecological Engineering* **90**, 215–224.

Zhang, L., Lv, T., Zhang, Y., Stein, O. R., Arias, C. A., Brix, H. & Carvalho, P. N. 2017a Effects of constructed wetland design on ibuprofen removal – a mesocosm scale study. *Science of the Total Environment* **609**, 38–45.

Zhang, Y., Lv, T., Carvalho, P. N., Zhang, L., Arias, C. A., Chen, Z. & Brix, H. 2017b Ibuprofen and iohexol removal in saturated constructed wetland mesocosms. *Ecological Engineering* **98**, 394–402.

Zhang, L., Lyu, T., Vargas, C. A. R., Arias, C. A., Carvalho, P. N. & Brix, H. 2018a New insights into the effects of support matrix on the removal of organic micro-pollutants and the microbial community in constructed wetlands. *Environmental Pollution* **240**, 699–708.

Zhang, X., Jing, R., Feng, X., Dai, Y., Tao, R., Vymazal, J., Cai, N. & Yang, Y. 2018b Removal of acidic pharmaceuticals by small-scale constructed wetlands using different design configurations. *Science of the Total Environment* **639**, 640–647.

Zhu, S. & Chen, H. 2014 The fate and risk of selected pharmaceutical and personal care products in wastewater treatment plants and a pilot-scale multistage constructed wetland system. *Environmental Science and Pollution Research* **21** (2), 1466–1479.

First received 29 September 2019; accepted in revised form 6 February 2020. Available online 31 March 2020

Downloaded from http://iwaponline.com/jwh/article-pdf/18/3/253/759747/jwh0180253.pdf
by guest