Science of the Total Environment 429 (2012) 123–155

Contents lists available at SciVerse ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Review

Occurrence of pharmaceutical compounds in urban wastewater: Removal, mass load and environmental risk after a secondary treatment—A review

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ARTICLE INFO

Article history:
Received 9 February 2012
Received in revised form 6 April 2012
Accepted 6 April 2012
Available online 12 May 2012

Keywords:
Pharmaceuticals
Urban wastewater
Activated sludge systems
Removal efficiency
Mass load
Environmental risk

ABSTRACT

This review focuses on 118 pharmaceuticals, belonging to seventeen different therapeutic classes, detected in raw urban wastewater and effluent from an activated sludge system, a usual treatment adopted for urban wastewaters worldwide prior to final discharge into surface water bodies. Data pertaining to 244 conventional activated sludge systems and 20 membrane biological reactors are analysed and the observed ranges of variability of each selected compound in their influent and effluent reported, with particular reference to the substances detected most frequently and in higher concentrations. A snapshot of the ability of these systems to remove such compounds is provided by comparing their global removal efficiencies for each substance. Where possible, the study then evaluates the average daily mass load of the majority of detected pharmaceuticals exiting the secondary treatment step. The final part of the review provides an assessment of the environmental risk posed by their presence in the secondary effluent by means of the risk quotient that is the ratio between the average pharmaceutical concentration measured in the secondary effluent and the predicted no-effect concentration.

Finally, mass load rankings of the compounds under review are compared with those based on their risk level. This analysis shows that the highest amounts discharged through secondary effluent pertain to one antihypertensive, and several beta-blockers and analgesics/anti-inflammatories, while the highest risk is posed by antibiotics and several psychiatric drugs and analgesics/anti-inflammatories. These results are reported with a view to aiding scientists and administrators in planning measures aiming to reduce the impact of treated urban wastewater discharge into surface water bodies.

Contents

1. Introduction . . . 124
   1.1. Review framework . . . 124
2. Materials and methods . . . 124
   2.1. Investigated pharmaceutical compounds . . . 124
   2.2. Main features of the investigated WWTPs . . . 132
   2.3. Quality assurance of literature data . . . 133
3. Results and discussion . . . 133
   3.1. Occurrence of pharmaceuticals in raw urban wastewater . . . 133
   3.2. Secondary biological effluent concentrations of pharmaceuticals . . . 135
   3.3. Observed removal efficiencies . . . 136
      3.3.1. Considerations on the observed removal efficiencies of the selected PhCs . . . 145
      3.3.2. Effect of biomass concentration and SRT . . . 145
      3.3.3. Effect of HRT . . . 146
      3.3.4. Effect of pH . . . 146
      3.3.5. Effect of temperature . . . 146
      3.3.6. Treatment configuration . . . 147

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0048-9697/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.scitotenv.2012.04.028

3.4. Average daily mass loads of PhCs in secondary effluent . . . 147
3.5. Environmental risk assessment of secondary biological effluent . . . 151
4. Final considerations and further needs . . . 152
Acknowledgements . . . 153
Appendix A. Supplementary data . . . 153
References . . . 153

1. Introduction

In recent years, pharmaceutical compounds (PhCs) have provoked increasing concern, particularly as no legal requirements have been set for discharge into surface water bodies of these ubiquitous, persistent and biologically active substances (Furhacker, 2008; Salgot et al., 2006; Ternes et al., 2007). Recent investigations document that PhC production and administration may vary both between countries and over time (Goossens et al., 2007, Kümmerer, 2009a), fluctuating not only on an annual basis, but also from one year to the next (Alexy et al., 2006). In addition, the continually ageing population and improving quality of life worldwide mean that their consumption is set to increase in future years (Van der Aa et al., 2011).

Once administered, PhCs are metabolised to varying degrees, and their excreted metabolites and unaltered parent compounds can also undergo further modification due to biological, chemical and physical processes in both sewage treatment facilities and receiving water bodies (Deblonde et al., 2011; Fatta-Kassinos et al., 2011; Miège et al., 2009; Monteiro and Boxall, 2010; Onesios et al., 2009). Municipal wastewater treatment plants (WWTPs) are generally not equipped to deal with complex pharmaceuticals, as they were built and upgraded with the principal aim of removing easily or moderately biodegradable carbon, nitrogen and phosphorus compounds and microbiological organisms, which regularly arrive at the WWTP in concentrations to the order of mg L^{-1} and at least 10^6 MPN/100 mL, respectively. PhCs in raw wastewaters are generally in the range of 10^{-3}–10^{-6} mg L^{-1}, in addition, their chemical and physical properties, namely solubility, volatility, adsorbability, absorbability, biodegradability, polarity and stability, vary greatly (Le Minh et al., 2010; Ziylan and Ince, 2011), with obvious repercussions on their behaviour during the treatments and consequently their removal efficiencies.

Indeed, several PhCs have been found in river biota, some at high levels (Rimkus, 1999), thereby evidencing the risk that environmental concentrations of PhCs can be higher than their predicted no-effect concentrations (PNECs) (Santos et al., 2007; Stuer-Lauridsen et al., 2000), especially in effluent-dominant rivers whose dilution capacity and self-purifying processes are insufficient to temper the risk to aquatic life (Kasprzyk-Hordern et al., 2009).

Although much research has been conducted on this topic, studies have generally been limited to single treatment plants. Hence, in order to provide an overview of the findings, we set out to collate the data pertaining to 264 WWTPs from various global locations, mostly in Europe.

Reflecting the abundance of conventional activated sludge systems (CAS) among existing municipal WWTPs, 244 of them were considered in this review, the remaining 20 plants examined were membrane biological reactors (MBR), included for comparative purposes.

Data pertaining to a wide spectrum of PhCs, 118 compounds belonging to 17 different classes distinguished by their function or biological activity, were considered: 23 analgesics/anti-inflammatories, 36 antibiotics, 1 antidiabetic, 1 antifungal, 3 antihypertensives, 1 barbiturate, 12 beta-blockers, 2 diuretics, 9 lipid regulators, 10 psychiatric drugs, 6 receptor antagonists, 4 hormones, 4 beta-agonists, 3 antineoplastics, 1 topical product, 1 antiseptic and 1 contrast agent.

First we reported raw influent and secondary effluent concentrations for the 118 PhCs, and their removal efficiencies observed in CAS and MBRs, the objective being to provide a snapshot of their occurrence and of the efficacy of suspended growth mass biological processes in their removal. Based on the collected data, we then evaluated the average daily mass load (mg/1000 inh/d) in the secondary effluent for the majority of the compounds under study, ranking them accordingly. The PhCs were then also ranked according to their environmental risk, using a quotient derived from the ratio between their measured concentrations in secondary effluents and their corresponding PNEC. This strategy provides an overview of the situation, clearly identifying a group of compounds in need of more intensive monitoring further to safeguarding the environment.

1.1. Review framework

The survey drew data from 78 peer-reviewed papers published in books or international journals, collating data on the occurrence of PhCs in raw urban wastewaters and secondary biological effluents from suspended growth biomass systems (CAS and MBRs) and/or the corresponding removal efficiencies achieved by these WWTPs. Compounds are grouped according to their therapeutic class and presented in terms of their chemical formula and molecular weight; literature references are also provided for each (Table 1). In addition, in the Supplementary data, their main physical and chemical properties (protonation constant as pK_a, octanol–water partition coefficient as Log K_{ow}, solubility S_w, sludge–water distribution coefficient as Log K_d, reaction rate constant k_{biol}, molecular charge at pH 7) as well as their molecular structure are provided (see Table SD1). The main features of the WWTPs are investigated in each study and details of the corresponding experimental campaigns are compiled in Table 2. Through the last column of Table 1, it is possible to know the previous works investigating the substance under study and then, once known the cited work, through Table 2 to know the details of the experimental campaign and the characteristics of the WWTPs under consideration.

Based on the collected literature data, we defined variability ranges for the concentration of each examined compound in both raw urban influent (Figs. 1–6 and Table SD2) and secondary effluent (Figs. 7–12 and Table SD3), as well as for their corresponding removal efficiencies (Figs. 14–19 and Table SD4). To complete the analysis of literature data, the percentage partitions, for some of the compounds under study, among biodegradation, sorption onto sludge and occurrence in the secondary effluent are provided (Table 3) as well as removal efficiencies for the different selected PhCs with respect to the sludge retention time of the corresponding biological reactor (referring to CAS in Table 4 and MBR in Table 5).

Subsequently, the average daily mass discharged from the secondary biological system was evaluated, where possible, for the examined compounds, and their corresponding risk quotients (average concentration/PNEC) in the secondary effluent (Figs. 20 and 21). As a whole, the results of these two analyses revealed the most critical compounds in terms of mass load and/or environmental risk.

2. Materials and methods

2.1. Investigated pharmaceutical compounds

Table 1 reports the list of the investigated contaminants, grouped according to their therapeutic class, in addition to their molecular weight (MW) and chemical formula, together with the number and details of the references reviewed.

Table 1
Pharmaceutical compounds examined, grouped according to their therapeutical class. For each substance, chemical formula and molecular weight (MW) are provided as well as number of papers and references dealing with it, included in the review.

Therapeutic class	Pharmaceutical compound	MW	Chemical formula	Number of papers	References
Analgesics/ anti-inflammatories **A**	5-Aminosalicylic acid	153	$C_7H_7NO_3$	1	Kasprzyk-Hordern et al., 2009
	Acetaminophen	151	$C_8H_9NO_2$	15	Choi et al., 2008; Coetsier et al., 2009; Foster, 2007; Gómez et al., 2007; Jones et al., 2007; Kasprzyk-Hordern et al., 2009; Khan and Ongerth, 2005; Kim et al., 2007; Radjenovic et al., 2007, 2009; Roberts and Thomas, 2006; Rosal et al., 2010; Snyder et al., 2006; Ternes, 1998; Yu et al., 2006
	Acetylsalicylic acid	180	$C_9H_8O_4$	2	Kasprzyk-Hordern et al., 2009; Ternes, 1998
	Aminopyrine	231	$C_{13}H_{17}N_3O$	2	Andreozzi et al., 2003; Ternes, 1998
	Codeine	299	$C_{18}H_{21}NO_3$	5	Foster, 2007; Gómez et al., 2007; Kasprzyk-Hordern et al., 2009; Rosal et al., 2010; Wick et al., 2009
	Dextropropoxyphene	339	$C_{22}H_{29}NO_2$	1	Roberts and Thomas, 2006
	Diclofenac	296	$C_{14}H_{11}Cl_2NO_2$	36	Andreozzi et al., 2003; Bendz et al., 2005; Bernhard et al., 2006; Clara et al., 2004, 2005a, 2005b; Coetsier et al., 2009; Gómez et al., 2007; Kasprzyk-Hordern et al., 2009; Kim et al., 2007; Kimura et al., 2005, 2007; Kreuzinger et al., 2004; Lindqvist et al., 2005; Lishman et al., 2006; Muñoz et al., 2009; Paxéus, 2004; Quintana et al., 2005; Radjenovic et al., 2007, 2009; Reif et al., 2008; Roberts and Thomas, 2006; Rosal et al., 2010; Santos et al., 2007, 2009; Snyder et al., 2006; Stumpf et al., 1999; Suárez et al., 2005; Tauxe-Wuersch et al., 2005; Ternes et al., 2003; Ternes, 1998; Thomas and Foster, 2005; Vieno et al., 2005; Weigel et al., 2004; Yu et al., 2006; Zorita et al., 2009
	Dipyrone	333	$C_{13}H_{16}N_3NaO_4S$	1	Gómez et al., 2007
	Fenoprofen	242	$C_{15}H_{14}O_3$	6	Andreozzi et al., 2003; Bendz et al., 2005; Coetsier et al., 2009; Lishman et al., 2006; Nakada et al., 2006; Ternes, 1998
	Flurbiprofen	244	$C_{15}H_{13}FO_2$	2	Andreozzi et al., 2003; Bendz et al., 2005
	Hydrocodone	299	$C_{18}H_{21}NO_3$	1	Snyder et al., 2006
	Ibuprofen	206	$C_{13}H_{18}O_2$	43	Andreozzi et al., 2003; Bendz et al., 2005; Bernhard et al., 2006; Carballa et al., 2004, 2005; Castiglioni et al., 2006; Clara et al., 2004, 2005a, 2005b; Coetsier et al., 2009; Gómez et al., 2007; Jones et al., 2007; Kasprzyk-Hordern et al., 2009; Khan and Ongerth, 2005; Kim et al., 2007; Kimura et al., 2005, 2007; Kreuzinger et al., 2004; Lindqvist et al., 2005; Lishman et al., 2006; Muñoz et al., 2009; Nakada et al., 2006; Paxéus, 2004; Quintana et al., 2005; Radjenovic et al., 2007, 2009; Reif et al., 2008; Roberts and Thomas, 2006; Rodriguez et al., 2003; Rosal et al., 2010; Santos et al., 2007, 2009; Snyder et al., 2006; Stumpf et al., 1999; Suárez et al., 2005; Tauxe-Wuersch et al., 2005; Ternes et al., 2003; Ternes, 1998; Thomas and Foster, 2005; Vieno et al., 2005; Weigel et al., 2004; Yu et al., 2006; Zorita et al., 2009
	Indomethacin	358	$C_{19}H_{16}ClNO_4$	8	Bendz et al., 2005; Lishman et al., 2006, Radjenovic et al., 2007, 2009; Rosal et al., 2010; Stumpf et al., 1999; Ternes et al., 2003; Ternes, 1998
	Ketoprofen	254	$C_{16}H_{14}O_3$	21	Andreozzi et al., 2003; Bendz et al., 2005; Kasprzyk-Hordern et al., 2009; Khan and Ongerth, 2005; Kimura et al., 2005, 2007; Lindqvist et al., 2005; Lishman et al., 2006; Nakada et al., 2006; Quintana et al., 2005; Radjenovic et al., 2007, 2009; Rosal et al., 2010; Santos et al., 2007, 2009; Stumpf et al., 1999; Tauxe-Wuersch et al., 2005; Ternes, 1998; Thomas and Foster, 2005; Vieno et al., 2005; Yu et al., 2006
	Ketorolac	255	$C_{15}H_{13}NO_3$	1	Rosal et al., 2010
	Meclofenamic acid	296	$C_{14}H_{11}Cl_2NO_2$	1	Ternes, 1998
	Mefenamic acid	241	$C_{15}H_{15}NO_2$	9	Jones et al., 2007; Kasprzyk-Hordern et al., 2009; Kimura et al., 2005, 2007; Radjenovic et al., 2007, 2009; Roberts and Thomas, 2006; Rosal et al., 2010; Tauxe-Wuersch et al., 2005
	Naproxen	230	$C_{14}H_{14}O_3$	30	Andreozzi et al., 2003; Bendz et al., 2005; Carballa et al., 2004, 2005; Kasprzyk-Hordern et al., 2009; Khan and Ongerth, 2005; Kim et al., 2007; Kimura et al., 2005, 2007; Lindqvist et al., 2005; Lishman et al., 2006; Nakada et al., 2006; Paxéus, 2004; Quintana et al., 2005; Radjenovic et al., 2007, 2009; Reif et al., 2008; Rodriguez et al., 2003; Rosal et al., 2010; Santos et al., 2007, 2009; Snyder et al., 2006; Stumpf et al., 1999; Suárez et al., 2005; Ternes, 1998; Ternes et al., 2003; Thomas and Foster, 2005; Vieno et al., 2005; Yu et al., 2006; Zorita et al., 2009
	Phenazone	188	$C_{11}H_{12}N_2O$	3	Andreozzi et al., 2003; Rosal et al., 2010; Ternes, 1998
	Propyphenazone	230	$C_{14}H_{18}N_2O$	3	Nakada et al., 2006; Radjenovic et al., 2007, 2009
	Salicylic acid	138	$C_7H_6O_3$	4	Kasprzyk-Hordern et al., 2009; Khan and Ongerth, 2005; Lishman et al., 2006; Ternes, 1998
	Tolfenamic acid	262	$C_{14}H_{12}ClO_2$	1	Ternes, 1998
	Tramadol	263	$C_{16}H_{25}NO_2$	2	Kasprzyk-Hordern et al., 2009; Wick et al., 2009
Antibiotics **B**	Amoxicillin	365	$C_{16}H_{19}N_3O_5S$	1	Watkinson et al., 2007
	Azithromycin	749	$C_{38}H_{72}N_2O_{12}$	4	Ghosh et al., 2009; Göbel et al., 2005, 2007; Yasojima et al., 2006
	Cefaclor	368	$C_{15}H_{14}ClN_3O_4S$	1	Watkinson et al., 2007
	Cefalexin	347	$C_{16}H_{17}N_3O_4S$	4	Costanzo et al., 2005; Gulkowska et al., 2008; Li and Zhang, 2011; Watkinson et al., 2007
	Cefotaxime	456	$C_{16}H_{17}N_5O_7S_2$	2	Gulkowska et al., 2008; Li and Zhang, 2011
	Chloramphenicol	323	$C_{11}H_{12}Cl_2N_2O_5$	3	Kasprzyk-Hordern et al., 2009; Li and Zhang, 2011; Peng et al., 2006
	Chlortetracycline	479	$C_{22}H_{23}ClN_2O_8$	2	Li and Zhang, 2011; Watkinson et al., 2007
	Ciprofloxacin	331	$C_{17}H_{18}FN_3O_3$	15	Andreozzi et al., 2003; Baumgarten et al., 2007; Castiglioni et al., 2006; Costanzo et al., 2005; Ghosh et al., 2009; Golet et al., 2003; Karthikeyan and Meyer, 2006; Li and Zhang, 2011; Lindberg et al., 2005, 2006; Muñoz et al., 2009; Rosal et al., 2010; Vieno et al., 2007; Watkinson et al., 2007; Zorita et al., 2009

(continued on next page)

Table 1 (*continued*)

Therapeutic class	Pharmaceutical compound	MW	Chemical formula	Number of papers	References
	Clarithromycin	748	$C_{38}H_{69}NO_{13}$	7	Castiglioni et al., 2006; Ghosh et al., 2009; Göbel et al., 2005, 2007; Sahar et al., 2011; Ternes et al., 2003; Yasojima et al., 2006
	Clindamycin	425	$C_{18}H_{33}ClN_2O_5S$	1	Watkinson et al., 2007
	Cloxacillin	436	$C_{19}H_{18}ClN_3O_5S$	1	Watkinson et al., 2007
	Doxycycline	463	$C_{22}H_{24}N_2O_8$	2	Lindberg et al., 2005; Watkinson et al., 2007
	Enoxacin	320	$C_{15}H_{17}FN_4O_3$	1	Andreozzi et al., 2003
	Enrofloxacin	359	$C_{19}H_{22}FN_3O_3$	3	Baumgarten et al., 2007; Ghosh et al., 2009; Watkinson et al., 2007
	Erythromycin	734	$C_{37}H_{67}NO_{13}$	19	Castiglioni et al., 2006; Göbel et al., 2005, 2007; Gulkowska et al., 2008; Karthikeyan and Meyer, 2006; Kasprzyk-Hordern et al., 2009; Kim et al., 2007; Li and Zhang, 2011; Muñoz et al., 2009; Radjenovic et al., 2007, 2009; Reif et al., 2008; Roberts and Thomas, 2006; Rosal et al., 2010; Sahar et al., 2011; Snyder et al., 2006; Ternes et al., 2003; Watkinson et al., 2007; Xu et al., 2007
	Lincomycin	407	$C_{18}H_{34}N_2O_6S$	3	Castiglioni et al., 2006; Ghosh et al., 2009; Watkinson et al., 2007
	Lomefloxacin	351	$C_{17}H_{19}F_2N_3O_3$	1	Andreozzi et al., 2003
	Metronidazole	171	$C_6H_9N_3O_3$	2	Kasprzyk-Hordern et al., 2009; Rosal et al., 2010
	Norfloxacin	319	$C_{16}H_{18}FN_3O_3$	12	Andreozzi et al., 2003; Coetsier et al., 2009; Costanzo et al., 2005; Ghosh et al., 2009; Golet et al., 2003; Gulkowska et al., 2008; Li and Zhang, 2011; Lindberg et al., 2005, 2006; Watkinson et al., 2007; Xu et al., 2007; Zorita et al., 2009
	Ofloxacin	361	$C_{18}H_{20}FN_3O_4$	12	Andreozzi et al., 2003; Brown et al., 2006; Castiglioni et al., 2006; Li and Zhang, 2011; Lindberg et al., 2005; Peng et al., 2006; Radjenovic et al., 2007, 2009; Rosal et al., 2010; Vieno et al., 2007; Xu et al., 2007; Zorita et al., 2009
	Oxytetracycline	460	$C_{22}H_{24}N_2O_9$	2	Li and Zhang, 2011; Watkinson et al., 2007
	Penicillin G	334	$C_{16}H_{18}N_2O_4S$	2	Gulkowska et al., 2008; Watkinson et al., 2007
	Penicillin V	350	$C_{16}H_{18}N_2O_5S$	1	Watkinson et al., 2007
	Roxithromycin	837	$C_{41}H_{76}N_2O_{15}$	12	Clara et al., 2005b; Ghosh et al., 2009; Göbel et al., 2005, 2007; Kreuzinger et al., 2004; Li and Zhang, 2011; Reif et al., 2008; Ruel et al., 2010; Sahar et al., 2011; Ternes et al., 2003, Watkinson et al., 2007; Xu et al., 2007
	Spiramycin	843	$C_{43}H_{74}N_2O_{14}$	1	Castiglioni et al., 2006
	Sulfachloropyridazine	285	$C_{10}H_9ClN_4O_2S$	1	Choi et al., 2008
	Sulfadiazine	250	$C_{10}H_{10}N_4O_2S$	3	Li and Zhang, 2011; García-Galán et al., 2011; Peng et al., 2006
	Sulfadimethoxine	310	$C_{12}H_{14}N_4O_4S$	3	Choi et al., 2008; García-Galán et al., 2011; Ghosh et al., 2009
	Sulfamethazine	278	$C_{12}H_{14}N_4O_2S$	4	García-Galán et al., 2011, Karthikeyan and Meyer, 2006; Li and Zhang, 2011; Sahar et al., 2011
	Sulfamethoxazole	253	$C_{10}H_{11}N_3O_3S$	31	Andreozzi et al., 2003; Bendz et al., 2005; Brown et al., 2006; Carballa et al., 2004, 2005; Castiglioni et al., 2006; Choi et al., 2008; Clara et al., 2005b; Foster, 2007; García-Galán et al., 2011; Ghosh et al., 2009; Göbel et al., 2005, 2007; Karthikeyan and Meyer, 2006; Kasprzyk-Hordern et al., 2009; Kim et al., 2007; Kreuzinger et al., 2004; Li and Zhang, 2011; Lindberg et al., 2005; Muñoz et al., 2009; Peng et al., 2006; Radjenovic et al., 2007, 2009; Reif et al., 2008; Rosal et al., 2010; Ruel et al., 2010; Sahar et al., 2011; Snyder et al., 2006; Ternes et al., 2003; Watkinson et al., 2007; Xu et al., 2007
	Sulfapyridine	249	$C_{11}H_{11}N_3O_2S$	4	García-Galán et al., 2011; Göbel et al., 2005, 2007; Kasprzyk-Hordern et al., 2009
	Sulfasalazine	398	$C_{18}H_{14}N_4O_5S$	2	Kasprzyk-Hordern et al., 2009; Watkinson et al., 2007
	Sulfathiazole	255	$C_9H_9N_3O_2S_2$	3	Choi et al., 2008; García-Galán et al., 2011; Watkinson et al., 2007
	Tetracycline	444	$C_{22}H_{24}N_2O_8$	5	Ghosh et al., 2009; Gulkowska et al., 2008; Li and Zhang, 2011; Karthikeyan and Meyer, 2006; Watkinson et al., 2007
	Trimethoprim	290	$C_{14}H_{18}N_4O_3$	25	Andreozzi et al., 2003; Batt et al., 2006; Bendz et al., 2005; Brown et al., 2006; Foster, 2007; Ghosh et al., 2009; Göbel et al., 2005, 2007; Gulkowska et al., 2008; Karthikeyan and Meyer, 2006; Kasprzyk-Hordern et al., 2009; Choi et al., 2008; Kim et al., 2007; Li and Zhang, 2011; Lindberg et al., 2005, 2006; Paxéus, 2004; Radjenovic et al., 2009; Reif et al., 2008; Roberts and Thomas, 2006; Rosal et al., 2010; Sahar et al., 2011; Snyder et al., 2006; Ternes et al., 2003; Watkinson et al., 2007
	Tylosin	916	$C_{46}H_{77}NO_{17}$	1	Watkinson et al., 2007
Antidiabetics **G**	Glibenclamide	494	$C_{23}H_{28}ClN_3O_5S$	1	Radjenovic et al., 2007, 2009
Antifungals **D**	Clotrimazole	345	$C_{22}H_{17}ClN_2$	1	Roberts and Thomas, 2006
Antihypertensives **E**	Diltiazem	415	$C_{22}H_{26}N_2O_4S$	3	Choi et al., 2008 Foster, 2007; Kasprzyk-Hordern et al., 2009;
	Enalapril	377	$C_{20}H_{28}N_2O_5$	1	Castiglioni et al., 2006
	Hydrochlorothiazide	298	$C_7H_8ClN_3O_4S_2$	5	Castiglioni et al., 2006; Muñoz et al., 2009; Radjenovic et al., 2007, 2009; Rosal et al., 2010;
Barbiturates **F**	Phenobarbital	232	$C_{12}H_{12}N_2O_3$	1	Yu et al., 2006
Beta-blockers **G**	Acebutolol	336	$C_{18}H_{28}N_2O_4$	2	Andreozzi et al., 2003; Vieno et al., 2007
	Atenolol	266	$C_{14}H_{22}N_2O_3$	14	Alder et al., 2010; Bendz et al., 2005; Carucci et al., 2006; Castiglioni et al., 2006; Kasprzyk-Hordern et al., 2009; Maurer et al., 2007; Muñoz et al., 2009; Paxéus, 2004; Radjenovic et al., 2007, 2009; Rosal et al., 2010; Ternes et al., 2003; Vieno et al., 2007; Wick et al., 2009
	Betaxolol	307	$C_{18}H_{29}NO_3$	3	Andreozzi et al., 2003; Ternes, 1998; Wick et al., 2009
	Bisoprolol	325	$C_{18}H_{31}NO_4$	2	Ternes, 1998; Wick et al., 2009
	Carazolol	298	$C_{18}H_{22}N_2O_2$	1	Ternes, 1998
	Celiprolol	379	$C_{20}H_{33}N_3O_4$	2	Ternes et al., 2003; Wick et al., 2009
	Metoprolol	267	$C_{15}H_{25}NO_3$	12	Alder et al., 2010; Andreozzi et al., 2003; Kasprzyk-Hordern et al., 2009; Maurer et al., 2007; Paxéus, 2004; Radjenovic et al., 2007, 2009; Rosal et al., 2010; Ternes, 1998; Ternes et al., 2003; Vieno et al., 2007; Wick et al., 2009
	Nadolol	309	$C_{17}H_{27}NO_4$	1	Ternes, 1998
	Oxprenolol	265	$C_{15}H_{23}NO_3$	1	Andreozzi et al., 2003
	Propranolol	259	$C_{16}H_{21}NO_2$	12	Alder et al., 2010; Andreozzi et al., 2003; Bendz et al., 2005; Coetsier et al., 2009; Kasprzyk-Hordern et al., 2009; Maurer et al., 2007; Radjenovic et al., 2009; Roberts and Thomas, 2006; Rosal et al., 2010; Ternes, 1998; Ternes et al., 2003; Wick et al., 2009

Table 1 (*continued*)

Therapeutic class	Pharmaceutical compound	MW	Chemical formula	Number of papers	References
	Sotalol	272	$C_{12}H_{20}N_2O_3S$	6	Alder et al., 2010; Maurer et al., 2007; Radjenovic et al., 2009; Ternes et al., 2003; Vieno et al., 2007; Wick et al., 2009
	Timolol	316	$C_{13}H_{24}N_4O_3S$	1	Ternes, 1998
Diuretics **H**	Bendroflumethiazide	421	$C_{15}H_{14}F_3N_3O_4S_2$	1	Kasprzyk-Hordern et al., 2009
	Furosemide	331	$C_{12}H_{11}ClN_2O_5S$	3	Castiglioni et al., 2006; Kasprzyk-Hordern et al., 2009; Rosal et al., 2010
Lipid regulators **I**	Bezafibrate	362	$C_{19}H_{20}ClNO_4$	15	Andreozzi et al., 2003; Castiglioni et al., 2006; Clara et al., 2004, 2005a, 2005b; Kasprzyk-Hordern et al., 2009; Kreuzinger et al., 2004; Lindqvist et al., 2005; Quintana et al., 2005; Radjenovic et al., 2007, 2009; Rosal et al., 2010; Stumpf et al., 1999; Ternes, 1998; Vieno et al., 2005
	Clofibrate	243	$C_{12}H_{15}ClO_3$	2	Andreozzi et al., 2003; Ternes, 1998
	Clofibric acid	215	$C_{10}H_{11}O_3Cl$	16	Andreozzi et al., 2003;Bendz et al., 2005; Bernhard et al., 2006; Kasprzyk-Hordern et al., 2009;Kimura et al., 2005, 2007; Lishman et al., 2006; Radjenovic et al., 2007; Roberts and Thomas, 2006; Rosal et al., 2010;Stumpf et al., 1999; Tauxe-Wuersch et al., 2005; Ternes, 1998; Ternes et al., 2003; Weigel et al., 2004; Zorita et al., 2009
	Etofibrate	364	$C_{18}H_{18}ClNO_5$	1	Ternes, 1998
	Fenofibrate	361	$C_{20}H_{21}ClO_4$	3	Andreozzi et al., 2003; Lishman et al., 2006;Ternes, 1998
	Fenofibric acid	319	$C_{17}H_{15}ClO_4$	5	Muñoz et al., 2009; Rosal et al., 2010;Stumpf et al., 1999; Ternes, 1998; Ternes et al., 2003
	Gemfibrozil	250	$C_{15}H_{22}O_3$	14	Andreozzi et al., 2003; Bendz et al., 2005; Khan and Ongerth, 2005;Kim et al., 2007; Lishman et al., 2006; Muñoz et al., 2009;Paxéus, 2004;Radjenovic et al., 2007, 2009; Rosal et al., 2010; Snyder et al., 2006; Stumpf et al., 1999; Ternes, 1998;Yu et al., 2006
	Pravastatin	425	$C_{23}H_{36}O_7$	4	Coetsier et al., 2009; Kasprzyk-Hordern et al., 2009; Radjenovic et al., 2007, 2009
	Simvastatin	419	$C_{25}H_{38}O_5$	1	Kasprzyk-Hordern et al., 2009
Psychiatric drugs **J**	Amitriptyline	277	$C_{20}H_{23}N$	1	Kasprzyk-Hordern et al., 2009
	Carbamazepine	236	$C_{15}H_{12}N_2O$	31	Andreozzi et al., 2003;Bendz et al., 2005; Bernhard et al., 2006; Castiglioni et al., 2006; Clara et al., 2004, 2005a, 2005b; Conti et al., 2011; Coetsier et al. 2009;Foster, 2007; Gómez et al., 2007; Kasprzyk-Hordern et al., 2009; Khan and Ongerth, 2005; Choi et al., 2008; Kim et al., 2007;Kreuzinger et al., 2004; Muñoz et al., 2009; Nakada et al., 2006; Paxéus, 2004;Radjenovic et al., 2007, 2009; Reif et al., 2008; Rosal et al., 2010;Santos et al., 2007, 2009;Snyder et al., 2006; Suárez et al., 2005; Ternes, 1998;Ternes et al., 2003; Vieno et al., 2007; Wick et al., 2009
	Diazepam	285	$C_{16}H_{13}ClN_2O$	6	Clara et al., 2005b; Kreuzinger et al., 2004; Reif et al., 2008; Suárez et al., 2005; Ternes, 1998; Wick et al., 2009
	Fluoxetine	309	$C_{17}H_{18}F_3NO$	8	Foster, 2007; Kim et al., 2007; Metcalfe et al., 2010; Muñoz et al., 2009; Radjenovic et al., 2009; Rosal et al., 2010; Snyder et al., 2006; Zorita et al., 2009
	Gabapentin	171	$C_9H_{17}N_1O_2$	2	Kasprzyk-Hordern et al., 2009; Yu et al., 2006
	Lorazepam	321	$C_{15}H_{10}C_{l2}O_2N_2$	1	Coetsier et al., 2009
	Norfluoxetine	295	$C_{16}H_{16}F_3NO$	2	Metcalfe et al., 2010; Zorita et al., 2009
	Oxcarbazepine	252	$C_{15}H_{12}N_2O_2$	1	Conti et al., 2011
	Paroxetine	329	$C_{19}H_{20}FNO_3$	2	Metcalfe et al., 2010; Radjenovic et al., 2007
	Valproic acid	144	$C_8H_{16}O_2$	1	Yu et al., 2006
Receptor antagonists **K**	Cimetidine	252	$C_{10}H_{16}N_6S$	2	Choi et al., 2008; Kasprzyk-Hordern et al., 2009
	Famotidine	337	$C_8H_{15}N_7O_2S_3$	1	Radjenovic et al., 2009
	Loratadine	383	$C_{22}H_{23}ClN_2O_2$	1	Radjenovic et al., 2009
	Omeprazole		$C_{17}H_{19}N_3O_3S$	1	Rosal et al., 2010
	Ranitidine	314	$C_{13}H_{22}N_4O_3S$	6	Carucci et al., 2006; Castiglioni et al., 2006; Kasprzyk-Hordern et al., 2009; Radjenovic et al., 2007, 2009; Rosal et al., 2010
	Valsartan	436	$C_{24}H_{29}N_5O_3$	1	Kasprzyk-Hordern et al., 2009
Hormones **L**	Estradiol	272	$C_{18}H_{24}O_2$	11	Andersen et al., 2003; Baronti et al., 2000; Carballa et al., 2004, 2005; Clara et al., 2005a; Foster, 2007; Joss et al., 2004; Kim et al., 2007; Lishman et al., 2006; Ternes et al., 1999; Zorita et al., 2009
	Estriol	288	$C_{18}H_{24}O_3$	4	Baronti et al., 2000; Clara et al., 2005a; Kim et al., 2007; Nakada et al., 2006
	Estrone	270	$C_{18}H_{22}O_2$	12	Andersen et al., 2003; Baronti et al., 2000; Carballa et al., 2004, 2005; Clara et al., 2005a; Joss et al., 2004; Kim et al., 2007; Lishman et al., 2006; Nakada et al., 2006; Ternes et al., 1999, 2003; Zorita et al., 2009
	Ethinylestradiol	296	$C_{20}H_{24}O_2$	10	Andersen et al., 2003; Baronti et al., 2000; Clara et al., 2004, 2005a; Foster, 2007; Joss et al., 2004; Kim et al., 2007; Kreuzinger et al., 2004; Ternes et al., 1999; Zorita et al., 2009
Beta-agonists **M**	Clenbuterol	277	$C_{12}H_{18}Cl_2N_2O$	1	Ternes, 1998
	Fenoterol	303	$C_{17}H_{21}NO_4$	1	Ternes, 1998
	Salbutamol	239	$C_{13}H_{21}NO_3$	4	Castiglioni et al., 2006; Jones et al., 2007; Kasprzyk-Hordern et al., 2009; Ternes, 1998
	Terbutaline	226	$C_{12}H_{19}NO_3$	1	Ternes, 1998
Antineoplastics **N**	Cyclophosphamide	261	$C_7H_{15}Cl_2N_2O_2P$	1	Ternes, 1998
	Ifosfamide	261	$C_7H_{15}Cl_2N_2O_2P$	3	Coetsier et al., 2009; Kümmerer et al., 1997; Ternes, 1998
	Tamoxifen	372	$C_{26}H_{29}NO$	2	Coetsier et al., 2009; Roberts and Thomas, 2006
Topical products **O**	Crotamiton	203	$C_{13}H_{17}NO$	1	Nakada et al., 2006
Antiseptics **P**	Triclosan	290	$C_{12}H_7Cl_3O_2$	13	Foster, 2007; Gómez et al., 2007; Kim et al., 2007; McAvoy et al., 2002; Muñoz et al., 2009; Nakada et al., 2006; Paxéus, 2004; Rosal et al., 2010; Ruel et al., 2010; Snyder et al., 2006; Thomas and Foster, 2005; Weigel et al., 2004; Yu et al., 2006
Contrast media **Q**	Iopromide	791	$C_{18}H_{24}I_3N_3O_8$	5	Batt et al., 2006; Carballa et al., 2004; Clara et al., 2005b; Kim et al., 2007; Kreuzinger et al., 2004

The majority of the compounds mentioned in the various studies are administrated orally, intramuscularly, endovenously or by inhalation, and in few cases on the skin.

An analysis of the data compiled in Table SD1 in the Supplementary data, referring to selected PhCs evidences their very different molecular structures, also in terms of basic or acidic functional groups (charge at

Table 2
Main characteristics of the treatment plants and monitoring campaigns included in this review.

	References	Details of treatment plants and experimental investigations
1	Alder et al. (2010)	24-h flow-proportional composite samples were taken at the influent and effluent of a conventional WWTP of Niederglatt, Switzerland (33,000 inhabitants, 16,800 m^3/d) and processed for four beta-blockers: atenolol, metoprolol, propanolol and sotalol. The plant includes nitrification–denitrification stages. Collected data refer to influent and effluent concentrations, average removal rates as well as average mass loads for each of the selected compounds.
2	Andersen et al. (2003)	24-h flow-proportional composite samples were taken at the influent and effluent of a conventional WWTP in Wiesbaden, Germany (300,000 population equivalent, pe) and processed for three oestrogens (n = 2). The plant includes pretreatments (screening, aerated grit removal), primary clarification and activated sludge systems for biological and chemical phosphate removal, denitrification and nitrification. SRT is roughly 11–13 d.
3	Andreozzi et al. (2003)	Grab samples and 24-h composite samples were taken between February and March 2001 at the inlet and outlet of the secondary treatment step of five CAS systems, treating domestic and industrial wastewaters, in different countries (Greece, Italy and Sweden). They serve populations ranging from 6000 to 900,000 inhabitants. All plants featured a primary settling phase and one a chemical phosphorus removal step. 26 PhCs were investigated.
4	Baronti et al. (2000)	24-h composite samples of the influent and secondary effluent of six CAS systems in the area of Rome, Italy, were collected once a month over five months (n = 5) and processed for four oestrogens. The plants have flow rates ranging between 10,000 and 734,000 m^3/d and HRT in the range 12–14 h. They serve populations ranging between 40,000 and 1,200,000 inhabitants.
5	Batt et al. (2006)	24-h flow-proportional composite samples were taken at the inlet and the outlet of the WWTP located in Amherst, NY. Samples were collected once a week for three consecutive weeks (n = 3), in 2006, and processed for iopromide and trimethoprim. The plant includes a primary clarifier and a two-stage secondary biological process (slurry system). Stage 1 is a CAS for substrate removal with HRT 1 h and SRT 6 d. Stage 2 is a CAS designed for nitrogen removal with HRT 2 h and SRT 49 d.
6	Baumgarten et al. (2007)	An investigation was carried out on an MBR pilot plant in order to evaluate the removal efficiencies of target pharmaceuticals during MBR treatment as well as to compare them with those obtained with simultaneously addition in the bioreactor of powdered activated carbon (PAC). Average elimination efficiencies are provided for some common antibiotics (in particular ciprofloxacin and enrofloxacin).
7	Bendz et al. (2005)	24-h flow-proportional and composite samples were taken at the inlet and secondary effluent of the Kallby WWTP (Sweden) in October 2002 (n = 1) and processed for 14 PhCs.
8	Bernhard et al. (2006)	The investigation carried out at the WWTP of Wiesbaden, Germany, receiving domestic (90%) and industrial (10%) wastewater, with a capacity equal to 282,000 pe. The plant consists of a grit removal tank, a clarification tank, a CAS for carbon and nitrogen removal (HRT = 22 h), a final clarification tank and microscreen. Moreover, a pilot submerged-MBR equipped with microfiltration membranes (pore size 0.4 μm) was installed and fed with preclarified water (HRT = 7–10 h). 24-h composite water samples (n = 10–11) were taken at the influent, the MBR permeate and the WWTP effluent between July 2004 and March 2005. Average removal rates for the two investigated systems were provided for 4 PhCs (diclofenac, ibuprofen, clofibric acid and carbamazepine). In addition, the concentrations of diclofenac are also provided at the three sampling points.
9	Brown et al. (2006)	48-h composite samples from the urban influent and the secondary effluent of the Albuquerque WWTP in New Mexico were taken and processed for 3 PhCs.
10	Carballa et al. (2004)	24-h composite samples were taken at the inlet and outlet of Galicia municipal WWTP (Spain) in October 2001, and in January and April 2002, and analysed for 6 PhCs. The plant has a capacity of 100,000 p.e. and consists of preliminary treatments (coarse and fine screening and aerated chambers for grit and fat removal), primary sedimentation and CAS (HRT 24 h).
11	Carballa et al. (2005)	24-h composite samples were taken at the influent and secondary effluent of the WWTP in Galicia (Spain, 100,000 inhabitants) in October 2001, January 2002, April 2002 and June 2002 and processed for five PhCs. The plant consists of preliminary treatment (fine screening, aerated chamber for grit and fat removal), primary sedimentation and CAS (mixed reactors followed by sedimentation tank). Average removal rates are provided for the selected compounds.
12	Carucci et al. (2006)	The investigation refers to a 2-L lab-scale SBR, working through six 4-h cycles each day, SRT 8–14 d, using the activated sludge system coming from municipal WWTP as inoculum and municipal wastewater as feed. Average removal rates are provided for ranitidine and atenolol.
13	Castiglioni et al., 2006	Six Italian large WWTPs were monitored for 16 PhCs during Winter (January–March 2004) and Summer (June–September 2004). All investigated plants are equipped with pre-treatments, primary sedimentation and CAS. 24-h composite samples were collected at the inlet and the outlet of each plant, and their average removal rates are provided.
14	Choi et al., 2008	Grab samples (n = 3) were taken between April and August 2005 at the influent and secondary effluent of four large municipal WWTPs within Seoul city boundary (Korea) and analysed for 9 PhCs.
15	Clara et al. (2004)	24-h composite samples were taken at the influent and the effluent of a CAS system in the South East of Austria (7000 pe, SRT 52–237 d) and in a pilot MBR (10–56 d, ultrafiltration membranes) during three monthly experimental campaigns in 2002. They were processed for 5 PhCs.
16	Clara et al. 2005a	24-h composite samples of influent and the secondary effluent of four full-scale CAS plants (SRTs: 2 d, 19 d, 48 d and 42 d) and a pilot MBR plant (SRT: 22–82) in Austria. Corresponding design capacities are $2.5 \cdot 10^6$ pe, $167 \cdot 10^3$ pe, $135 \cdot 10^3$ pe, $6 \cdot 10^3$ pe, and 50 pe. Mean average concentrations were provided for 8 PhCs.
17	Clara et al. (2005b)	Three urban CAS WWTPs and one pilot MBR plant, equipped with ultrafiltration membranes, were monitored in the South East of Austria. 24-h composite samples were taken at the inlet and outlet of each plant and analysed for 8 PhCs. The corresponding SRTs are: 52–114 d (CAS 1), 2 d (CAS 2) and 46 (CAS 3) and 10–55 d (MBR).
18	Coetsier et al. (2009)	24-h averaged flow-proportional samples were collected (n = 8) between June 2007 and February 2008 at the effluent of the WWTP of Alès in France (90,000 pe). The plant consists of a CAS system with extended aeration and simultaneous phosphorus precipitation.
19	Conti et al. (2011)	24-h flow-proportional samples were taken at the inlet of the large conventional WWTP in Pavia, Italy (160,000 inhabitants, HRT = 4 h) and processed for carbamazepine and oxcarbamazepine.
20	Costanzo et al. (2005)	Samples were taken (n = 2) at the influent and effluent of a CAS in Brisbane (Australia) and processed for three antibiotics (ciprofloxacin, norfloxacin and cephalexin).
21	Foster (2007)	Grab samples were taken at the raw influent and secondary effluent of the municipal WWTP of San Marco, Texas (USA) during periods of normal operation from October 2006 to March 2007. The plant includes preliminary treatments (screening, degritting), primary clarification and CAS. Average concentrations and variability ranges were provided for 10 PhCs.
22	García-Galán et al. (2011)	Collected data refer to the removal efficiencies observed for selected sulphonamide antibiotics in three municipal wastewater treatment plants in Spain, along the Ebro river basin. The three WWTPs consist of primary treatments followed by a conventional activated sludge system. HRT and SRT were respectively 10 h and 4 d for the first plant, 10 h and 6 d for the second one, 24–46 h and 19 d for the third one.
23	Ghosh et al. (2009)	Samples were collected at the influent and secondary effluent of four medium–large capacity CAS systems in Japan (flow rate: 576,000 m^3/d, 9500 m^3/d, 50,000 m^3/d, 57,000 m^3/d; SRT: 16–19 d, 13 d, 17 d, 14–18 d and HRT: 9.5–12 h, 14 h, 11 h, 2.8–5.5 h). Average influent concentrations and average removal rates are reported for 11 antibiotics.
24	Göbel et al. (2005)	24-h composite samples were taken at the influent and effluent of two conventional municipal WWTPs in Switzerland (55,0000 pe and 80,000 pe) and processed for 7 antibiotics between March 2002 and November 2003. The plants consist of preliminary treatments (screening and aerated gritting), primary clarification and nitrification–denitrification steps.

Table 2 (*continued*)

	References	Details of treatment plants and experimental investigations
25	Göbel et al. (2007)	Two full-scale CAS systems (55,000 pe, HRT = 15 h, SRT = 10–12 d; and 80,000 pe, HRT = 31 h and SRT = 21–25 d, respectively) and one pilot MBR (100 pe, SRT = 16–80 d) were investigated in Switzerland in order to compare their capacity to remove 7 selected antibiotics. CASs include denitrification and nitrification tanks, and the MBR consists of a cascade of stirred anaerobic, anoxic, aerobic compartments. 24-h flow-proportional composite samples were taken three times at each sampling point in each of the three experimental campaigns (March 2002, February 2003 and November 2003, n = 9). Only percentage removal rates are provided.
26	Golet et al. (2003)	24-h flow-proportional composite water samples were taken at the influent and secondary effluent of the largest urban WWTP in Zurich (600,000 pe), Switzerland and analysed for 2 antibiotics, ciprofloxacin and norfloxacin (n = 7), in October 2000. The plant consists of pretreatments (screening, gritting and primary clarification) and CAS steps (predenitrification–nitrification–secondary clarifier; HRT = 20 h and SRT = 11 d).
27	Gómez et al. (2007)	The inlet and the outlet of the municipal CAS system in Almeria (Spain, 62,000 inhabitants) were monitored during July 2003 and April 2004. Ten 24-h composite water samples and 12 discrete samples (monthly) were analysed for 7 PhCs.
28	Gulkowska et al. (2008)	Grab samples at the inlet and secondary effluent of two large CAS systems in Hong Kong operating at different HRTs (16 h and 21 h) but the same SRT (20 d) were processed for 7 antibiotics in December 2006.
29	Jones et al. (2007)	Grab samples were taken every 6 h at the inlet and outlet of a municipal CAS plant (150,000 pe) in southern England during the four dry investigation days in June 2004. The plant consists of preliminary treatments (screening, gritting), primary clarification and biological treatment (nitrification–denitrification), operating at a SRT of 13 d and HRT of 13.5 h. Average removal rates are provided for 4 selected PhCs (ibuprofen, acetaminophen, salbutamol and mefenamic acid).
30	Joss et al. (2004)	An experimental investigation was carried out in November 2002 at the conventional WWTP of Kloten (Switzerland) where a pilot-scale MBR was installed in parallel with the conventional WWTP of Altenrhein (Switzerland). The Kloten plant serves 55,000 pe and includes primary treatments (screening, aerated grit and primary clarifier), secondary treatments (denitrification, nitrification and simultaneous phosphorus removal with Fe^{+3}); its SRT is about 10–12 d. The MBR is a 100-pe pilot plant fed with primary effluent from the Kloten plant and equipped with stirred anaerobic and anoxic tanks followed by an aerobic filtration compartment, operating at SRT 30 d. Microfiltration and ultrafiltration membranes were tested. 24-h composite flow-proportional samples were taken at the influent and effluent of each plant and processed for 3 compounds (n = 6).
31	Karthikeyan and Meyer (2006)	24-h composite samples were collected from the inlet and the outlet of two WWTPs in the USA (serving 73,000 and 150,000 inhabitants) and processed for 6 PhCs (n = 2) in October 2001 and December 2002.
32	Kasprzyk-Hordern et al. (2009)	24 h composite samples (n = 10) of urban influent and secondary effluent of the Coslech WWTP (UK) (flow rate range between 150 and 300 L/s) during the period April–August 2007. 35 compounds were investigated and their removal rates evaluated in the CAS plant deployed as an extended aeration/oxidation ditch for carbon and nitrogen removal.
33	Khan and Ongerth (2005)	24-h composite samples were taken at the influent and the effluent of the municipal WWTP located in the outer western suburbs of Sidney, Australia (23,000 inhabitants). The plant consists of preliminary and primary treatments followed by a CAS system with additional phosphorus removal. Seven compounds were monitored over five week-days.
34	Kim et al. (2007)	The influent and the secondary effluent of six South Korean urban CAS systems were sampled for 15 PhCs between 2004 and 2005.
35	Kimura et al. (2005)	Samples were taken at the inlet and the outlet of a full-scale CAS system and two pilot MBRs to compare the removal rates of 6 PhCs. The two pilot plants were equipped with hollow-fibre microfiltration membranes and fed by raw (the same feeding the full-scale plant) and pretreated (pre-coagulated/clarified) municipal wastewater, respectively. In both MBRs HRT was 9 h, in CAS, HRT was 13 h.
36	Kimura et al. (2007)	Grab samples (n = 11) were taken at the influent and outlet of 1 full-scale CAS (Soseigawa, Japan, 125,000 m^3/d, HRT = 12 h and SRT = 7 d) and two MBRs (equipped with hollow fibre microfiltration membranes, fed by the same influent as the conventional treatment plant and operating at the same flow rate = 0.624 m^3/d and HRT = 6.7 h but at different SRT: 15 d and 65 d) between August–November 2005. 6 compounds were monitored.
37	Kreuzinger et al., 2004	Samples were taken at the inlet and secondary effluent of two full-scale Austrian CAS systems and at a pilot MBR plant (equipped with ultrafiltration membranes) operating at different SRTs: 9.6 d and 96 d for the full-scale plants, 20 and 41 for the MBR over a period of 7–14 days. Average removal rates are given for 9 selected PhCs.
38	Kümmerer et al. (1997)	8-h composite samples were taken from the influent to a WWTP in Forchheim (Germany) between January and April 1995 (n = 7) and processed for ifosfamide.
39	Li and Zhang (2011)	Removal efficiencies for selected antibiotics were investigated in two conventional Chinese WWTPs: Shatin, 600,000 inhabitants served and Stanley 27,000 inhabitants served. The two systems include an anoxic–aerobic activated sludge process, the first is characterised by HRT of 10 h and SRT of 12 d, while the second by a RT of 17 h and SRT of 7 d.
40	Lindberg et al. (2005)	Fourteen 24-hour flow-proportional composite samples were taken at the inlet and outlet of four Swedish conventional WWTPs in August 2002 and February 2003 and analysed for 6 antibiotics. The plants receive municipal and industrial wastewaters and have a capacity ranging from 50,000 and 644,000 inhabitants. HRTs are: 8 h, 11 h, 16 h and 24 h and corresponding SRTs are: 20 d, 22 d, 11 d and 15 d. Each plant consists of preliminary treatments (screening, sand and fat removal, chemical phosphorus removal, primary clarification) followed by a CAS system. For three out of the four plants, nitrogen removal is also performed.
41	Lindberg et al. (2006)	24-h composite samples of the influent and secondary effluent of the municipal WWTP of Umea, Sweden were investigated in the period November–December 2004. The influent is mechanically (3-mm split screen) and chemically (flocculation–precipitation) pretreated. Its HRT is 8 h and SRT 20 d; 3 antibiotics were monitored.
42	Lindqvist et al. (2005)	24-h composite samples of the influent and secondary effluent of seven full-scale CAS systems in Finland were taken in September 2003 and processed for 5 PhCs. Four of the CAS systems used a denitrification–nitrification process for nitrogen removal and all of them feature a simultaneous biological treatment for removal of P.
43	Lishman et al. (2006)	24-h composite samples were taken at the influent and secondary effluent of 7 CAS systems in Canada. The investigation lasted between October and December 2002 and monitored 12 PhCs.
44	Maurer et al. (2007)	24-h composite samples were taken during a 3-day study period at the inlet and the outlet of two CAS systems (including nitrification–denitrification) near Zurich, Switzerland, and processed for 4 beta-blockers. The first plant has a capacity of 50,000 inhabitants, an HRT of 6.6 h and an SRT of 8–10 d. The second serves a population of about 36,000 inhabitants, operates at an HRT of 18 h and at an SRT of 14 d.
45	McAvoy et al., 2002	24-h flow-proportional composite samples (n = 2) were taken at the inlet and the outlet of one CAS plant in Loveland (27,000 p.e., 12,000 m^3/d, HRT = 6 h) in the USA. They were processed for triclosan in November 1997.
46	Metcalfe et al. (2010)	24-h composite water samples were collected at the influent and secondary outlet of a WWTP, in Southern Ontario, serving a population of approximately 69,000 using conventional activated sludge system and tertiary treatment followed by UV disinfection. The WWTP consists of two parallel trains (HRT = 11.9 h in both lines and SRT of 8.1 d and 10.4 d).
47	Muñoz et al. (2009)	Samples were taken at the outlet of two large WWTPs in Spain: El Ejido (64,000 inhabitants) and Alcalá (375,000 inhabitants) and processed for 12 PhCs. The plants include coarse-solid and grease removal, primary settling and anoxic–aerobic biological treatment with activated sludge for C and N removal.
48	Nakada et al. (2006)	24-h composite samples (n = 16) of the influent and secondary effluent of five conventional activated sludge plants serving populations ranging from 464,000 to 2,020,000 inhabitants (HRT from 7.1 to 9.4 h and SRT from 3.8 to 8.4 d) in Tokyo, Japan, from December 2001 and February 2003. 10 PhCs from different classes were investigated.

(*continued on next page*)

Table 2 (*continued*)

	References	Details of treatment plants and experimental investigations
49	Paxéus (2004)	24-h composite flow-proportional and grab samples were taken at the inlet and secondary effluent of 10 different full-scale CAS systems processing domestic and industrial wastewater in different European countries. All feature primary settling followed by CAS. Investigations were carried out between February 2001 and March 2003 on 9 PhCs (n = 2–10). Effluent average concentrations are provided for each compound for all plant and average removal rates where possible.
50	Peng et al. (2006)	Grab samples were taken at the influent and effluent of Guangzhou conventional WWTP (China, 195,000 pe) and processed for 4 antimicrobials (sulfadiazine, sulfamethoxazole, ofloxacin and chloramphenicol). Average influent and effluent concentrations were provided.
51	Quintana et al. (2005)	24-h composite samples (n = 7) were taken at the inlet and outlet of a pilot MBR plant (HRT = 8.8–10 d; SRT = 37 d) equipped with Kubota plate membranes (0.4 μm) and fed by municipal wastewater in Germany. Average influent and effluent concentrations and average removal rates were provided for 5 PhCs (diclofenac, ketoprofen, bezafibrate, naproxen, ibuprofen) monitored between January and April 2004.
52	Radjenovic et al. (2007)	24-h composite water samples were taken at the inlet and the outlet of the municipal CAS system in Rubi (Spain, 125,000 pe) and in a pilot MBR fed in parallel. Pretreatments consist of screening, gritting and primary sedimentation. Biological system includes denitrification–nitrification sedimentation and has SRT 3 d and HRT 12 h. MBR was equipped with Kubota flat sheet microfiltration membranes (0.4 μm) operating at HRT 14 h and "infinite" SRT (as no sludge was discharged from the reactor during the investigation period, May–June 2005). 22 selected PhCs were monitored, and their range of variability in the influent and the removal achieved by CAS and MBR were reported.
53	Radjenovic et al. (2009)	24-h flow-proportional composite samples (n = 9) were taken at the influent and secondary effluent of the municipal conventional WWTP in Terrassa (Barcelona, Spain) and at the effluent of two pilot MBR plans fed in parallel after preliminary treatments and primary clarification. The full-scale plant serves 277,000 pe and has an average flow rate 42,000 m^3/d, SRT 10 d and HRT 11.5 h. It consists of preliminary treatment (grit and sand removal), primary clarification and aeration, followed by secondary clarification. The first pilot plant is equipped with hollow-fibre ultra-filtration membranes (nominal porosity 0.05 μm) and operates at HRT 7.2 h. The second features micro-filtration flat-sheet membranes (nominal porosity 0.4 μm) and operates at HRT 15 h. Variability ranges and average influent concentrations of 26 PhCs and their corresponding removal rate are given; data was collected between March and April 2007.
54	Reif et al. (2008)	The investigation carried out on a pilot MBR plant equipped with submerged hollow-fibre membrane module (0.04 μm) fed by synthetic water simulating domestic sewage. Its HRT is 12–24 h and its SRT 44–72 d. Influent and permeate concentrations were sampled and processed for 9 PhCs.
55	Roberts and Thomas (2006)	24-h composite samples were taken at the influent and the effluent of Howdon WWTP (230,000 m^3/d) (UK) consisting of screening, primary clarification and CAS (SRT = 2.4 d, HRT = 12.5 h). 11 PhCs were investigated, and average concentrations at the two sampling points and average removal rates are provided.
56	Rodriguez et al. (2003)	24-h composite samples were taken at the influent and effluent of a municipal WWTP in Spain (serving 100,000 inhabitants) and processed for ibuprofen and naproxen between October 2001 and February 2002. Their influent and effluent concentrations as well as their average removal rates are reported.
57	Rosal et al. (2010)	The influent and secondary effluent of the 10,000 pe WWTP of Alcalà (Spain) was monitored every month over a year. The plant featured a traditional A2O multistage configuration with nitrification–denitrification and enhanced simultaneously phosphorus removal. 30 PhCs were monitored.
58	Ruel et al. (2010)	24-h composite water samples were taken at the influent and effluent of 6 different CAS plants (SRT range 13–26) in France and processed for 3 PhCs: the antibiotics roxithromycin and sulfamethoxazole and the antiseptic triclosan.
59	Sahar et al. (2011)	Water samples were taken at the raw influent of one municipal WWTP in Tel Aviv (Israel) and at the inlet and outlet of a municipal WWTP in Berlin (Germany) and processed for 6 antibiotics. The Berlin plant consists of a conventional CAS (HRT = 24 h, SRT = 9–15 d) and an MBR (HRT = 15 h; SRT > 70 d, equipped with submerged non-woven flat sheet pillow membranes (10 μm). Variability ranges and average concentrations of the influents are provided, together with the average removal rates measured in the Berlin CAS and pilot MBR.
60	Santos et al. (2007)	24-h flow-proportional composite samples (n = 21) were taken at the inlet and secondary effluent of four urban full-scale CAS systems in Spain. 5 PhCs were analysed for 21 days between July and September 2004. The plants have nominal capacity ranges between 20,000 and 950,000 pe, HRT between 12 and 17 h, and SRT between 1.5 and 5 d.
61	Santos et al. (2009)	24-h flow-proportional composite samples (n = 63) were taken at the inlet and secondary effluent of two CAS systems in Spain between June 2004 and June 2005 and processed for 5 PhCs. Their design capacities are 350,000 pe and 950,000 pe, the corresponding operating conditions: HRT 12 h and 17 h and SRT 1.5 d and 2.7 d.
62	Snyder et al. (2006)	The investigation refers to a pilot MBR equipped with ultrafiltration membranes (nominal pore size 0.08 μm) fed by primary effluent. 12 selected PhCs were monitored at the influent of the WWTP and at the MBR permeate.
63	Stumpf et al. (1999)	24-h composite samples were taken at the inlet and the outlet of one CAS system in Rio de Janeiro (Brazil) during June 1997 (n = 6) and processed for 9 PhCs (anti-inflammatories and lipid regulators).
64	Suárez et al. (2005)	Water samples were taken at the inlet and the outlet of a pilot CAS system and processed for 5 common PhCs of different therapeutic classes. The plant operated at SRT = 60 d and HRT = 1 d. It includes a denitrification–nitrification sequence.
65	Tauxe-Wuersch et al. (2005)	24-h flow-proportional composite water samples were taken (n ranging between 4 and 7) at the inlet and outlet of three CAS systems in Berne (Switzerland, 23,000 inhabitants, 9300 m^3/d), Morges (Switzerland, 29,000 inhabitants, 8500 m^3/d) and Lausanne (Switzerland, 220,000 inhabitants, 100,200 m^3/d). Each plant consists of a screen and sand trap, fat separator, primary clarifier and biological activated sludge reactor with simultaneous phosphorus chemical precipitation, and secondary clarifier. Variability ranges and average influent and effluent concentrations and average removal rates are provided for 5 PhCs.
66	Ternes et al. (1999)	24-h flow-proportional composite samples (n = 6) were taken at the influent and effluent of two CAS systems in Frankfurt Main (German) and Penha Rio de Janeiro (Brazil) in 1997 and processed for 3 oestrogens (estrone, 17β-estradiol, 17α-ethinylestradiol). In addition in the same periods, effluents of 16 municipal German WWTPs and 10 Canadian WWTPs were also investigated for the same PhCs.
67	Ternes et al. (2003)	The effluent of a conventional municipal WWTP (380,000 pe) was monitored (n = 6) and analysed for 18 PhCs. The plant consists of mechanical pretreatment, followed by nitrification–denitrification, biological phosphate removal and secondary clarification.
68	Ternes (1998)	24-h composite samples were taken at the inlet and outlet of a full scale conventional WWTP near Frankfurt (312,000 pe, preliminary clarification, followed by aerator tank and addition of Fe(II)chloride for phosphate removal and final clarification) over a period of six days covering 5 weeks in different periods between May 1996 and November 1997. Average removal rates are provided for 14 PhCs. 49 full-scale municipal treatment plants (all containing preliminary treatment, aeration tank and final clarification steps; 43 plants are equipped with phosphate removal, 25 plants with nitrification, and 13 denitrification steps) were also investigated between November 1995 and November 1997, and average effluent concentrations were provided for 35 PhCs.
69	Thomas and Foster (2005)	24-h flow-and time integrated composite samples were collected at the influent and the secondary outlet of the urban WWTP in Arlington, VA, USA (194,000 served population) and processed for four analgesics/anti-inflammatories and one antiseptic. The same compounds were monitored in grab samples withdrawn at the influent and outlet of other two urban WWTPs (City of Alexandria Sanitation Authority and Noman M Cole Water Pollution Control Plant, serving a population of 375,000 and 500,000 respectively). Each WWTP consists of preliminary treatments (bar screens and grit removal), primary settling, conventional activated sludge/biological nutrient removal. In addition phosphorus precipitation, gravity filtration and disinfection are included.
70	Vieno et al. (2005)	24-h composite samples were taken at the influent and effluent of Aura municipal WWTP (Finland) in four days between September 2003 and March 2004. The WWTP is a ditch oxidation tank, consisting of an activated sludge compartment (SRT 20 d and HRT 36 h) with simultaneous phosphorus precipitation by adding ferric salt. Average concentrations of 5 selected PhCs (bezafibrate, diclofenac, ketoprofen, naproxen and ibuprofen) were provided for the two sampling points.

Table 2 (*continued*)

	References	Details of treatment plants and experimental investigations
71	Vieno et al. (2007)	24-h composite samples were taken at the inlet and outlet of 9 full-scale conventional municipal plants (SRT range 2–15 d and HRT range 7–20 h) in Finland between 2004 and 2005 and processed for 7 common PhCs.
72	Watkinson et al. (2007)	The urban influent and secondary effluent of a large CAS system (140,000 m^3/d) in Brisbane, Australia, were monitored for the 22 most commonly administered PhCs (n = 5). Bioreactor HRT was 11 h and SRT 12.5 d. Pretreatments consisted of screening, gritting and primary settling.
73	Weigel et al. (2004)	Samples were taken at the influent and effluent of Hamburg WWTP (Germany) in November 2002, and processed for 4 PhCs (ibuprofen, diclofenac, clofibric acid, triclosan).
74	Wick et al. (2009)	48-h and 72 h-composite samples were collected from the inlet and outlet of a German municipal WWTP in (1,350,000 pe) on 7 days in March 2007, May 2007 and July 2007 (n = 9). The WWTP consists of a cascade of two CAS units operating under aerobic (HRT = 1 h and SRT = 0.5 d) and anoxic–aerobic conditions (HRT = 5 h and SRT = 18 d), respectively. Pretreatments include screen, aerated grit-removal tank and primary clarifier. The second biological step includes simultaneous phosphate precipitation. 11 PhCs (beta-blockers and psychiatric drugs) were monitored.
75	Xu et al. (2007)	24-h composite water samples were taken at the inlet and effluent of the CAS system in New Territory (Hong Kong) and processed for 5 PhCs (n = 6). The plant serves 300,000 inhabitants and operates at HRT = 15–22 h and SRT = 5.6–8.2 d. It consists of preliminary treatments (screening, aerated gritting), primary clarifier and biological treatment, including denitrification–nitrification sequence. Sampling and analysis were performed in October 2005.
76	Yasojima et al. (2006)	24-hour flow-proportional composite samples were taken at the inlet and the outlet of six full-scale CAS systems in Japan and processed for two antimicrobials (clarithromycin and azithromycin). Their HRT range between 4 and12 h and their SRT 5–9 d.
77	Yu et al. (2006)	24-h composite samples were taken at the inlet and the effluent of the Baltimore WWTP that receives about 8.5×10^5 m^3/d of residential and urban wastewaters. The plant is a CAS system (SRT = 8–10 d) designed for biological nutrient removal. 10 between pharmaceuticals and antiseptics were monitored.
78	Zorita et al. (2009)	24-h composite samples were collected from the inlet and outlet of the municipal WWTP in Kristianstad (Sweden, 150,000 inhabitants, HRT range 24–40 h and SRT roughly 8 d) in June 2007 and April 2008 (n = 3) and processed for 12 PhCs. Pretreatments include screening, aerated grit removal and primary sedimentation, the biological section includes denitrification–nitrification.

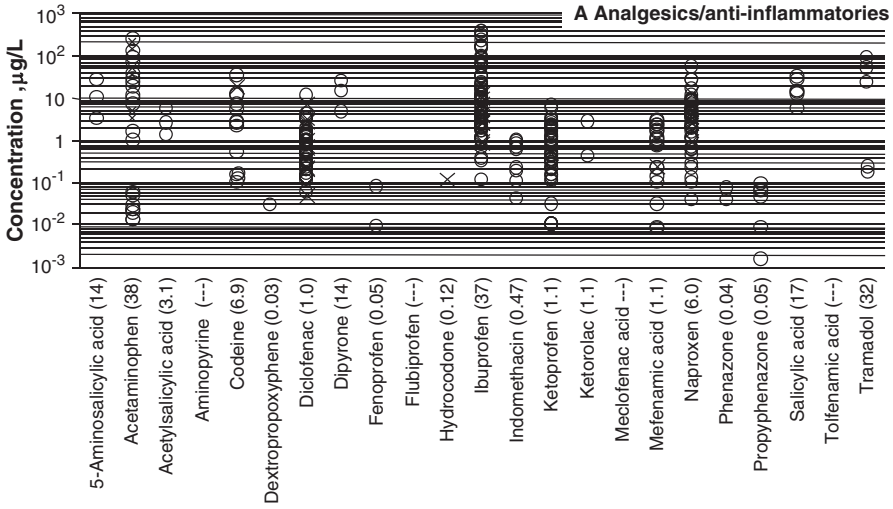


Fig. 1. Concentration of selected analgesics/anti-inflammatories measured in the raw influent to municipal WWTP (○ refers to CAS and × to MBR) and corresponding average values (in brackets).

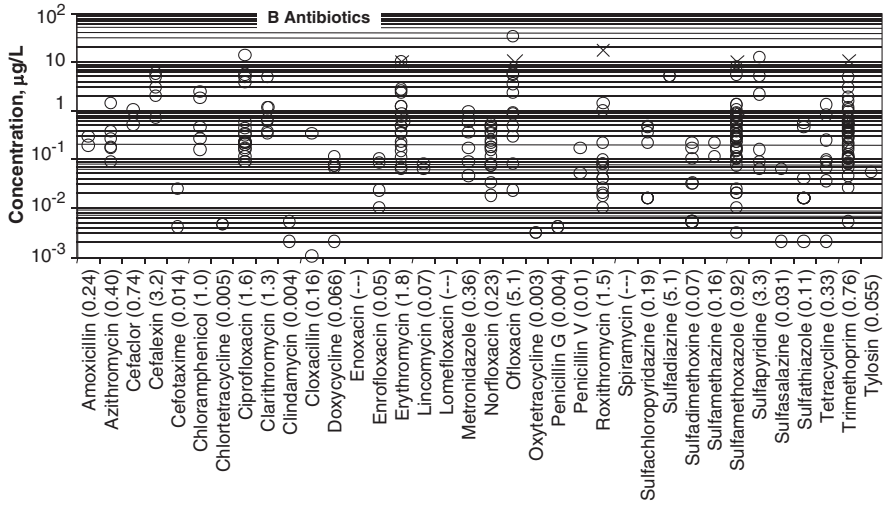


Fig. 2. Concentrations of selected antibiotics measured in the raw influent to municipal WWTPs (○ refers to CAS and × to MBR) and corresponding average values (in brackets).

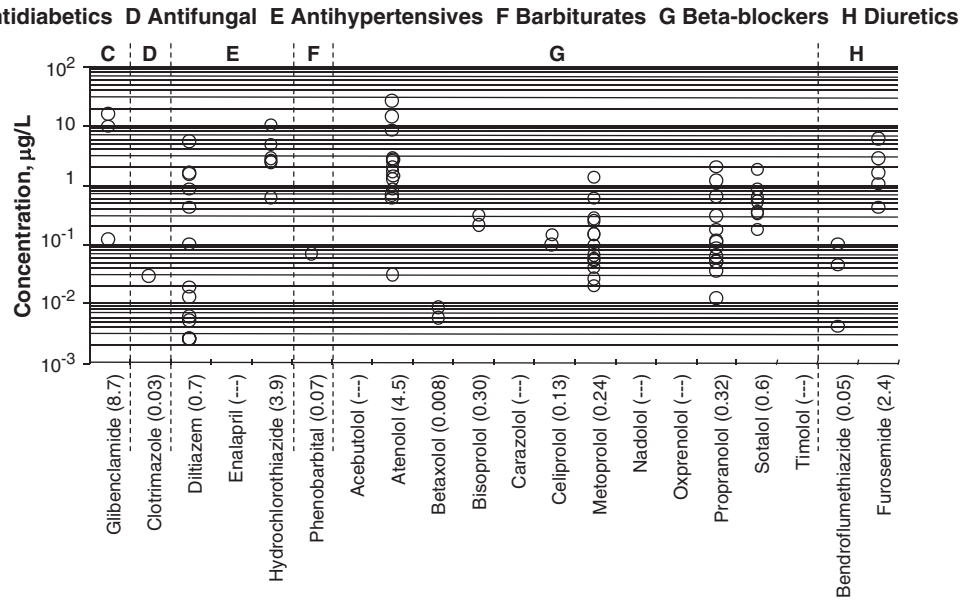


Fig. 3. Concentrations of selected PhCs belonging to six therapeutic classes measured in the raw influent to municipal WWTPs (○ refers to CAS and × to MBR) and corresponding average values (in brackets).

pH = 7). These, if found on the same molecule (e.g. ciprofloxacin), can cause it to be neutral, cationic, anionic or zwitterionic under different environmental conditions, (Kümmerer, 2009a; Ternes and Joss, 2006) resulting in (very) different behaviours during treatment processes as it will be discussed later.

2.2. Main features of the investigated WWTPs

Table 2 lists the main features of the WWTPs investigated in each study (second column), as well as the details of the experimental campaigns (sampling mode, number of samples, observation period, number of investigated PhCs). 244 CAS systems (242 full-scale and 2 pilot plants) and 20 MBRs (all pilot plants) situated in various world locations were included in this study: 68% of the WWTPs are situated in European countries (Spain, Germany, Italy, Switzerland, Sweden, Austria, UK, Finland, France, Greece and Denmark), 14% in the Americas (USA, Canada and Brazil), 14% in Asia (China, Japan, Israel, South Korea and North Korea) and 4% in Australia.

The raw wastewaters influent to these plants are generally subjected to preliminary treatments (bar screening and grit removal), then primary sedimentation followed by the secondary biomass growth treatment (CAS or MBR, the majority of the latter equipped with ultrafiltration or, in a few cases microfiltration, membranes). This final step usually included denitrification–nitrification and carbon removal processes, and in some cases simultaneous precipitation of phosphate by the addition of Fe salts. CAS operates at an HRT ranging from 2 to 24 h and at an SRT generally equal to 2–20 d with some exceptions, while MBR at the HRT of 7–15 h (with few exceptions) and at the SRT equal to 15–80 d (with a few exceptions).

In general, chemical analysis of PhCs was performed on 24-h composite water samples, quite often flow-proportional, thereby avoiding the risk of under- or over-estimating the average daily concentrations

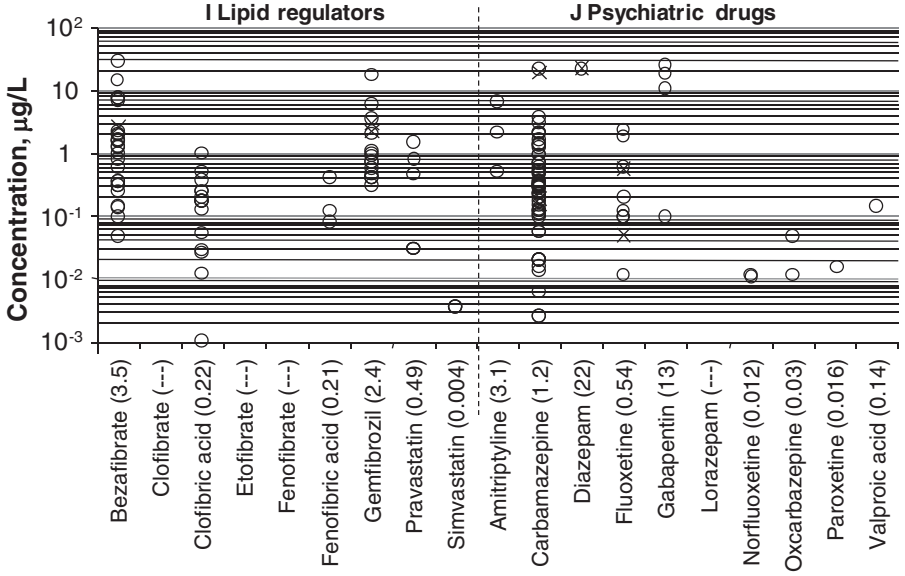


Fig. 4. Concentrations of selected lipid regulators and psychiatric drugs measured in the raw influent to municipal WWTPs (○ refers to CAS and × to MBR) and corresponding average values (in brackets).

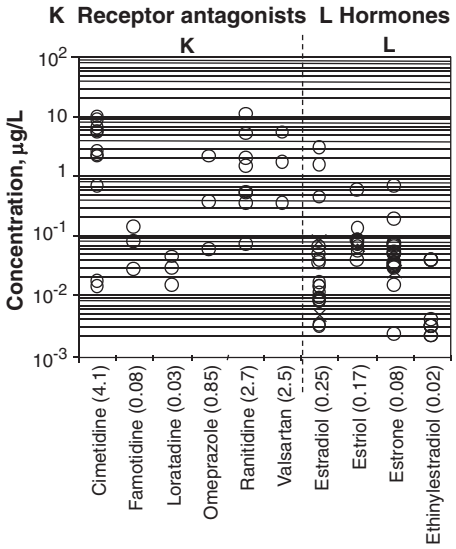


Fig. 5. Concentrations of selected receptor antagonists and hormones measured in the raw influent to municipal WWTPs (○ refers to CAS and × to MBR) and corresponding average values (in brackets).

in the wastewater. Experimental investigations were mainly based on a number of samples ranging between 3 and 12. Few studies collected multiple data sets for each sampling point. Water samples were generally taken in dry days in order to avoid dilution of the influent in case of combine sewage and due to parasite streams and dilution of the effluent caused by washout of the biological tanks.

Collected data report the pharmaceutical concentrations in raw urban wastewaters and in the corresponding treated biological effluent, as well as the global removal efficiencies achieved after the secondary treatment. The urban wastewater considered includes both the effluent produced by domestic users and that from (small) industrial activities, which, according to the local regulation, may be discharged into the public sewer network and conveyed to the municipal WWTP.

Experimental investigations were carried out at different times of the year, and the overall data therefore covers periods characterised by higher and lower PhC consumptions, enabling this review to provide

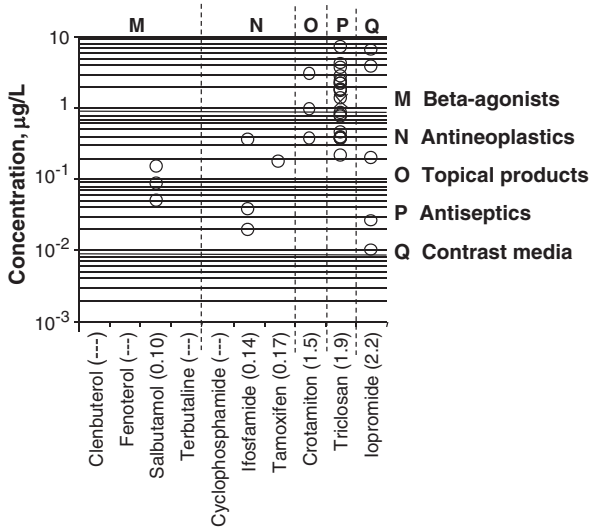


Fig. 6. Concentrations of other classes of micropollutants measured in the raw influent to municipal WWTPs (○ refers to CAS and × to MBR) and their corresponding average values (in brackets).

a balanced overview, bolstered by taking into account the different consumption habits in the different countries worldwide.

2.3. Quality assurance of literature data

As reported by the EC Technical Guidance Document on risk assessment (EC, 2003) and as remarked by many Authors (among them Liebig et al., 2006; Ternes and Joss, 2006), it is vital that the quality of literature data is assured. For this reason, to be included in the present review, references had to feature a description of the analytical methodology used for the assessment of measured concentrations and the quality assurance programme adopted for sampling, analysis and elaboration. In particular, they provide the following information: list of analytes, solvents and chemicals used; details of sampling, transport and storage in addition to sample volume; analytical methods adopted, including pH adjustment, filtration and filter material, extraction and solvent evaporation techniques; derivatisation and detection method; surrogate and/or instrumental standards used; methods and limits of quantification, recovery measurements, procedural and instrumental blanks used; sampling conditions, location, frequency and period and compartment characteristics.

3. Results and discussion

The first 19 figures report literature data pertaining to the compounds listed in Table 1 collected, while the last two figures report daily mass loads (Fig. 20) and risk quotient (Fig. 21) for most of the selected compounds, calculated as described below. In Figs. 1–19, data referring to CAS and MBR are indicated by circles and crosses, respectively, allowing clear distinction between the two. In this way, for each compound and for each class, the number of data collected, the most commonly investigated compounds and the data spread in variability range are evident. Moreover, in the Supplementary data, for each compound under review, three tables provide the variability ranges of its concentrations in the influent (Table SD2), in the effluent of CAS and MBR systems examined (Table SD3) and its removal efficiencies (Table SD4) together with its corresponding references.

3.1. Occurrence of pharmaceuticals in raw urban wastewater

Literature data referring to the concentrations of PhCs, grouped in alphabetic order in their therapeutic classes, in the raw influent to a municipal WWTP are reported in Figs. 1–6. The average of the considered data is shown in brackets after the name of each compound on the X-axis. Influent data was not available for some compounds, for example the analgesic aminopyrine, but these are nevertheless included in the graphs as data referring to their secondary effluent concentrations and/or removal efficiencies were available.

Referring to Fig. 1, the variability of analgesics/anti-inflammatories was found to range between 0.0016 and 373 µg/L. The most commonly investigated compounds were ibuprofen, diclofenac, naproxen and ketoprofen. Ibuprofen was the compound with the highest registered absolute influent concentration (373 µg/L), followed by acetaminophen (246 µg/L), tramadol (86 µg/L) and naproxen (53 µg/L). Acetaminophen and ibuprofen also had the highest average influent concentrations (respectively 38 µg/L and 37 µg/L), followed by tramadol (32 µg/L).

As to Fig. 2, the range of variability of antibiotic concentrations was between 0.001 and 32 µg/L. The most commonly investigated compounds were trimethoprim, sulfamethoxazole, erythromycin and ciprofloxacin. The highest absolute concentrations were found for ofloxacin (32 µg/L), roxithromycin (17 µg/L) and ciprofloxacin (14 µg/L). Other antibiotics exhibiting measured concentrations greater than 10 µg/L are: sulfapyridine (12.4 µg/L), trimethoprim (10.5 µg/L) and erythromycin (10.2 µg/L). The highest average antibiotic concentrations were found for ofloxacin and sulfadiazine (5.1 µg/L), followed by sulfapyridine (3.3 µg/L) and cefalexim (3.2 µg/L). No data

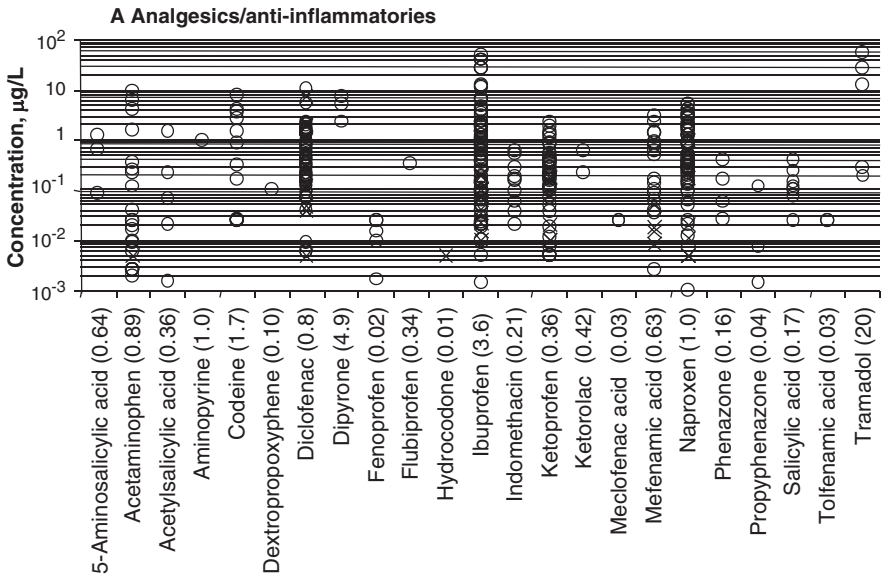


Fig. 7. Concentration of selected analgesics/anti-inflammatories measured in the secondary effluent (○ refers to CAS and × to MBR) and corresponding average values (in brackets).

were provided for enoxacin, lomefloxacin and spiramycin concentrations in the raw urban wastewater.

Fig. 3 reports data for six, less investigated, classes, comprising 20 compounds; indeed, only one antifungal, barbiturate and antidiabetic were reported. The observed ranges of variability were: 0.12–16 µg/L for antidiabetics, 0.0025–10 µg/L for antihypertensives, 0.006–25 for beta-blockers, and 0.004–6 for diuretics. The single values found for the antifungal and barbiturate were respectively: 0.029 µg/L (clotrimazole) and 0.07 µg/L (phenobarbital).

The highest concentrations were found for the beta-blocker atenolol (25 µg/L), followed by the antidiabetic glibenclamide (16 µg/L) and the antihypertensive hydrochlorothiazide (10 µg/L). The highest average concentrations were found for glibenclamide (8.7 µg/L), followed by atenolol (4.5 µg/L), hydrochlorotiazide (3.9 µg/L) and furosemide (2.4 µg/L).

Raw urban wastewater concentration data were unavailable for five out of the 12 beta-blockers and the antihypertensive enalapril. The data spread within the observed variability range was the greatest for diltiazem, another antihypertensive.

Referring to Fig. 4, the variability for the selected lipid regulators was found to range between 0.001 and 30 µg/L, and for psychiatric drugs between 0.0025 and 25 µg/L. In the former class, the most commonly detected compounds were bezafibrate, gemfibrozil and clofibric acid, in the second one carbamazepine and fluoxetine. The highest absolute concentrations were found for bezafibrate (30 µg/L), gabapentin (25 µg/L), diazepam (23 µg/L), carbamazepine (22 µg/L) and gemfibrozil (17 µg/L), whereas the highest average concentrations were found for diazepam (22 µg/L), gabapentin (13 µg/L), bezafibrate (3.5 µg/L) and amitriptyline (3.1 µg/L). Only one datum is present for paroxetine (0.0016 µg/L) as well as for valproic acid (0.0014 µg/L). Data are not available for the lipid regulators clofibrate, etofibrate and fenofibrate, or for the psychiatric drug lorazepam.

As to Fig. 5, the variability range of selected receptor antagonists was between 0.014 and 11 µg/L, and that of hormones between 0.002 and 3 µg/L. The most frequently detected compounds were the four hormones (estrone, estradiol, ethinylestradiol and estriol) and cimetidine. The highest absolute concentrations were found for ranitidine (11 µg/L) and cimetidine (10 µg/L), while the highest

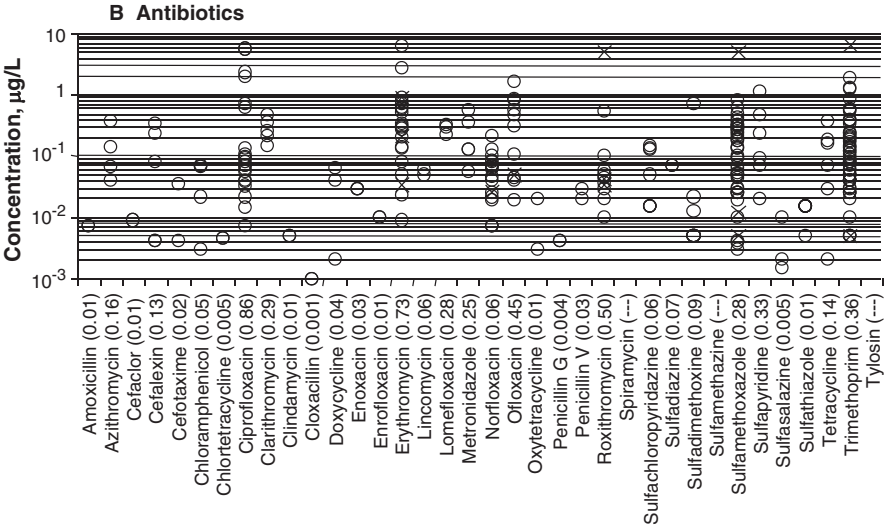


Fig. 8. Concentration of selected antibiotics measured in secondary effluent (○ refers to CAS and × to MBR) and corresponding average values (in brackets).

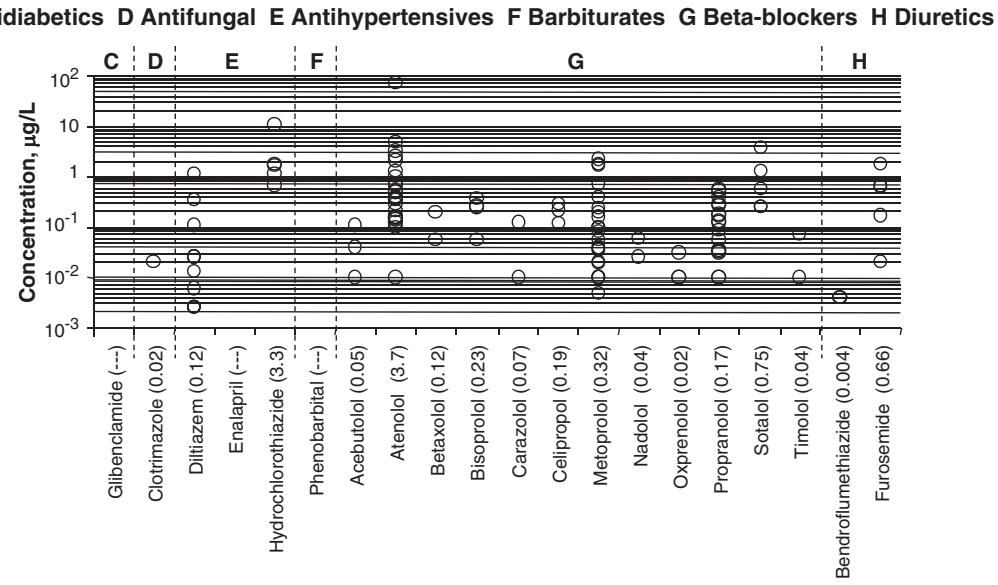


Fig. 9. Concentrations of selected PhCs from different classes measured in secondary biological effluent (○ refers to CAS and × to MBR) and corresponding average values (in brackets).

average values were found for cimetidine (4.1 μg/L), ranitidine (2.7 μg/L) and valsartan (2.5 μg/L). Among the four hormones included in the review, the estradiol presented the highest absolute concentration (3 μg/L) as well as the highest average observed value (0.25 μg/L).

Fig. 6 reports data pertaining to 5 classes, three of which (topical products, antiseptics and contrast media) feature only one investigated compound. Out of the four beta-agonists under review, only one (salbutamol) exhibits values of influent concentrations and, out of the three antineoplastics, only two compounds were found (ifosfamide and tamoxifen). The observed ranges of variability are: 0.05–0.15 μg/L for beta-agonists, 0.019–0.36 μg/L for antineoplastics, 0.38–3 μg/L for the topical product crotamiton, 0.22–7 μg/L for the antiseptic triclosan and 0.01–6.6 μg/L for the contrast agent iopromide. The highest absolute concentrations were found for triclosan (7 μg/L) and iopromide (6.6 μg/L). The highest average concentrations were found for iopromide (2.2 μg/L) and triclosan (1.9 μg/L).

3.2. Secondary biological effluent concentrations of pharmaceuticals

Figs. 7–12 refer to the concentrations of PhCs detected in the effluent of the WWTPs included in this review. As reported in Table 2, these generally consist of preliminary treatments (bar screening and grit removal), primary sedimentation and secondary biological suspended mass reactor, i.e. CAS (with different configurations, quite often including an anoxic–aerobic reactor and sometimes with a simultaneous precipitation of phosphate), followed by a secondary settler or an advanced MBR with anoxic–aerobic compartments. As reported above, in the X-axis of Figs. 7–12, average concentrations are reported alongside each compound in brackets.

Referring to Fig. 7, concentrations of analgesics/anti-inflammatories in the secondary effluent ranged between 0.001 and 57 μg/L. The most frequently detected compounds were ibuprofen, diclofenac, naproxen, ketoprofen and acetaminophen. The highest absolute concentrations

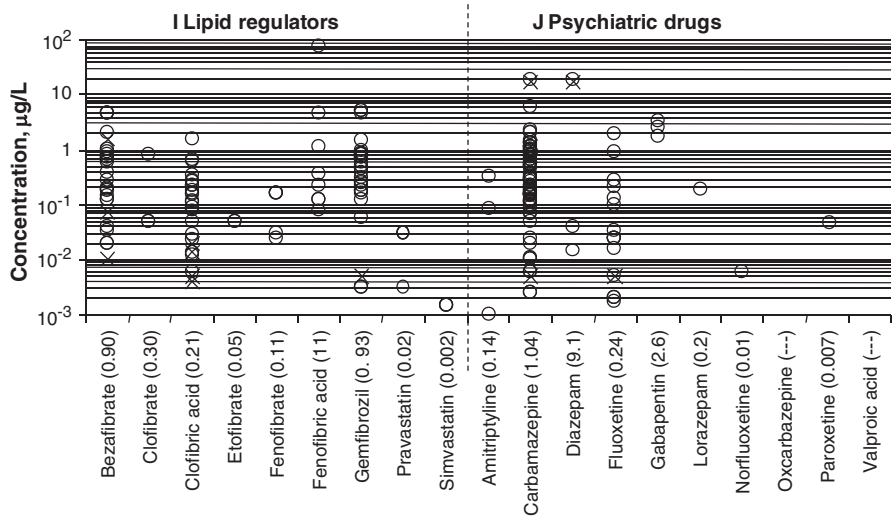


Fig. 10. Concentrations of selected lipid regulators and psychiatric drugs measured in secondary biological effluent (○ refers to CAS and × to MBR) and corresponding average values (in brackets).

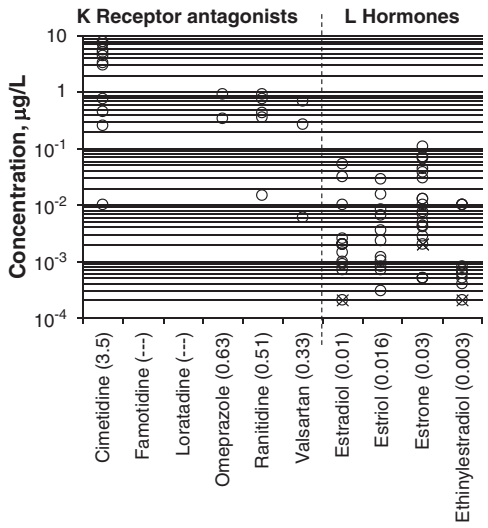


Fig. 11. Concentrations of receptor antagonists and hormones measured in secondary biological effluent (○ refers to CAS and × to MBR) and corresponding average values (in brackets).

were found for tramadol (57 µg/L), ibuprofen (48 µg/L) and diclofenac (11 µg/L), and the highest average values were found for tramadol (20 µg/L), dipyrone (4.9) and ibuprofen (3.6 µg/L).

Fig. 8 shows that, the range of variability for selected antibiotics in the secondary effluent was 0.001–6.7 µg/L. The most investigated compounds were trimethoprim, sulfamethoxazole, erythromycin, ciprofloxacin and norfloxacin. The highest absolute concentrations were found for trimethoprim (6.7 µg/L), erythromycin (6.3 µg/L), ciprofloxacin (5.7 µg/L), sulfamethoxazole and roxithromycin (5 µg/L), while the highest average values were found for ciprofloxacin (0.86 µg/L), erythromycin (0.73 µg/L), roxithromycin (0.50 µg/L) and ofloxacin (0.45 µg/L).

Referring to Fig. 9, two classes (antidiabetics and barbiturates), represented by only one compound, were never detected in any investigation. The range of variability for antihypertensives was 0.0025 to 11 µg/L, beta-blockers were detected between 0.005 and 73 µg/L, and diuretics between 0.004 and 1.8 µg/L. The most commonly detected compounds were the beta-blockers atenolol, metoprolol

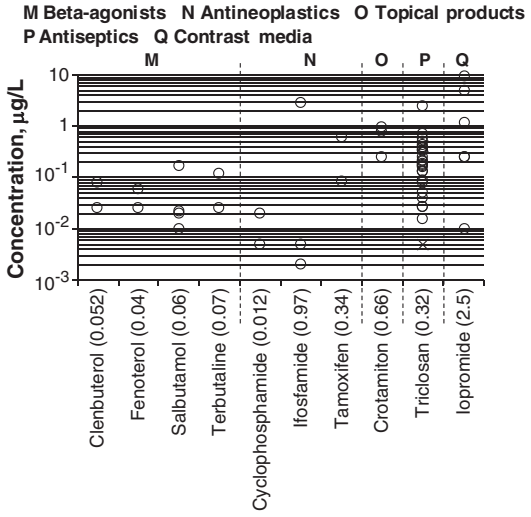


Fig. 12. Concentrations of other classes of micropollutants measured in secondary biological effluent (○ refers to CAS and × to MBR) and corresponding average values (in brackets).

and propranolol and the antihypertensive diltiazem. The antifungal clotrimazole was found only once, while data are not available for the antihypertensive enalapril. The highest absolute concentrations in these classes were found for atenolol (73 µg/L), hydrochlorothiazide (11 µg/L) and furosemide (1.8 µg/L). The same compounds exhibited the highest average concentrations: atenolol 3.7 µg/L, hydrochlorothiazide 3.3 µg/L and furosemide 0.66 µg/L.

It is worth remarking that the average concentration of all the other compounds remained less than 1 µg/L.

As shown in Fig. 10, the range of variability observed in the secondary effluent was 0.0015–80 µg/L for lipid regulators and 0.001–20 µg/L for psychiatric drugs. The most frequently investigated compounds were carbamazepine, gemfibrozil, bezafibrate and clofibric acid. Data were unavailable for oxcarbazepine and valproic acid. The highest absolute concentrations were found for fenofibric acid (80 µg/L), carbamazepine (20 µg/L), diazepam (19 µg/L) and gemfibrozil (5.2 µg/L), while the highest average concentrations were found for fenofibric acid (11 µg/L), diazepam (9.1 µg/L), gabapentin (2.6 µg/L) and carbamazepine (1.04 µg/L). All the other compounds had average values less than 1 µg/L. It is worth noting that the variability ranges are quite wide for most compounds: up to 5 orders of magnitude for carbamazepine.

As to Fig. 11, the range of variability observed after the secondary treatment was 0.006–7.8 µg/L for receptor antagonists and 0.0002–0.11 µg/L for hormones. The most commonly investigated compounds were estrone, estradiol, ethinylestradiol and cimetidine. The highest absolute and average concentrations were found for cimetidine (7.8 µg/L and 3.5 µg/L, respectively), which was the only receptor antagonist found with an average concentration greater than 1 µg/L; famotidine and loratidine were never detected in the effluent. Hormones were found at consistently lower concentrations, always lower than 0.11 µg/L.

Finally, the graph in Fig. 12 shows that the ranges of variability were 0.01–0.17 µg/L for beta-agonists, 0.002–2.9 µg/L for antineoplastics, 0.25–0.97 µg/L for topical products, 0.005–2.5 µg/L for antiseptics and 0.01–9.3 µg/L for contrast media. The most investigated compound was triclosan, while the others were monitored at a far lower frequency. Iopromide showed both the highest measured (9.3 µg/L) and the highest average concentrations (2.5 µg/L).

Fig. 13 summarises the range of variabilities of the different classes based on collected data for the influent and effluent of all CAS (244 plants) and MBRs (20 plants). At the bottom of the figure, a table reports the number of collected data for each class in the influent and effluent of all the CAS (circle) and MBRs (cross) under review. It is important to remark that data pertaining to MBRs are quite limited and these systems were always pilot plants.

A rapid glance at these intervals shows that the different classes have different trends. In fact, the range of variability of measured concentrations in secondary effluents is narrower and lower than in the influent for analgesics/anti-inflammatories (A), antibiotics (B), antifungal (D), diuretics (H), psychiatric drugs (J), receptor antagonists (K), hormones (L), topical products (O) and antiseptics (P), being quite similar for antihypertensives (E) and beta-agonists (M), but higher for beta-blockers (G), lipid regulators (I), antineoplastics (N) and contrast media (Q). For antidiabetics (C), and barbiturates (F) the comparison is not possible as data are not available for the effluent. Moreover, ranges of variability referring to MBR permeates are narrower than those referring to CAS effluents for all of the investigated classes.

3.3. Observed removal efficiencies

Figs. 14–19 report the observed removal efficiencies of PhCs from the aqueous phase achieved after secondary biological treatment in the WWTPs under study. These data are directly provided by listed references, in some cases, when it was possible, they were estimated by Eq. (1), assuming a constant WWTP influent and effluent flow rate, equal to the average daily flow rate and as influent and effluent

Table 3
Fractions with respect to the influent mass load of selected PhCs removed during secondary biological treatment, sorbed to sludge and discharged with secondary effluent. Data with an asterisk as apex refer to MBR systems.

Therapeutic class	Compound	Sludge age [d]	Biolog transform %	Sorption onto sludge %	Effluent %	References
Analgesic and anti-inflammatories **A**	Diclofenac	4–60	5–45	<5	55–95	Joss et al. (2005)
		6	25	<5	70–75	Jelic et al. (2011)
		16	10	5	85	Jelic et al. (2011)
		<20	5	0	95	Suárez et al. (2010)
		>50	10–30	0	70–90	Suárez et al. (2010)
	Ibuprofen	4–60	90–100	<5	0–10	Joss et al. (2005)
		2	<5	<5	95–100	Clara et al. (2005b)
		10–55*	95–100	<5	0–5	Clara et al. (2005b)
		<20	35–40	0	60–65	Suárez et al. (2010)
		>50	95	0	5	Suárez et al. (2010)
	Indomethacin	6	27	0	73	Jelic et al. (2011)
		16	40	<5	58–60	
	Ketoprofen	6	70	0	30	Jelic et al. (2011)
		16	<95		5–10	
	Mefenamic acid	6	65	7	28	Jelic et al. (2011)
		16	55–58	<30	<20	
	Naproxen	10–30	55–85	<5	15–45	Joss et al. (2005)
		6	77	0	23	Jelic et al. (2011)
		16	95–98	0	<5	Jelic et al. (2011)
		<20	5	0	95	Suárez et al. (2010)
		>50	85–90		10–15	Suárez et al. (2010)
Antibiotics **B**	Azithromycin	10–30	<40	<10	60–90	Göbel et al. (2007)
	Chloramphenicol	6	0	0	100	Jelic et al. (2011)
	Ciprofloxacin	10–12	<10	70–80	≤30	Golet et al. (2003)
		20	<10	77	<4	Lindberg et al. (2006)
	Clarithromycin	<20	<10	<5	75–90	Göbel et al. (2007)
		>50	90	<5	10	Göbel et al. (2007)
		<20	<10	≤10	>90	Göbel et al. (2007)
		6	0	18	82	Jelic et al. (2011)
		16	0	<45	55–60	Jelic et al. (2011)
	Enrofloxacin	20–25	19	65	17	Jia et al. (2012)
	Erythromycin	<20	20		80	Suárez et al. (2010)
	Lomefloxacin	20–25		60	40	Jia et al. (2012)
	Metronidazole	6	15–18		100	Jelic et al. (2011)
		16			82–85	
	Norfloxacin	10–12	<10	80–90	≤20	Golet et al. (2003)
		20	<10	72	<4	Lindberg et al. (2006)
	Ofloxacin	20–25		60	40	Jia et al. (2012)
	Roxithromycin	4–30	<60	<5	>35	Göbel et al. (2007)
		<20	18	2	80	Suárez et al. (2010)
	Sulfamethazine	6	<85	0	<20	Jelic et al. (2011)
		16	15–18	20	60–65	
	Sulfamethoxazole	4–12	50–90	<5	10–50	Göbel et al. (2007)
		<20	20	0	80	Suárez et al. (2010)
	Sulfapyridine	10–30	≤70	<10	≥30	Göbel et al. (2007)
	Trimethoprim	<50	~90	≤5	~10	Göbel et al. (2007)
		<20	<10	≤5	>90	Göbel et al. (2007)
		6	40	<5	<60	Jelic et al. (2011)
		16	38–40	5–10	50–55	Jelic et al. (2011)
		<20	18		72	Suárez et al. (2010)
Antidiabetics **C**	Glibenclamide	6		<10	90–95	Jelic et al. (2011)
		16		60	40	
Antihypertensives **E**	Enalapril	6	95–98		2–5	Jelic et al. (2011)
		16	95–98		2–5	
	Hydrochlorothiazide	6		100		Jelic et al. (2011)
		16		100		
Beta-blockers **G**	Atenolol	6	<70	<5	<35	Jelic et al. (2011)
	Metoprolol	6	~35	0	~65	Jelic et al. (2011)
		16	0	0	100	
	Nadolol	6	35–40	<5	60	Jelic et al. (2011)
		16	70	30		
	Sotalol	6	10	<5	<90	Jelic et al. (2011)
		16	<50	<5	50	
	Timolol	6	<40	<5	<65	Jelic et al. (2011)
		16	40–45	0	55–60	
Diuretics **H**	Furosemide	6	35–40	<5	60–65	Jelic et al. (2011)
		16	75–80	2–5	20	
Lipid regulators **I**	Bezafibrate	6	12	2	86	Jelic et al. (2011)
		16	<80	<5	20–25	Jelic et al. (2011)
		2	45–50	<5	50	Clara et al. (2005b)
	Fenofibrate	6	0	100	0	Jelic et al. (2011)
		16	25–30	65–70		
	Gemfibrozil	6	0	3	97	Jelic et al. (2011)
		16	90	<5	5–10	Jelic et al. (2011)

(continued on next page)

Table 3 (*continued*)

Therapeutic class	Compound	Sludge age [d]	Biolog transform %	Sorption onto sludge %	Effluent %	References
	Pravastatin	6	45	0	55	Jelic et al. (2011)
		16	62	2	<40	
Psychiatric drugs **J**	Carbamazepine	4–60	<40	<5	>60	Joss et al. (2005)
		6	22	3	75	Jelic et al. (2011)
		16	0	5	95	Jelic et al. (2011)
	Diazepam	6	0	42	58	Jelic et al. (2011)
		16		65	35	
	Fluoxetine	<20	80	0	20	Suárez et al. (2010)
		>50	90	0	10	Suárez et al. (2010)
	Lorazepam	6	30	<5	65–70	Jelic et al. (2011)
		16	30	5–8	65	
Receptor antagonists **K**	Cimetidine	6	42	4	54	Jelic et al. (2011)
		16	60	5–8	32–35	
	Famotidine	6	<10	10	85	Jelic et al. (2011)
		16	80	20	0	
	Ranitidine	6	<20	<5	80	Jelic et al. (2011)
		16	75	<5	20–25	
Hormones **L**	Estradiol	10–30	85–99	<5	<15	Joss et al. (2004)
	Estrone	10–30	35–97	≤5	5–60	Joss et al. (2004)
	Ethinylestradiol	10–30	45–95	≤5	5–50	Joss et al. (2004)
		<20	25	5	70	Suárez et al. (2010)
		>50	80–90	0	10–20	Suárez et al. (2010)
Beta-agonist **M**	Salbutamol	6	<60	<5	<45	Jelic et al. (2011)
		16	40–42	2	55–60	
Contrast agent **Q**	Iopromide	10–30	20–95	<5	5–80	Joss et al. (2005)

concentrations their corresponding average daily values (based on 24-h composite water samples). In Table SD4 in the Supplementary data it is possible to distinguish between removal data provided by the Authors and evaluated by means of Eq. (1):

$$\eta = \frac{c_{inf} - c_{eff}}{c_{inf}} \times 100 \quad (1)$$

η is the percentage removal efficiency and c is the average PhC concentration measured in the raw influent (subscript *inf*) or secondary effluent (subscript *eff*). As stated in Table 2, almost all the plants investigated include preliminary and primary treatments. As a consequence, η refers to the overall WWTP removal efficiency and takes into consideration removal by all the mechanisms occurring during preliminary, primary and secondary biological treatments: sorption onto coarse solids and sedimentation, in preliminary and primary treatments, and a combination of biodegradation/biotransformation due to suspended biomass and sorption onto particles, flocs and then sludge in biological processes.

According to many Authors (Khan and Ongerth, 2005; Ternes and Joss, 2006; Yasojima et al., 2006; Watkinson et al., 2007; Zorita et al., 2009), the efficacy in removing PhCs by preliminary and primary treatments is in general quite poor, and in some cases compounds may even be released during the process, probably caused by the simultaneous presence of deconjugable substances, that is human metabolites, of these compounds in the raw influent (Carballa et al., 2004, Göbel et al., 2005). In particular, in the pre-treatment and sedimentation step no significant reduction was found for ibuprofen and naproxen (Carballa et al., 2004). This can be correlated to their acidic structures (negative charge of the molecule at pH 7, as shown in Table SD1 in the Supplementary data), with very low solid–liquid partition coefficient K_d (according to Ternes et al., 2004, K_d<500 L/kg or Log K_d<2.7 implies very poor sorption onto sludge) which results in their presence mainly in the aqueous phase. For the hormone estrone, a higher concentration was observed at the end of the primary sedimentation with respect to the influent (Carballa et al., 2004), very likely due to the oxidation of the estradiol present, which explains the high negative removal efficiencies obtained for the estrone and the positive reduction of estradiol. (This is quite important to remember for the next sections as if the compound is found at a lower concentration in the secondary effluent than in the raw influent, the biological treatment is generally the greatest contributor).

As remarked above, biodegradation/biotransformation and sorption are the two main mechanisms occurring in the biological reactor, volatilisation being quite scarce. The constant K_d and k_{biol} reported in Table SD1 in the Supplementary data may provide some first simple information on the potential behaviour of a compound during treatment, but, as it will be discussed in the following, it is quite complex to describe its real removal mechanisms.

Sorption on the sludge is a mechanism depending on many factors, including pH, redox potential, stereochemical structure and chemical nature of both the sorbent and the sorbed molecule (Kümmerer, 2009b). It may occur by means of: (*i*) *absorption* due to hydrophobic interactions of the aliphatic and aromatic groups of a compound with the lipophilic cell membrane of the microorganisms or the lipid fractions of the suspended solids and (*ii*) *adsorption* due to electrostatic interactions of positively charged groups of chemicals with the negatively charged surfaces of the microorganisms.

Biodegradation processes are strictly correlated to the characteristics of the biomass, the compounds (often quite persistent), the plant configuration and operation parameters, in this case, in particular CAS and MBR.

Apart from the final liquid/sludge separation stage, obtained by means of (ultrafiltration or microfiltration) membranes in MBR and sedimentation in CAS, these systems are mainly distinguished by their SRT, which is generally longer for MBR (15–80 d) with respect to CAS (7–20 d), as well as by their biomass concentration, generally higher in the MBR than in the CAS (8–10 kg/m^3 in MBRs and 3–5 kg/m^3 in CAS. Unfortunately these data were not always provided in the papers included in Table 2, hence we reported the commonest operating values). In order to better evidence the removal efficiencies achieved by both systems, at the bottom of each of Figs. 14–19 a table reports the average percentage removal achieved by CAS and MBR for each compound. It is important to remark again, that in any case, a comparison between these data has to consider that only 20 MBRs are included in the review (against 244 CAS), and they are always pilot plants (against only 2 pilot CAS and 242 full scale plants), and finally a limited number of PhC concentration is available (and collected) for MBRs with respect to CAS.

Occasionally, negative removal efficiencies were found. These are not reported in the graphs of Figs. 14–19, but PhCs, with at least

Table 4
Average removal efficiencies obtained in CAS systems for the selected pharmaceuticals with respect to the operating SRT in the bioreactor and the corresponding references.

Class	Pharmaceutical	SRT [d]	Removal efficiency CAS [%]	References
A	Acetaminophen	2.4/3	100/86.4	Roberts and Thomas, 2006/Radjenovic et al., 2007
		8/10/13	99.5/99.9/92	Yu et al., 2006/Radjenovic et al., 2009/Jones et al., 2007
	Codeine	18.5	82	Wick et al., 2009
	Diclofenac	1.5/2/2.4/2.7/3	50/7.1/65.1/50/50	Santos et al., 2009/Clara et al., 2005a/Roberts and Thomas,
		5/7/8/9.6/10	50/42/18/9/22	2006/Santos et al., 2009/Radjenovic et al., 2007
		19/20	9.7/13	Santos et al., 2007/Kimura et al., 2007/Yu et al.,
		42/46/48/52/52/60	47/14/14/63/60/3	2006/Kreuzinger et al., 2004/Radjenovic et al., 2009
				Clara et al., 2005a/Vieno et al., 2005
				Clara et al., 2005a/Clara et al., 2005b/Clara et al.,
				2005a/Clara et al., 2005b/Clara et al., 2004/Suárez
				et al., 2005
	Ibuprofen	1.5/1.5/2/2.4/2.7/3	89.5/87/−4.4/−13/84/82.5	Santos et al., 2007/Santos et al., 2009/Clara et al.,
		5/7/8/8/9.6/10	88.4/98/87/99/92/99	2005a/Roberts and Thomas, 2006/Santos et al.,
		13/19/20	86/92/99.8	2009/Radjenovic et al., 2007
		42/46/48/52/60	99/98/98/97/82	Santos et al., 2007/Kimura et al., 2007/Yu et al.,
				2006/Zorita et al., 2009/Kreuzinger et al.,
				2004/Radjenovic et al., 2009
				Jones et al. 2007/Clara et al. 2005a/Vieno et al., 2005
				Clara et al., 2005a/Clara et al., 2005b/Clara et al.,
				2005a/Clara et al.,2004/Suarez et al.,2005
	Indomethacin	3/10	23/<10	Radjenovic et al., 2007, 2009
	Ketoprofen	1.5/1.5/2.7/3	37/52/56/52	Santos et al., 2007/Santos et al., 2009/Santos et al.,
		5/7/8/10/20	30/55/77/55/92	2009/Radjenovic et al., 2007
				Santos et al., 2007/Kimura et al., 2007/Yu et al.,
				2006/Radjenovic et al., 2009/Vieno et al., 2005
	Mefenamic acid	3/7/10/13	29/72/5/92	Radjenovic et al., 2007/Kimura et al., 2007/Radjenovic
				et al., 2009/Jones et al., 2007
	Naproxen	1.5/1.5/2.7/3	35/43/71/85	Santos et al., 2007/Santos et al., 2009/Santos et al.,
		5/7/8/8/10	89/64/88/93/72	2007/Radjenovic et al., 2007
		20/60	95/68	Santos et al., 2007/Kimura et al., 2007/Yu et al.,
				2006/Zorita et al., 2009/Radjenovic et al., 2009
				Vieno et al., 2005/Suárez et al., 2005
	Propyphenazone	3/10	42/38	Radjenovic et al., 2007, 2009
	Tramadol	18.5	4	Wick et al., 2009
B	Amoxicillin	12.5	96	Watkinson et al., 2007
	Azithromycin	5/18	74/39;45	Yasojima et al., 2006/Ghosh et al., 2009;
	Cefaclor	12.5	98	Watkinson et al., 2007
	Cefalexin	7	91	Li and Zhang, 2011
		12/12.5/20	53/100/64;87	Li and Zhang, 2011/Watkinson et al., 2007/Gulkowska
				et al., 2008
	Cefotaxime	12/20	43/83	Li and Zhang, 2011/Gulkowska et al., 2008
	Chlortetracycline	7;12	82;85	Li and Zhang, 2011
	Ciprofloxacin	7/8/11	55/71/78	Li and Zhang, 2011/Zorita et al., 2009/Golet et al.,
		11/12/12.5/15/18/20	93/18/83/96/50;73/79	2003/Lindberg et al., 2005/Li and Zhang, 2011/Watkinson
		22	72	et al., 2007/Lindberg et al., 2005/; Ghosh et al.,
				2009/Lindberg et al., 2006/
				Lindberg et al., 2005
	Clarithromycin	5/9	46/62	Yasojima et al., 2006/Sahar et al., 2011
		11/18	4.5/50;83	Göbel et al., 2007/Ghosh et al., 2009
	Doxycycline	11/15;20	14/100;99	Lindberg et al., 2005/Lindberg et al., 2005
	Enrofloxacin	18	70;38	Ghosh et al., 2009
	Erythromycin	3	24	Radjenovic et al., 2007
		5.6/7/9/10	4.4/26/19/35	Xu et al., 2007/Li and Zhang, 2011/Sahar et al.,
		11/12/20	3/15/19	2011/Radjenovic et al., 2009
				Göbel et al., 2007/Li and Zhang, 2011/Gulkowska
				et al., 2008
	Lincomycin	12.5/18	17/57;33	Watkinson et al., 2007/Ghosh et al., 2009
	Norfloxacin	5.6/7/8	18/45/−6	Xu et al., 2007/Li and Zhang, 2011/Zorita et al., 2009
		11/11/12/12.5/15/18/20/20/20;22	84/91/30/85/96/75;90/79/23;78/91;72	Golet et al., 2003/Lindberg et al., 2005/Li and Zhang,
				2011/Watkinson et al., 2007/Lindberg et al., 2005/Ghosh
				et al., 2009/Lindberg et al., 2006/Gulkowska et al.,
				2008/Lindberg et al., 2005
	Ofloxacin	3	24	Radjenovic et al., 2007
		5.6/7/8/10	38/59/13/76	Xu et al., 2007/Li and Zhang, 2011/Zorita et al.,
		11/12	84/26	2009/Radjenovic et al., 2009
				Lindberg et al., 2005/Li and Zhang, 2011
	Penicillin V	12.5	60	Watkinson et al. (2007)
	Oxytetracycline	12	4	Li and Zhang (2011)
	Roxithromycin	2/5.6/7/9/9.6	27/12.5/40/22/−4	Clara et al., 2005b/Xu et al., 2007/Li and Zhang,
		11/12/18	19/46/39;−32	2011/Sahar et al., 2011/Kreuzinger et al., 2004
		46;52	−80;44	Göbel et al., 2007/Li and Zhang, 2011/Ghosh et al., 2009
				Clara et al. 2005b
	Sulfadiazine	6/7/12	78–98/87/100	García-Galán et al., 2011/Li and Zhang, 2011
	Sulfadimethazine	6;19	100	García-Galán et al., 2011

(continued on next page)

Table 4 (*continued*)

Class	Pharmaceutical	SRT [d]	Removal efficiency CAS [%]	References
	Sulfamethazine	4;6/7;12/19	100;16/100/100	García-Galán et al., 2011/Li and Zhang, 2011/García-Galán et al., 2011
	Sulfamethoxazole	3/6/7/9/10 11/12/12.5/15/18/18 20/46	56/54;71/62/10/74 4.5/90/25/100/39/26 42/32	Radjenovic et al., 2007/García-Galán et al., 2011/Sahar et al., 2011/Radjenovic et al., 2009/Li and Zhang, 2011 Göbel et al., 2007/Li and Zhang, 2011/Watkinson et al., 2007/Lindberg et al., 2005/Ghosh et al., 2009/Ghosh et al., 2009 Lindberg et al., 2005/Clara et al., 2005b
	Sulfapyridine	4/6/19	20/77;89/6	García-Galán et al., 2011
	Sulfathiazole	4;6/12.5	100;65/75	García-Galán et al., 2011/Watkinson et al., 2007
	Tetracycline	7/12 18/20	36/24 40;72/−88;72	Li and Zhang, 2011 Ghosh et al., 2009/Gulkowska et al., 2008
	Trimethoprim	2.4 7/9/10 11/11/12/12.5/15/18/20/20/22/55	−56 42/0/40 −2/7/13/85/41/−88;35/14/−17;63/−34/53	Roberts and Thomas, 2006 Li and Zhang, 2011/Sahar et al., 2011/Radjenovic et al., 2009 Lindberg et al., 2005/Göbel et al., 2007/Li and Zhang, 2011/Watkinson et al., 2007/Lindberg et al., 2005/Ghosh et al., 2009/Lindberg et al., 2006/Gulkowska et al., 2008/Lindberg et al., 2005/Batt et al., 2006
C	Glibenclamide	3/10	44.5/46	Radjenovic et al., 2007, 2009
D	Clotrimazole	2.4	31	Roberts and Thomas, 2006
E	Hydrochlorothiazide	3/10	76/<10	Radjenovic et al., 2007, 2009
F	Phenobarbital	8	99.5	Yu et al., 2006
G	Atenolol	3/8/9/10 14.6/18.5	<10/71/76/61 73/44	Radjenovic et al., 2007/Carucci et al., 2006/Maurer et al., 2007/Radjenovic et al., 2009 Maurer et al., 2007/Wick et al., 2009
	Bisoprolol	18.5	0	Wick et al., 2009
	Metoprolol	3/9/10 14.6/18.5	<10/31/25 29/21	Radjenovic et al., 2007/Maurer et al., 2007/Radjenovic et al., 2009 Maurer et al., 2007/Wick et al.,2009
	Propranolol	9/10 14.6/18.5	28/59 35/0	Maurer et al., 2007/Radjenovic et al., 2009 Maurer et al., 2007/Wick et al.,2009
	Sotalol	9/10 14.6/18.5	26/21 27/18	Maurer et al., 2007/Radjenovic et al., 2009 Maurer et al., 2007/Wick et al., 2009
I	Bezafibrate	2/3 9.6/10 19/20 42/46/48/52/52	36.8/48 36/81 37/94 90/53.9/53.8/99.9/97	Clara et al., 2005a/Radjenovic et al., 2007 Kreuzinger et al., 2004/Radjenovic et al., 2009 Clara et al., 2005a/Vieno et al., 2005 Clara et al., 2005a/Clara et al., 2005b/Clara et al., 2005a/Clara et al., 2005b/Clara et al., 2004
	Clofibric acid	2.4/3 7/8	84/28 50/55	Roberts and Thomas, 2006/Radjenovic et al., 2007 Kimura et al., 2007/Zorita et al., 2009
	Gemfibrozil	3/8/10	39/68/5	Radjenovic et al., 2007/Yu et al., 2006/Radjenovic et al., 2009
	Pravastatin	3/10	62/59	Radjenovic et al., 2007, 2009
J	Carbamazepine	1.5/1.5/2/2.7/3 5/9.6/10 18.5/19 42/46/48/52/52/60	−4/11/−3/7/<10 −67/35/<10 −12/−47 −35/−43/−43/−11/0/<10	Santos et al., 2007/Santos et al. 2009/Clara et al. 2005a/Santos et al., 2009/Radjenovic et al. 2007 Santos et al., 2007/Kreuzinger et al., 2004/Radjenovic et al., 2009/ Wick et al., 2009/Clara et al., 2005a Clara et al., 2005a/Clara et al., 2005b/Clara et al., 2005a/Clara et al., 2005b/Clara et al., 2004/Suárez et al., 2005
	Diazepam	60	8	Suárez et al., 2005
	Fluoxetine	8/10	54.5/33	Zorita et al., 2009/Radjenovic et al., 2009
	Gabapentin	8	99.5	Yu et al., 2006
	Norfluoxetine	8	48	Zorita et al., 2009
	Paroxetine	3	91	Radjenovic et al., 2007
	Valproic acid	8	>99	Yu et al., 2006
K	Famotidine	10	60	Radjenovic et al., 2009
	Loratadine	10	15	Radjenovic et al., 2009
	Ranitidine	3/8/10	42/28.5/25	Radjenovic et al., 2007/Carucci et al., 2006/Radjenovic et al., 2009
L	Estradiol	8/10	22/98	Zorita et al., 2009/Joss et al., 2004
	Estrone	10/11/19 42/48	96/99/−35 94/99.9	Joss et al., 2004/Andersen et al., 2003/Clara et al., 2005a Clara et al., 2005a/Clara et al., 2005a
	Ethinylestradiol	9.6/10 52	70/94 70	Kreuzinger et al., 2004/Joss et al., 2004 Clara et al., 2004
M	Salbutamol	13	95	Jones et al., 2007
P	Triclosan	8	69	Yu et al., 2006
Q	Iopromide	2/9.6 55	−32/50 50	Clara et al., 2005b/Kreuzinger et al., 2004 Batt et al., 2006

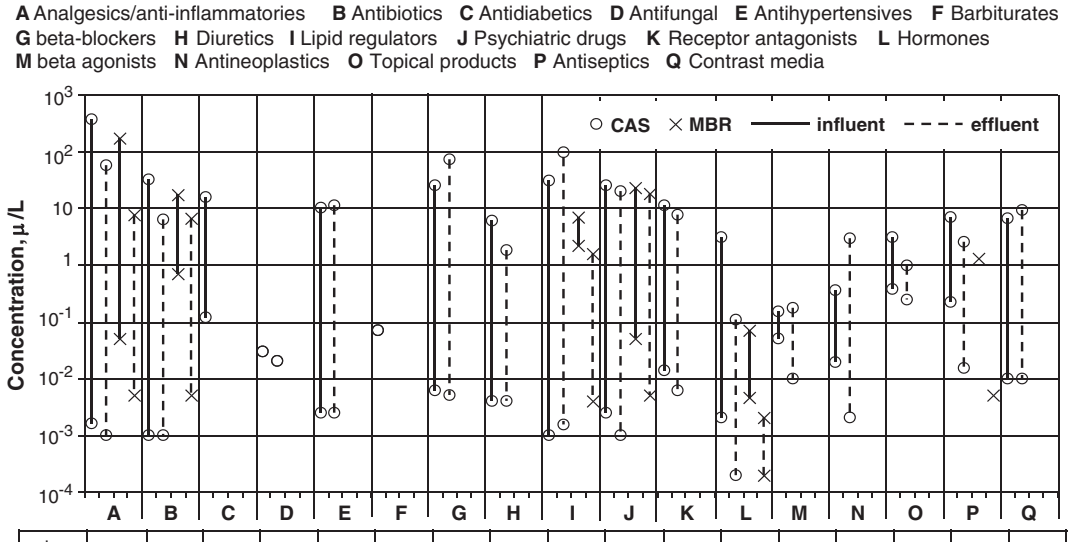
one negative percentage removal, are indicated with an asterisk and values are reported below the legend. While in some substances this phenomenon is clearly ascribable either to the presence of deconjugates interfering with biological transformation of the deconjugated compounds or to the release of PhC sorbed onto the particulate dissolving after the biological treatment, in others further investigation is required. Moreover, it is important to note that at the low level of concentrations found for some PhCs in the influent as well as in the secondary effluent, instrumental errors may lead to “apparent” releases of the investigated substance rather than a neglectable

Table 5
Average removal efficiencies obtained in MBRs for the selected pharmaceuticals with respect to the operating SRT in the bioreactor and the corresponding references.

Class	Pharmaceutical compound	SRT [d]	Removal efficiency MBR [%]	References
Analgesics/anti-inflammatories **A**	Diclofenac	10/15	60/51	Clara et al., 2004/Kimura et al., 2007
		22/27/37/65	33/51/23/82	Clara et al., 2005a/Clara et al., 2005b/Quintana et al., 2005/Kimura et al., 2007
	Ibuprofen	10/11/15/20	97/99/95/97	Clara et al., 2004/Kreuzinger et al., 2004/Kimura et al., 2007/Kreuzinger et al., 2004;
		22/27/37/65	97/99/97/98	Clara et al., 2005a/Clara et al., 2005b/Quintana et al., 2005/Kimura et al., 2007
	Ketoprofen	15	83	Kimura et al., 2007
		37/65	62/99	Quintana et al., 2005/Kimura et al., 2007
	Mefenamic acid	15/65	77/93	Kimura et al., 2007
	Naproxen	15	96	Kimura et al., 2007
		37/65	71/98	Quintana et al., 2005/Kimura et al., 2007
Antibiotics **B**	Azithromycin	33/70	5/24	Göbel et al., 2007
	Clarithromycin	16	57	Göbel et al., 2007
		33/70/70	41/92/88	Göbel et al., 2007/Sahar et al., 2011/Göbel et al., 2007/
	Erythromycin	16	34	Göbel et al., 2007
		33/70/70	26/79/87	Göbel et al., 2007/Sahar et al., 2011/Göbel et al., 2007
	Roxithromycin	16/20	39/75	Göbel et al., 2007/Kreuzinger et al., 2004
		27/33/70/70	34/62/59/59	Clara et al., 2005b/Göbel et al., 2007/Sahar et al., 2011/Göbel et al., 2007
	Sulfamethoxazole	11/16	57/37	Kreuzinger et al., 2004/Göbel et al., 2007
		33/70/70	38/0/37	Göbel et al., 2007/Sahar et al., 2011/Göbel et al., 2007
	Sulfapyridine	16	60	Göbel et al., 2007
		33/70	50/58	Göbel et al., 2007/Göbel et al., 2007
	Trimethoprim	16	30	Göbel et al., 2007
		33/70/70	34/88/87	Göbel et al., 2007/Sahar et al., 2011/Göbel et al., 2007
Lipid regulators **I**	Bezafibrate	10/11/20	97/94/76	Clara et al., 2004/Kreuzinger et al., 2004/Kreuzinger et al., 2004
		22/27/37	77/96/91	Clara et al., 2005a/Clara et al., 2005b/Quintana et al., 2005
	Clofibric acid	15/65	50/82	Kimura et al., 2007
Psychiatric drugs **J**	Carbamazepine	10/11	0/11/	Clara et al., 2004/Kreuzinger et al., 2004
		22/27	−13/4.4	Clara et al., 2005a/Clara et al., 2005b/
Hormones**L**	Estradiol	30	99	Joss et al., 2004
	Estrone	22/30	97/96	Clara et al., 2005a/Joss et al., 2004
	Ethinylestradiol	10/11;20	70/66;25	Clara et al., 2004/Kreuzinger et al., 2004
		30	76	Joss et al., 2004

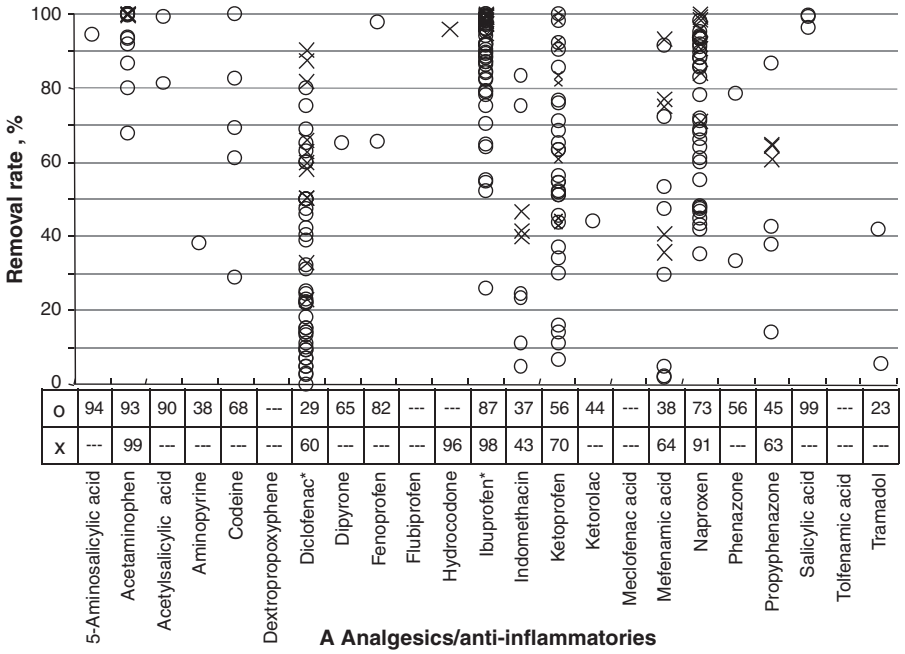
removal during the passage through the treatment plant. Sampling variation may also have contributed to this negative removal, as reported by Clara et al. (2005b), where the collection of effluent samples is not time-adjusted to account for long HRTs. Collecting composite samples over a period longer than plant HRT may improve the comparability between influent and effluent (Roberts and Thomas, 2006). Generally analysis was performed on influent and effluent water samples averaged over 24 h, a period higher than the corresponding WWTP HRT (Table 2).

Fig. 14 reports the removal efficiencies for 18 out of 25 analgesics/anti-inflammatories in CAS and 9 out of 25 in MBR. The average percentage removals vary between 23% (tramadol) and 99% (salicylic acid) in CAS, and between 43% (indomethacin) and 99% (acetaminophen) in MBR. For compounds investigated in both systems, MBR



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
o, in	374	263	3	1	20	1	56	9	69	84	31	65	3	4	3	23	6
o, out	420	274	0	1	19	0	94	8	99	103	21	54	10	7	3	29	6
x, in	14	9	0	0	0	0	0	0	3	5	0	6	0	0	0	1	0
x, out	36	8	0	0	0	0	0	0	8	6	0	4	0	0	0	1	0

Fig. 13. Comparison between the ranges of variability for the selected classes in the influent and effluent of all the CAS and MBRs under study. The table below reports the number of all the collected data pertaining to each single class for CAS systems (circle) and MBRs (cross).



***Observed negative percentage removal efficiencies**

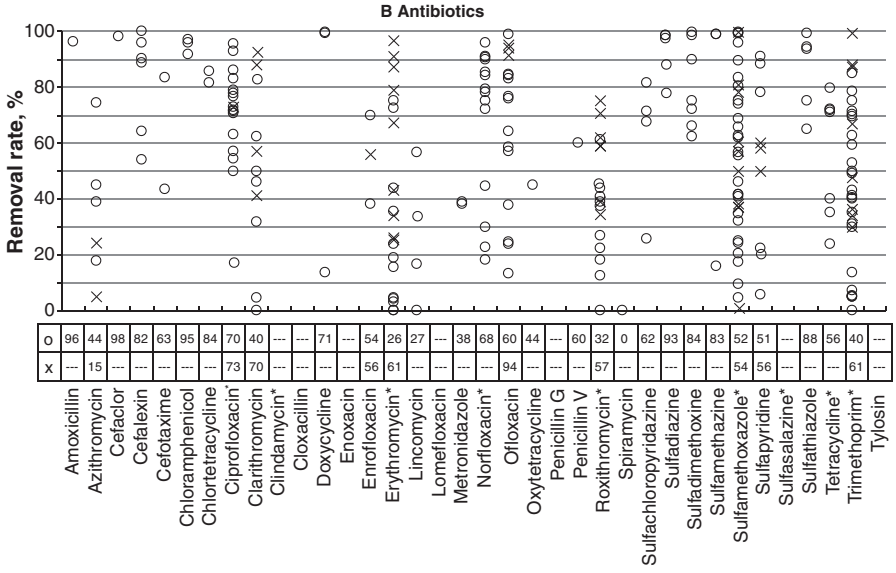
Diclofenac: in CAS: -12, -11, -111; in MBR: -8, -7.

Ibuprofen: in CAS: -4.4, -4.3, -13

Fig. 14. Percentage removal efficiencies for analgesics/anti-inflammatories in WWTPs, and corresponding average values for CAS (○) and MBR (×).

always exhibited a higher removal capacity than CAS. The graph shows that 12 compounds exhibited at least one value of their percentage removals in the range of 90–100% (5-aminosalycilic acid, acetaminophen, acetylsalycic acid, codeine, diclofenac, fenoprofen, hydrocodone, ibuprofen, ketoprofen, mefenamic acid, naproxen and salicylic acid).

Values lower than 10% were found for five substances: diclofenac, ibuprofen, indomethacine, ketoprofen, mefenamic acid and tramadol. It is quite interesting to observe that some PhCs (diclofenac, ketoprofen, mefenamic acid) exhibited a wide range of variability in their removal by secondary treatments. According to Ziylan and Ince (2011), higher



***Observed negative removal efficiencies**

Ciprofloxacin: in CAS: -44; Clindamycin: in CAS: -150; Erythromycin: in CAS: -84, -14, -11; Norfloxacin: in CAS: -6, Roxithromycin: in CAS: -4, -80, -32; Sulfamethoxazole: in CAS: -24; -20; Sulfasalazine: in CAS: -50; Tetracycline: in CAS: -88; Trimethoprim: in CAS: -11, -17, -34, -106, -2, -88, -56

Fig. 15. Percentage removal efficiencies of antibiotics in WWTPs and corresponding average values for CAS (○) and MBR (×).

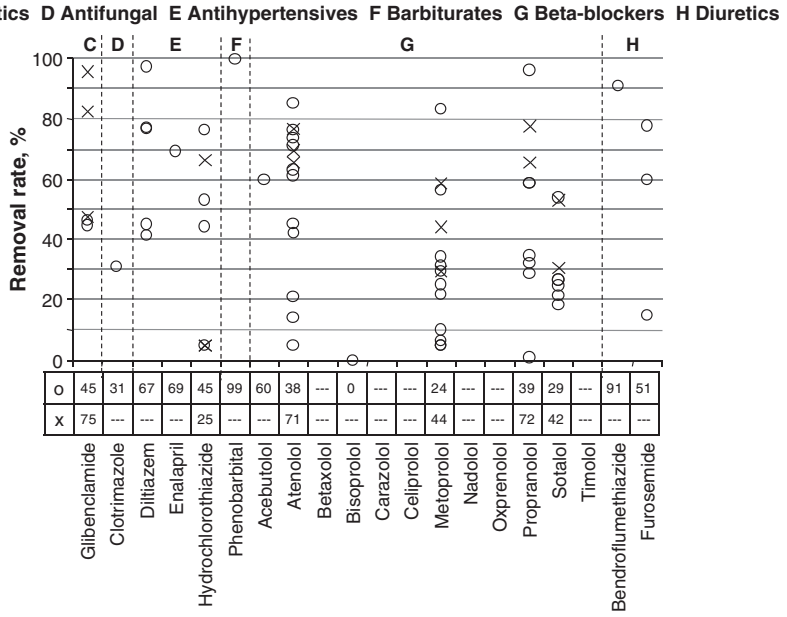


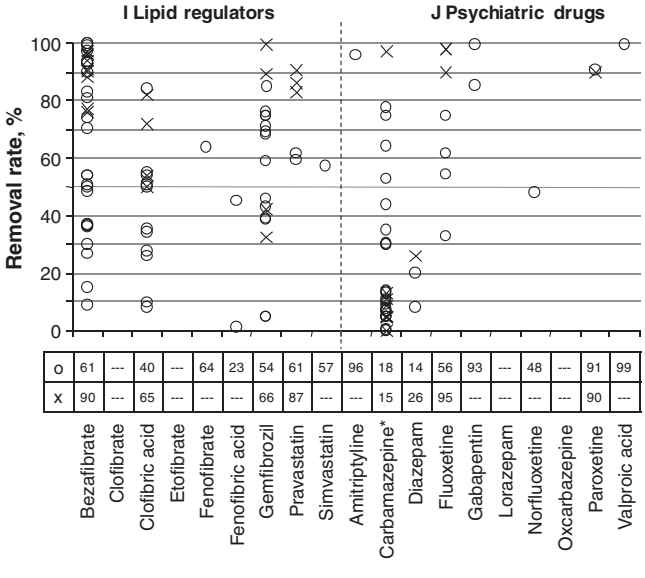
Fig. 16. Percentage removal efficiencies for some PhCs from different therapeutic classes in WWTPs, and corresponding average values for CAS (○) and MBR (×).

removal efficiencies of analgesics and anti-inflammatories are achieved at longer HRT and SRT, in reactors including nitrification and denitrification steps, at higher temperature. pH is another significant parameter especially for those compounds characterised by an increasing water–sludge partition coefficient and elevated acidity (acetaminophen, salicylic acid and ibuprofen).

In addition, negative removal efficiencies were observed for diclofenac and ibuprofen. Possible release of diclofenac can be explained by deconjugation of glucuronidated or sulphated diclofenac (Kimura et al., 2005) or its desorption from particles (Zorita et al., 2009). Ibuprofen is largely (90%) transformed to its hydroxyl and carboxy derivatives that may later be hydrolyzed and converted to the parent compounds (Ziylan and Ince, 2011; Roberts and Thomas, 2006).

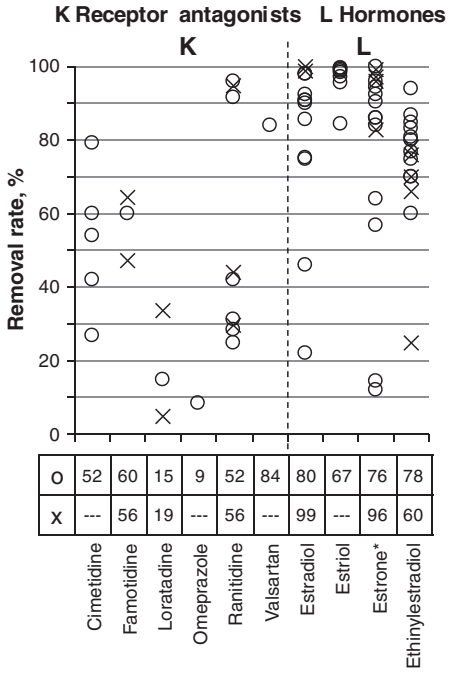
Fig. 15 shows the removal efficiency variability for 29 antibiotics in CAS and 10 in MBR out of 36 reviewed substances. The most investigated compounds are sulfamethoxazole, trimethoprim, ciprofloxacin, roxithromycin, norfloxacin and erythromycin. Their ranges of variability are generally wide. The corresponding average values vary between 0% (spiramycin) and 98% (cefachlor) in CAS and between 15% (azithromycin) and 94% (ofloxacin) in MBRs. Only one (azithromycin) out of 10 compounds investigated in both systems featured higher average removal efficiencies in CAS than in MBR.

Antibiotic release was observed for nine compounds. For some of them the phenomenon has been investigated whereas for others it is not completely clear. Referring to clindamycin, very low concentrations (0.002–0.005 ng/L) were detected in the influent and effluent



*Observed negative removal efficiencies
Carbamazepine: in CAS: -122, -3, -47, -43, -35, -4, -67, -11, -3, -43, -12. In MBR: -13

Fig. 17. Percentage removal efficiencies of selected lipid regulators and psychiatric drugs (○ refers to CAS and × to MBR).



*Observed negative removal efficiencies
Estrone: In CAS: -112, -35, -83, -40.

Fig. 18. Percentage removal efficiencies for selected receptor antagonists and hormones, and corresponding average removal efficiencies in CAS (○) and MBR (×).

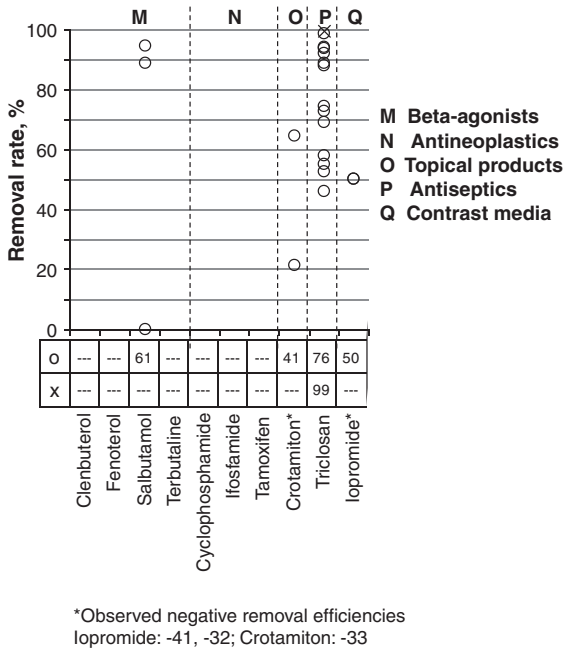


Fig. 19. Percentage removal efficiencies of other micropollutants, and corresponding removal efficiencies for CAS (○) and MBR (×).

and possible instrumental errors may influence the evaluation of the negative removal efficiency (Watkinson et al., 2007). As to the two sulphonamides sulfamethoxazole and sulfasalazine, their main metabolites entering the sewage are biologically inactive N4-acetylated products and may retransform back to the initial parent compound (Göbel et al., 2007).

The presence of de-conjugable metabolites seems unlikely for the macrolides erythromycin and roxithromycin. Since they are mainly excreted with bile and faeces, they are probably partly enclosed in faeces particles and released during biological treatment. The load entering biological treatment is therefore underestimated, taking only in consideration the dissolved fraction and sorption to the suspended solids (Göbel et al., 2007). According to Lindberg et al. (2005), the increment in the effluent concentrations for trimethoprim can be explained by an underestimation of the actual amount entering the WWTP due to particulate matter with adsorbed antibiotics being filtered out during sample preparation. Higher concentration of ciprofloxacin, tetracycline and norfloxacin in the secondary effluent rather than the raw influent could be ascribed to a change in the adsorption behaviour of the analytes to particles during treatment processes, influencing the ratio between influent and effluent (Gulkowska et al., 2008, Plósz et al., 2010).

Fig. 16 refers to twenty PhCs from six classes, but data are available only for fourteen, all of which were investigated in CAS and six in MBRs. Five compounds were only reported in one study (clotrimazole, enalapril, phenobarbital, acetobutol and bisoprolol), while more data, spread over quite wide ranges, were available for the remaining compounds. For compounds investigated in both systems, the average removal efficiencies are consistently higher in MBR than in CAS, except in the case of hydrochlorothiazide (45% in CAS and 25% in MBR).

Fig. 17 refers to the removal efficiencies obtained for selected lipid regulators and psychiatric drugs; the most investigated compounds were: bezafibrate, gemfibrozil, clofibric acid, pravastatin in the former group and carbamazepine and fluoxetine in the latter. Only one data set is available for fenofibrate, simvastatin, amitriptyline, norfluoxetine and valproic acid in CAS and for paroxetine in CAS and MBR. No removal data were provided for clofibrate, etofibrate, lorazepam and oxcarbazepine, and few data sets were provided for the remaining compounds (fenofibric acid and gabapentin).

For the most frequently investigated pharmaceuticals, the removal efficiencies variability ranges are generally quite wide, but, in general, higher removal efficiencies were achieved by MBRs except in the case of carbamazepine, which exhibited similar (low) average values in the two systems. This compound is not only one of the most persistent, but it can also be released in the WWTP, as shown in the data reported below the graph, presumably due to enzymatic cleavage of its glucuronic conjugate and release of the parent compound in the effluent (Radjenovic et al., 2007; Vieno et al., 2007).

Fig. 18 refers to receptor antagonists and hormones; more data is available for the latter. Removal efficiencies for receptor antagonists were lower than 80%, with the exception of ranitidine and valsartan, and average values were between 50 and 60%, with a few exceptions: valsartan (84% in CAS), loratadine (15% in CAS and 19% in MBR) and omeoprazol (9% in CAS). In contrast, observed removal efficiencies for hormones were consistently higher, on average between 67% and 80% in CAS and 60% and 99% in MBRs. Estradiol is the compound most removed (on average 80% in CAS and 99% in MBR). However, negative removals of estrone were observed in CAS in several investigations, the assumption being that this is produced in the sewage treatment system by the oxidation of estradiol and by partial deconjugation of other oestrogens present in the wastewater (D'Ascenzo et al., 2003).

Very few data are reported for the removal of the compounds belonging to the classes M–Q (Fig. 19). A wide range was observed for the removal of salbutamol (0–98%) and a slightly smaller one (21–65%) for crotamiton. Triclosan is removed to a greater extent, even exceeding 98% in both CAS and MBR, and its average removal efficiency is quite high (76% in CAS and 99% in MBR). Iopromide, on the other hand, was scarcely removed by biological processes, and in some investigations it was found to be released, as shown by the data reported below the graph. Its persistence is due to the fact that, as a diagnostic agent, it is designed to be highly stable.

No reasonable justification for the increasing of iopromide concentrations within the WWTP could be identified, according to Clara et al. (2005b). As to crotamiton, its releases can be explained by breakdown of conjugates of the pharmaceutical (Nakada et al., 2006).

All the data reported in the graphs above refer to PhC removal from aqueous phase, as defined by Eq. (1): in this way, attention is paid to the WWTP influent and effluent quality in order to evaluate how efficient is a specific treatment plant in *retaining* the selected compounds from the aqueous phase, without distinguishing between sorption onto sludge (hence transfer to another phase) and/or biological degradation/transformation processes. Sometimes it may be also called "apparent removal".

Another approach in evaluating PhC removal efficiencies considers the WWTP as a black box with one entrance (influent) and *two* outputs (liquid effluent and sludge). In this case, the removal efficiency, also called overall removal, $\eta_{overall}$ is evaluated through Eq. (2):

$$\eta_{overall} = \frac{c_{inf}Q - \left(c_{eff}Q + c_{sludge}P_{sludge}\right)}{c_{inf}Q} x100. \quad (2)$$

In Eq. (2), c_{sludge} is the concentration of the selected PhC in the treated sludge (ng/g) and P_{sludge} is the daily sludge production for the plant under examination (g/d). Influent and effluent flow rates are assumed constant and equal to Q. The numerator represents the mass load of the selected PhC, subjected to biological reactions.

Few Authors investigated these two mechanisms in details, providing sorption and biodegradation contributions to the overall removal based on liquid and sludge concentration, influent and effluent flow rates and sludge production collected on full scale plants. Table 3 compiles these findings available only for some of the selected compounds with the corresponding references.

A rapid glance to the data compiled in Table 3 shows that sorption onto activated sludge is of minor importance for most of the selected

PhCs: due to their hydrophilic characteristics (Log K_{ow}<2.5 high hydrophilic compound, see Table SD1), their sorption removal keeps quite low (<20%). According to a simple rule (Ternes and Joss, 2006), compounds with K_d > 500 L/kg (Log K_d > 2.7) potentially tend to adsorb onto sludge and particles. Table SD1 compiles Log K_d values for most of the selected substances and evidences that for most of them, they are less than 2.7 confirming their low tendency to adsorb. The value of the PhC molecular charge at pH 7 provides information about its potential to create electrostatic interactions with the (usually) negatively charged biomass surface.

Data of Table 3 show that, only for the antibiotics ciprofloxacin, norfloxacin, ofloxacin and lomefloxacin, the antihypertensive hydrochlorotiazide and the lipid regulator fenofibrate, the removal percentage due to sorption is in the range of 60–100%. The antibiotics appear not be readily biodegradable (Ternes and Joss, 2006; Jia et al., 2012) and their removal during activated sludge processes is assumed to be due to the formation of flocs by microbial activity, via electrostatic and hydrophobic interactions (Lindberg et al., 2006; Jia et al., 2012). The four antibiotics are characterised by high sorption constant Log K_d (>4 as reported in Table SD1 in the Supplementary data), confirming a good tendency to sorption (Kümmerer, 2009a) and to create electrostatic interactions, as suggested by Vieno et al. (2007) and Göbel et al. (2007). Data of high removal by sorption referring to hydrochlorothiazide (Jelic et al., 2011) were not expected by the Authors during their investigation as this compound was never detected in the influent and effluent of the WWTP, but only it was detected in the sludge. Perhaps its presence in the sludge is correlated to previous processes of accumulation in the solid phase, inside the biological reactor. Further research is necessary to better investigate the fate of hydrochlorothiazide as well as fenofibrate (Jelic et al., 2011).

Sorption of compounds is in general pH dependent, however, in WWTPs it is not significantly affected by the narrow range of pH variability normally observed (Lindberg et al., 2006).

For compounds with a high sorption potential, the removal efficiency in an MBR may be slightly higher due to the absence of suspended solids in the effluent (Clara et al., 2004): Fig. 15 shows that ciprofloxacin and norfloxacin have higher removals in MBRs rather than CAS systems.

Attempts to correlate biodegradation removal of a compound to its molecular characteristics were made by Tunkel et al. (2000). On the basis of a large set of organic chemicals, they found that compounds including esters, nitriles and aromatic alcohols have functional groups that may increase biodegradability, while aromatic amines, iodide, nitro and azo groups increase the persistence of the compound. Jones et al. (2005) reported that long and highly branched side chains (i.e. omeoprazole and ranitidine) render a compound more persistent as well as complicated aromatic ring structures (including norfluoxetine, diazepam) and halogen groups (i.e. iopromide, diazepam).

3.3.1. Considerations on the observed removal efficiencies of the selected PhCs

As previously mentioned, compounds of the same class may have quite different chemical and physical properties (Ternes and Joss, 2006) resulting in different behaviours during treatment processes (tendency to remain in dissolved phase, to adhere to flocs or particles or to undergo biodegradation), which can explain why compounds belonging to the same therapeutic class do not exhibit similar removal efficiencies (Figs. 14–19). In the Supplementary materials, Table SD1 provides the main chemical and physical properties of the selected compounds and some simple rules in order to predict their "expected" behaviour based on the compiled characteristics. However, as reported by Tadkaew et al. (2011), it is always difficult to correlate physical properties of pharmaceuticals to their corresponding removal efficiency achieved in an activated sludge system, as many other factors contribute to it, in particular operating parameters such as biomass concentration, SRT, HRT, pH, temperature, configuration and type of plant. A brief discussion is now reported.

3.3.2. Effect of biomass concentration and SRT

Many authors (among them Kreuzinger et al., 2004; Weiss and Reemtsma, 2008) have found that a long SRT promotes the adaptation of different kinds of microorganisms, as well as the presence of slower growing species that could have a greater capacity for removing xenobiotics while simultaneously greatly improving suspended solid separation: this is the case for ibuprofen and diclofenac as reported by Suárez et al. (2010) whose removal was only achieved after the growth of specific bacteria. Moreover, Kimura et al. (2007) found that a greater removal of diclofenac was achieved in an MBR operating at longer SRT (up to 65 d) with respect to a CAS (SRT on average 7 d) due to a different composition of the two sludges resulting in different sorption capacities with respect to the selected PhC.

Schröder (2002) suggested that MBR systems provide a competitive advantage for organisms able to degrade persistent compounds by eliminating bacterial washout. The high biomass concentrations in an MBR lead not only to a decreased sludge production, but also to a higher stability and persistence to shock loads (Lee et al., 2003).

The higher biomass concentration in MBRs results in a decrease of the food to microorganisms ratio (F/M). The relative shortage in biodegradable substance may induce microorganisms to metabolise also poorly degradable compounds. This can explain why removal efficiencies for some persistent PhCs (including ketoprofen and naproxen) are higher in MBRs than in CAS systems and why this can be obtained at lower HRT (Weiss and Reemtsma, 2008). High SRT combined with reduced F/M ratios may result in an increased biodiversity and may also favour elimination of compounds, like the antibiotics trimethoprim, erythromycin and other macrolides, by co-metabolism processes (Göbel et al., 2007).

High SRTs have also beneficial effects on the removal of PhCs that tend to accumulate in the sludge flocs, either due to intrinsic hydrophobicity or via electrostatic interactions with the biomass (i.e. tetracycline, ciprofloxacin, ofloxacin, norfloxacin) (Kim et al., 2007). Moreover the biomass in an MBR has a more viable fraction compared to a CAS system (Cicek et al. 1999) that can be attributed to an improved mass transfer due to the presence of smaller flocs (10–100 μm in MBR against 100–500 μm in CAS) and a large fraction of planktonic microorganisms. These factors favour the contact between microorganisms and pollutants and stimulate their biodegradation, as well as some enzymatic activities (Cirja et al., 2008). Radjenovic et al. (2009) found higher concentrations in MBR sludge rather than CAS sludge for hydrochlorothiazide, azithromycin, carbamazepine and ketoprofen.

Clara et al. (2005a) found that a SRT > 10 d is needed for some biodegradable PhCs (in particular hormones, bezafibrate and ibuprofen) to achieve low effluent concentrations, although other studies (Joss et al., 2005; Vieno et al., 2007) noticed no clear correlation between percentage elimination and SRT in particular for beta-blockers, carbamazepine and the antibiotics ciprofloxacin, ofloxacin and norfloxacin.

Tables 4 and 5 report removal efficiencies for the selected compounds with the corresponding SRT and references distinguishing between CAS and MBR.

The positive effect of increasing SRT appears for several compounds, in particular for hormones, ibuprofen, ketoprofen, naproxen, bezafibrate, gemfibrozil, fluoxetine, antibiotics mainly removed by biodegradation, as also confirmed by Strenn et al. (2004).

Increasing SRT beyond 30 days does not usually result in a consistent increment in the removal for most compounds (Suárez et al., 2008). This could be explained with the fact that biodegradation of micropollutants, including PhCs, is mostly due to cometabolic processes as the low concentrations do not likely sustain growth for specific microorganisms, because in this case the SRT necessary for an efficient biodegradation of the primary substrate is the relevant parameter (Sipma et al., 2010).

Clara et al. (2004) reported that they did not find significant differences in the removal efficiency of pharmaceuticals like diclofenac, ibuprofen, carbamazepine, bezafibrate and ethinylestradiol between CAS and MBR systems when operated at similar sludge retention times, which suggests that the reactor type is of less importance than the SRT. Although SRT has been reported as determinative for pharmaceutical biodegradation due to enrichment of certain microbial communities that excrete enzymes able to break down PhCs (Cirja et al., 2008), the effect of an increasing SRT does not become clear for other compounds, including naproxen and sulfamethoxazole (Lishman et al., 2006;Vieno et al., 2007): often very fluctuating removal efficiencies are encountered with an increase of its values, as reported in Tables 4 and 5.

As MBRs generally operate at longer SRTs (at least 15 d, as stated in Table 2) than CAS (generally at maximum 15 d), this could explain higher removal efficiencies achieved by the former with respect to the latter as reported in Clara et al. (2005b), Radjenovic et al. (2009) and Weiss and Reemtsma (2008). Moreover, in MBRs, membranes detain particulate matter, including any adsorbed or absorbed PhCs, leading to an effluent free of suspended solids and relatively free of contaminants (for instance glibenclamide).

Weiss and Reemtsma, 2008 found that the major advantage of MBR lies in the range of compounds with moderate removal in CAS (including naproxen, diclofenac, phenazone, clofibric acid). For these MBR is capable of delivering lower and more stable effluent concentrations in comparison to CAS—even with lower HRT.

3.3.3. Effect of HRT

The influence of HRT on the removal efficiencies of selected PhCs was investigated by different Authors. Among them, Bernhard et al. (2006) and Vieno et al. (2007) found no significant correlation between HRT and removal of respectively diclofenac and the beta-blockers atenolol, metoprolol, acebutolol and sotalol. Gros et al. (2010) and García-Galán et al. (2011) investigated in two full scale WWTPs in Spain operating at different HRTs, respectively 7–10 h and 32 h, the removal of several compounds, covering different therapeutic classes: analgesics/anti-inflammatories, antibiotics, lipid regulators, diuretics, beta-blockers the former and sulphonamide antibiotics the latter. They correlated observed PhC removal efficiencies to the corresponding PhC half-lives $t_{1/2}$ evaluated on the assumption that a decrease of the concentration through time is proportional to the concentration remaining in the matrix (that is assuming a pseudo-first order kinetic for the degradation). Half-lives were estimated through Eq. (3)

$$t_{1/2} = \frac{\ln 2}{k} \tag{3}$$

where k is the loss rate constant calculated according to Eq. (4), where c is the PhC concentration in the influent (subscript *inf*) and effluent (subscript *eff*).

$$\ln\left(c_{eff}/c_{inf}\right) = -kt \tag{4}$$

They found that those compounds with a half-life time $t_{1/2}$ less than WWTP HRT generally exhibited high removal efficiencies, concluding that $t_{1/2}$ gives an idea about the required permanence time of the compounds in the biological reactor to ensure an efficient removal of them.

In particular they found three different situations: (*a*) for compounds with high removal efficiency and high degradation rate (low $t_{1/2}$), like ibuprofen, naproxen, salicylic acid, acetaminophen and enalapril; (*b*) for compounds with poor or no elimination and low degradation (high $t_{1/2}$) like carbamazepine, HRT does not influence compound removal; (c) for compounds with medium removal and degradation rate, HRT seems to play a role, as their removal efficiencies were higher when increasing HRT (including famotidine, ranitidine and pravastatin). Gros et al. (2010) conclude that substances that are biodegradable (high k_{biol} or low $t_{1/2}$) and have low Log K_d (low sludge–water distribution coefficient, corresponding to low tendency to adsorb on sewage sludge) are more influenced by HRT, while compounds with high Log K_d and low k_{biol} are more influenced by SRT. However, there are other PhCs like ibuprofen with high k_{biol} and low Log K_d that are well removed independently of HRT and SRT. Based on experimental findings on Canadian WWTPs (SRT from 2 to 10 d), Metcalfe et al. (2003) proposed the following correlation for naproxen and ibuprofen, between HRT and PhC percentage removal η:

$$\eta = 1.735e^{0.886HRT}. \tag{5}$$

They conclude that due to high half-lives observed for most of the investigated compounds in WWTP effluents, higher HRT should be required in order to enhance compound degradation.

3.3.4. Effect of pH

pH values can also greatly affect the behaviour of PhCs, in particular antibiotics (ciprofloxacin, tetracycline and penicillin G), which possess different functional groups within the same molecule. In fact, under different pH conditions, the molecule can be neutral, cationic, anionic or zwitterionic and so its physical, chemical and biological properties (sorption, photo-reactivity, antibiotic activity and toxicity) will change accordingly (Kümmerer, 2009b, Cirja et al., 2008). Tadkaew et al. (2010) investigated the effects of mixed liquor pH (pH between 5 and 9) on the removal of trace organics (sulfamethoxazole, carbamazepine, diclofenac, ibuprofen and ketoprofen) by a submerged MBR system. They found that removal efficiencies of ionisable compounds (sulfamethoxazole, diclofenac, ibuprofen and ketoprofen) were strongly pH-dependent. At pH 5, the high removal of the ionisable compounds can be due to their speciation behaviour. At this pH, these compounds exist mainly in their hydrophobic form. As a consequence, they could readily adsorb onto the activated sludge, resulting in higher removal efficiencies in comparison to under less acidic conditions in the reactor. Removal efficiencies of the non-ionisable carbamazepine were relatively independent of the mixed liquor pH. These findings are consistent with those by Urase et al. (2005). Watkinson et al. (2007) found strong pH sensitivity resulting in the formation of a degraded erythromycin product (erythromycin-H_2O) through the loss of a water molecule and the inability to detect the parent erythromycin at pH<7.

3.3.5. Effect of temperature

Biological reactions are greatly affected by temperature, and lower efficiencies have been observed during winter seasons in colder climates (Vieno et al., 2005). Moreover, based on removal data collected on six different large WWTPs in Italy, Castiglioni et al. (2006) found that there are PhCs that present really higher removal efficiencies in summer than in winter: amoxicillin (with a median of 75% in winter and 100% in summer), atenolol (10% and 55%), bezafibrate (15% and 87%), enalapril (18% and 100%), furosemide (8% and 54%), ibuprofen (38% and 93%), ranitidine (39% and 84%) and sulfamethoxazole (17% and 71%). Another group of compounds has similar removal in the two seasons: ciprofloxacin (60%), hydrochlorotiazide (30%) and ofloxacin (50%). Finally a third group has removal efficiencies close to zero in winter and in summer: carbamazepine, clarithromycin, erythromycin and salbutamol.

Hai et al. (2011) investigated the effect of temperature on the removal of selected PhCs contained in a synthetic wastewater fed to a lab scale MBR. They reported that the removal of most hydrophobic compounds (including estrone, ethinyl-estradiol, estradiol and triclosan) was stable during operations under the temperature range of 10–35 °C. On the other hand, for the less hydrophobic compounds (salicylic acid, ketoprofen, naproxen, metronidazole, ibuprofen, acetaminophen, diclofenac, gemfibrozil, carbamazepine and estriol) a comparatively more pronounced variation between removals in

the lower temperature regimes (10–35 °C) was observed. With a few exception, operation at 45 °C clearly exerted detrimental effects on the removal efficiency of the investigated compounds.

However, it is still unclear whether temperature dependence, commonly observed for biological degradation of common pollutants (C, N and P compounds), also applies to the transformation of antibiotics or PhCs in general (Göbel et al., 2007; Tauxe-Wuersch et al., 2005; Ternes, 1998).

3.3.6. Treatment configuration

Nitrifying bacteria have been found capable of co-metabolising a wide range of persistent compounds like iopromide and trimethoprim (Batt et al., 2006; Perez et al., 2005). Wastewater treatment processes performing a complete biological nutrient removal are characterised by separate zone with aerobic, anoxic and anaerobic conditions to optimise C and N removal that may affect PhCs removal as well (US EPA 2009; Zwiener and Frimmel, 2003). High removal efficiencies of PhCs have been suggested to occur in WWTPs with high levels of nitrogen removal (Batt et al., 2006; Clara et al., 2005a). Vieno et al. (2007) found that atenolol and sotalol were slightly more efficiently eliminated in the WWTPs where nitrogen removal was greater than 60% compared with those that removed nitrogen only less than 30%. Suárez et al. (2010) divided into three groups PhCs with respect to their potential to be removed in biological reactor: highly biodegradable compounds under aerobic and anoxic conditions, including ibuprofen, fluoxetine, natural estrogens; highly biodegradable compounds under aerobic conditions, but persistent in anoxic conditions, including diclofenac, naproxen, ethinylestradiol, roxithromycin and erythromycin and finally resistant compounds to biological transformations (sulfamethoxazole, trimethoprim, carbamazepine and diazepam).

It is important to remark that low removal efficiencies could also be due to the fact that contaminants are present at *very low* concentrations in the influent, and unavoidable instrumental errors may affect their "observed" removal values. At the other extreme, high removal efficiencies, greater than 99%, corresponding to a reduction of two orders of magnitude of the influent concentrations, may not be enough to consistently reduce the PhC concentrations to a low level of risk to aquatic life. For instance if ibuprofen presents an influent concentration at 350 μg/L and 99% is removed, its final concentration would still amount to 3.5 μg/L, i.e. a consistent mass load discharged by the WWTP, as described below.

3.4. Average daily mass loads of PhCs in secondary effluent

Where possible, to complete this analysis, the average daily mass load, L_i, of each PhC, i, in the secondary biological effluent was estimated. L_i was evaluated as the average of mass load $L_{i,j}$ at WWTP j, provided by the cited literature or evaluated via Eq. (6), on the basis of the average effluent concentration $c_{i,j}$ from the WWTP j, the average treated flow rate Q_j and the population served by the WWTP j. Each mass load is expressed in mg/1000 inh/d.

$$L_{i,j} = \frac{c_{i,j} Q_j}{\text{served population}} \times 1000 \quad i = \text{generic PhC}; j = \text{generic WWTP} \tag{6}$$

It was possible to evaluate the average mass load of 73 out of 118 compounds, as those WWTPs lacking one or more of the following variables were excluded: effluent concentration, treated flow rate and population served.

The graph in Fig. 20 reports, in descending order, average mass loads L_i greater than 10 mg/1000 inh/d, and below is a list of the references used in the evaluation.

These findings may be affected by different sources of uncertainty as discussed in Ort and Gujer (2006), for this reason they have to be prudently considered.

The highest average mass loads (greater than 200 mg/1000 inh/d) were found for the antihypertensive hydrochlorothiazide (368 mg/1000 inh/d), the psychiatric drug carbamazepine (364 mg/1000 inh/d), the topical product crotamiton (360 mg/1000 inh/d), the receptor antagonist cimetidine (332 mg/1000 inh/d) and the beta-blocker atenolol (316 mg/1000 inh/d), followed by the analgesics/anti-inflammatories: naproxen (295), ibuprofen (273), diclofenac (241), ketoprofen (217) and mefenamic acid (211). Antibiotics showed lower average daily mass loads: spiramycin (155), clarithromycin (140), trimethoprim (124), ofloxacin (123), and erythromycin (100).

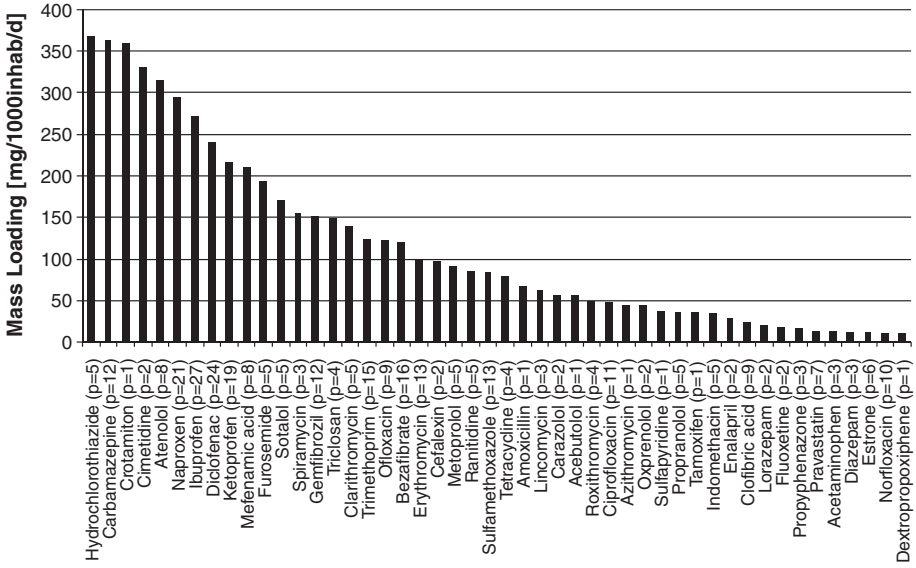


Fig. 20. Average daily mass loads evaluated for most of the compounds under review. The number p of treatment plants considered in the analysis are shown in brackets after the name in the X-axis.
Data from: Alder et al. (2010), Baronti et al. (2000), Bendz et al. (2005), Castiglioni et al. (2006), Conti et al. (2011), Göbel et al. (2005), Golet et al. (2003), Gulkowska et al. (2008), Jones et al. (2007), Karthikeyan and Meyer (2006), Kimura et al. (2007), Lindberg et al. (2005), Lindqvist et al. (2005), McAvoy et al. (2002), Nakada et al. (2006), Paxéus (2004), Radjenovic et al. (2007, 2009), Roberts and Thomas (2006), Santos et al. (2009), Tauxe-Wuersch et al. (2005), Ternes (1998), Ternes et al. (1999, 2003), Vieno et al. (2005, 2007), Xu et al. (2007), Yu et al. (2006), and Zorita et al. (2009).

Table 6
PNEC for the PhCs included in this review and corresponding assayed species.

Compounds	Species assayed	Test (endpoint)	Toxicity (mg/004C)	References	PNEC (μg/L)
Acetaminophen	*DAPHNIA*	EC50 (24 h)	136	Stuer-Lauridsen et al. (2000)	**1**
	Daphnia	EC50 (48 h)	9.2	Stuer-Lauridsen et al. (2000)	
	S. proboscideu	LC50(24 h)	29.6	Stuer-Lauridsen et al. (2000)	
	Fish	**EC50 ECOSAR**	**1**	**Sanderson et al. (2003)**	
	DAPHNIA	EC50 ECOSAR	42	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	2549	Sanderson et al. (2003)	
	Invertebrates	EC50	300	Boillot (2008)	
	Algae	EC50	105	Boillot (2008)	
	Fish	EC50	900	Boillot (2008)	
	Daphnia	EC50 (48 h-immobility)	9.2	Kühn (1989)	
Acetylsalicylic acid	*Fish*	EC50 ECOSAR	796	Sanderson et al. (2003)	**61**
	Daphnia	EC50 ECOSAR	8858	Sanderson et al. (2003)	
	Algae	**EC50 ECOSAR**	**61**	**Sanderson et al. (2003)**	
	Daphnia	**EC50 ECOSAR**	61	US EPA (1999)	
Aminopyrine	*Fish*	EC50 ECOSAR	3.7	Sanderson et al. (2003)	**1.3**
	Daphnia	EC50 ECOSAR	8.3	Sanderson et al. (2003)	
	Algae	**EC50 ECOSAR**	1.3	**Sanderson et al. (2003)**	
Codeine	*Fish*	EC50 ECOSAR	238	Sanderson et al. (2003)	**16**
	Daphnia	**EC50 ECOSAR**	**16**	**Sanderson et al. (2003)**	
	Algae	EC50 ECOSAR	23	Sanderson et al. (2003)	
Dextropropoxyphene	*Fish*	EC50 ECOSAR	13	Sanderson et al. (2003)	**1**
	Daphnia	EC50 ECOSAR	24	Sanderson et al. (2003)	
	Algae	**EC50 ECOSAR**	**1**	**Sanderson et al. (2003)**	
Diclofenac	*Fish*	EC50 ECOSAR	532	Sanderson et al. (2003)	**9.7**
	Daphnia	EC50 ECOSAR	5057	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	2911	Sanderson et al. (2003)	
	Daphnia	EC50 (48 h-mortality)	22.4	Ferrari et al. (2004)	
	Algae	EC50 (96 h-growth)	16.3	Ferrari et al. (2004)	
	Bacteria	EC50 (30 min-luminescence)	11.4	Ferrari et al. (2004)	
	Bacteria	**EC50 (15 min-inhibition)**	**9.7**	**Ra et al. (2008)**	
	Microtox	EC50 (30 min)	11.45	Ferrari et al. (2003)	
	Daphnia	EC50 (48 h)	22.43	Ferrari et al. (2003)	
	C. dubia	EC50 (48 h)	22.7	Ferrari et al. (2003)	
	Algae	EC50 (96 h-growth)	14.5	Ferrari et al. (2004)	
	Invertebrates	EC50	90	Boillot (2008)	
	Algae	EC50-inhibition	72	Cleuvers (2004)	
	Daphnia	EC50-immobilisation	68	Cleuvers (2004)	
Ibuprofen	*Fish*	EC50 ECOSAR	5	Sanderson et al. (2003)	**1.65**
	Daphnia	EC50 ECOSAR	38	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	26	Sanderson et al. (2003)	
	Bacteria	EC50 (15 min-inhibition)	37.5	Ra et al. (2008)	
	Bacteria	EC50 (15 min)	12.1	Farré et al., 2001	
	Daphnia	EC50 (48 h)	9.06	Halling-Sørensen et al. (1998)	
	Invertebrates	**EC50 (96 h)**	**1.65**	**Quinn et al. (2008)**	
	Invertebrates	EC50	100	Boillot (2008)	
	Algae	EC50	500	Boillot (2008)	
	Fish	EC50	110	Boillot (2008)	
	Algae	EC50-inhibition	342.2	Cleuvers (2004)	
	Daphnia	EC50-immobilisation	101.2	Cleuvers (2004)	
Indomethacin	***Fish***	**EC50 ECOSAR**	**3.9**	**Sanderson et al. (2003)**	**3.9**
	Daphnia	EC50 ECOSAR	26	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	18	Sanderson et al. (2003)	
Ketoprofen	*Fish*	EC50 ECOSAR	32	Sanderson et al. (2003)	**15.6**
	Daphnia	EC50 ECOSAR	248	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	164	Sanderson et al. (2003)	
	Bacteria	**EC50 (15 min)**	**15.6**	**Farré et al. (2001)**	
Mefenamic acid		**EC50 ECOSAR**	**0.43**	**Jones et al. (2002)**	**0.43**
Naproxen	*Fish*	EC50 ECOSAR	34	Sanderson et al. (2003)	**2.62**
	Daphnia	EC50 ECOSAR	15	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	22	Sanderson et al. (2003)	
	Algae	EC50-inhibition	626	Cleuvers (2004)	
	Invertebrates	LC50(96 h)	22.4	Quinn et al. (2008)	
	Bacteria	EC50(15 min)	21.2	Farré et al. (2001)	
	Invertebrates	**EC50(96 h)**	**2.62**	**Quinn et al. (2008)**	
	Invertebrates	EC50	150	Boillot (2008)	
	Fish	EC50	600	Boillot (2008)	
	Daphnia	EC50-immobilisation	166.3	Cleuvers (2004)	
Phenazone	*Fish*	EC50 ECOSAR	3	Sanderson et al. (2003)	**1.1**
	Daphnia	EC50 ECOSAR	6.7	Sanderson et al. (2003)	
	Algae	**EC50 ECOSAR**	**1.1**	**Sanderson et al. (2003)**	
Propyphenazone	***Fish***	**EC50 ECOSAR**	**0.8**	**Sanderson et al. (2003)**	**0.8**
	Daphnia	EC50 ECOSAR	3.5	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	1	Sanderson et al. (2003)	
Salicylic acid	***Fish***	**EC50 ECOSAR**	**1.28**	**Sanderson et al. (2003)**	**1.28**
	Daphnia	EC50 ECOSAR	59	Sanderson et al. (2003)	

Table 6 (*continued*)

Compounds	Species assayed	Test (endpoint)	Toxicity (mg/004C)	References	PNEC (μg/L)
	Algae	EC50 ECOSAR	48	Sanderson et al. (2003)	
	Invertebrates	EC50 (48 h)	1147	Marques et al. (2004)	
	Invertebrates	LC50 (48 h)	112	Han et al. (2006)	
	Algae	EC50 (48 h)	>100	Henschel et al. (1997)	
	Bacteria	EC50 (15 min)	43.1	Farré et al. (2001)	
Tolfenamic acid	***Fish***	**EC50 ECOSAR**	**0.4**	**Sanderson et al. (2003)**	**0.4**
	Daphnia	EC50 ECOSAR	1.7	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	1.3	Sanderson et al. (2003)	
Amoxicillin			0.1	Kümmerer and Henninger (2003)	**0.0037**
	Algae	**EC 50**	**0.0037**	**Halling-Sørensen (2000)**	
Azithromycin			**0.15**	**Kümmerer and Henninger (2003)**	**0.15**
Cefaclor	*Algae*	EC50 ECOSAR	734.05	Lee et al. (2008)	**687.42**
	Daphnia	**EC50 ECOSAR**	**687.42**	**Lee et al. (2008)**	
	Fish	EC50 ECOSAR	11,524	Lee et al. (2008)	
Cefalexin			**2.5**	**Kümmerer and Henninger (2003)**	**2.5**
Cefotaxime			**0.04**	**Kümmerer and Henninger (2003)**	**0.04**
Chloramphenicol			**1.6**	**Kümmerer and Henninger (2003)**	**1.6**
Ciprofloxacin	*Fish*	EC50 ECOSAR	246,000	Sanderson et al. (2003)	**938**
	Daphnia	EC50 ECOSAR	991	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	938	Sanderson et al. (2003)	
Clarithromycin	*Invertebrates*	EC50	20	Boillot (2008)	**0.07**
	Algae	**EC50**	**0.07**	**Boillot (2008)**	
Clindamycin			**0.5**	**Kümmerer and Henninger (2003)**	**0.5**
Doxycycline			**0.3**	**Kümmerer and Henninger (2003)**	**0.3**
			316	Brain et al. (2004)	
Enoxacin			0.15	Kümmerer and Henninger (2003)	**0.15**
Erythromycin	*Fish*	EC50 ECOSAR	61	Sanderson et al. (2003)	**0.02**
	Daphnia	EC50 ECOSAR	7.8	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	4.3	Sanderson et al. (2003)	
	Invertebrates	EC50	15	Boillot (2008)	
	Algae	**EC50**	**0.02**	**Boillot (2008)**	
	Fish	EC50	900	Boillot (2008)	
Lincomycin	*Fish*	EC50 ECOSAR	1391	Sanderson et al. (2003)	**82**
	Daphnia	**EC50 ECOSAR**	**82**	**Sanderson et al. (2003)**	
	Algae	EC50 ECOSAR	86	Sanderson et al. (2003)	
Metronidazole			**2.5**	**Kümmerer and Henninger (2003)**	**2.5**
	Algae	EC50	39.1	Halling-Sørensen (2000)	
	Algae	EC50	40.4	Halling-Sørensen (2000)	
Norfloxacin	***Algae***	**EC50**	**15**	**Boillot (2008)**	**15**
Ofloxacin	*Algae*	EC50 (96 h-growth)	0.016	Ferrari et al. (2004)	**0.016**
	Invertebrates	EC50	30	Boillot (2008)	
	Algae	EC50	1.5	Boillot (2008)	
	Fish	EC50	10	Boillot (2008)	
Oxytetracycline	***Algae***	**EC50**	**0.207**	**Halling-Sørensen (2000)**	**0.207**
	Fish	EC50 ECOSAR	166,000	Sanderson et al. (2003)	
	Daphnia	EC50 ECOSAR	2432	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	2294	Sanderson et al. (2003)	
	Invertebrates	EC50 (96 h)	40.13	Quinn et al. (2008)	
Penicillin G	***Algae***	**EC50**	**0.006**	**Halling-Sørensen (2000)**	**0.006**
Penicillin V	***Daphnia***	**EC50**	**177**	**Jones et al. (2002)**	**177**
Roxithromycin	*Fish*	EC50 ECOSAR	50	Sanderson et al. (2003)	**4**
	Daphnia	EC50 ECOSAR	6	Sanderson et al. (2003)	
	Algae	**EC50 ECOSAR**	**4**	**Sanderson et al. (2003)**	
Sulfachloropyridazine	***Bacteria***	**EC 50(15 min-florescence)**	**26.4**	**Kim et al. (2007)**	**26.4**
Sulfadiazine			5	Kümmerer and Henninger (2003)	**0.135**
	Algae	**EC50**	**0.135**	**Halling-Sørensen (2000)**	
Sulfadimethoxine	*Fish*	EC50 ECOSAR	226	Sanderson et al. (2003)	**3.5**
	Daphnia	**EC50 ECOSAR**	**3.5**	**Sanderson et al. (2003)**	
	ALGAE	EC50 ECOSAR	24	Sanderson et al. (2003)	
Sulfamethoxazole	*Fish*	EC50 ECOSAR	890	Sanderson et al. (2003)	**0.027**
	DAPHNIA	EC50 ECOSAR	4.5	Sanderson et al. (2003)	
	ALGAE	EC50 ECOSAR	51	Sanderson et al. (2003)	
	FISH	EC50 (96 h)	563	Kim et al. (2007)	
	DAPHNIA	EC50 (48 h-mortality)	>100	Ferrari et al. (2004)	
	BACTERIA	EC50 (15 min)	78.1	Kim et al. (2007)	
	ALGAE	EC50 (96 h-growth)	0.15	Ferrari et al. (2004)	
	ALGAE	**EC50 (96 h-growth)**	**0.027**	**Ferrari et al. (2004)**	
Sulfapyridine	***Invertebrates***	**EC50 (96 h)**	**21.61**	**Quinn et al. (2008)**	**21.61**
Sulfathiazole	***DAPHNIA***	**EC50 (96 h-immobility)**	**85.4**	**Kim et al. (2007)**	**85.4**
Tetracycline			0.3	Kümmerer and Henninger (2003)	**0.09**
	ALGAE	**EC50**	**0.09**	**Halling-Sørensen (2000)**	
Trimethoprim	*Fish*	EC50 ECOSAR	795	Sanderson et al. (2003)	**2.6**
	Daphnia	EC50 ECOSAR	4.8	Sanderson et al. (2003)	
	Algae	**EC50 ECOSAR**	**2.6**	**Sanderson et al. (2003)**	
	Bacteria	EC50 (15 min)	177	Kim et al. (2007)	
	Daphnia	EC50 (96 h-immobility)	121	Kim et al. (2007)	

(*continued on next page*)

Table 6 (*continued*)

Compounds	Species assayed	Test (endpoint)	Toxicity (mg/004C)	References	PNEC (μg/L)
	Invertebrates	LC50 (96 h)	>100	Quinn et al. (2008)	
	Fish	EC50 (48 h)	>100	Kim et al. (2007)	
	Invertebrates	EC50	110	Boillot (2008)	
	Algae	EC50	90	Boillot (2008)	
	Fish	EC50	100	Boillot (2008)	
Diltiazem	*Daphnia*	EC50 (96 h-immobility)	8.2	Kim et al. (2007)	**1.9**
	Fish	EC50 ECOSAR	23	Sanderson et al. (2003)	
	Daphnia	EC50 ECOSAR	2.9	Sanderson et al. (2003)	
	Algae	**EC50 ECOSAR**	**1.9**	**Sanderson et al. (2003)**	
Atenolol	***Invertebrates***	**EC50**	**30**	Boillot (2008)	**30**
Metoprolol	*Fish*	EC50 ECOSAR	116	Sanderson et al. (2003)	**8**
	Daphnia	**EC50 ECOSAR**	**8**	**Sanderson et al. (2003)**	
	Algae	EC50 ECOSAR	14	Sanderson et al. (2003)	
	Invertebrates	LC50 (48 h)	>100	Huggett et al. (2002)	
	Invertebrates	LC50 (48 h)	8.8	Huggett et al. (2002)	
	Invertebrates	LC50 (48 h)	63.9	Huggett et al. (2002)	
	Fish	LC50 (48 h)	>100	Huggett et al. (2002)	
Nadolol	***Invertebrates***	**EC50**	**110**	**Boillot (2008)**	**110**
Propranolol	*Fish*	EC50 ECOSAR	29.5	Sanderson et al. (2003)	**0.244**
	Daphnia	EC50 ECOSAR	2.3	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	5.5	Sanderson et al. (2003)	
	Bacteria	EC50 (30 min-luminescence)	61	Ferrari et al. (2004)	
	Algae	EC50 (48 h)	0.7	Cleuvers (2005)	
	Diatoms	**EC50 (96 h-growth)**	**0.244**	**Ferrari et al. (2004)**	
	Invertebrates	LC50 (48 h)	29.8	Huggett et al. (2002)	
	Invertebrates	LC50 (48 h)	0.8	Huggett et al. (2002)	
	Invertebrates	LC50 (48 h)	1.6	Huggett et al. (2002)	
	Fish	LC50 (48 h)	24.3	Huggett et al. (2002)	
	Invertebrates	EC50	11	Boillot (2008)	
	Algae	EC50	0.8	Boillot (2008)	
	Fish	EC50	20	Boillot (2008)	
Timolol	*Fish*	EC50 ECOSAR	126	Sanderson et al. (2003)	**9**
	Daphnia	**EC50 ECOSAR**	**9**	**Sanderson et al. (2003)**	
	Algae	EC50 ECOSAR	15.5	Sanderson et al. (2003)	
Bezafibrate	***Fish***	**EC50 ECOSAR**	**5.3**	**Sanderson et al. (2003)**	**5.3**
	Daphnia	EC50 ECOSAR	25	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	18	Sanderson et al. (2003)	
	Invertebrates	EC50	50	Boillot (2008)	
Clofibrate	*Fish*	EC50 ECOSAR	5	Sanderson et al. (2003)	**0.5**
	Daphnia	EC50 ECOSAR	6.5	Sanderson et al. (2003)	
	Algae	**EC50 ECOSAR**	**0.5**	**Sanderson et al. (2003)**	
Clofibric acid	*Fish*	EC50 ECOSAR	53	Sanderson et al. (2003)	**40.2**
	Daphnia	EC50 ECOSAR	293	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	192	Sanderson et al. (2003)	
	Algae	EC50 (96 h-growth)	94	Ferrari et al. (2004)	
	Bacteria	EC50 (30 min)	91.8	Ferrari et al. (2003)	
	Invertebrates	EC50 (48 h)	83.5	Rosal et al. (2009)	
	Invertebrates	EC50 (48 h)	72	Cleuvers (2003)	
	Microtox	EC50 (30 min)	91.8	Ferrari et al. (2003)	
	Algae	**EC50 (96 h-growth)**	**40.2**	**Ferrari et al. (2004)**	
Fenofibrate	*Fish*	EC50 ECOSAR	0.8	Sanderson et al. (2003)	**0.1**
	Daphnia	EC50 ECOSAR	0.35	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	0.1	Sanderson et al. (2003)	
Fenofibric acid	***Fish***	**EC50 ECOSAR**	**7.6**	**Sanderson et al. (2003)**	**7.6**
	Daphnia	EC50 ECOSAR	38	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	26	Sanderson et al. (2003)	
Gemfibrozil	***Fish***	**EC50 ECOSAR**	**0.9**	**Sanderson et al. (2003)**	**0.9**
	Daphnia	EC50 ECOSAR	6	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	4	Sanderson et al. (2003)	
	Bacteria	EC50 (15 min)	35.3	Rosal et al. (2009)	
	Bacteria	EC50 (15 min)	18.8	Farré et al. (2001)	
	Invertebrates	EC50 (48 h)	10.4	Han et al. (2006)	
	Invertebrates	EC50 (96 h)	1.18	Quinn et al. (2008)	
Pravastatin	***Fish***	**EC50**	**1.8**	**Ginebreda et al. (2010)**	**1.8**
Carbamazepine	*Fish*	EC50 ECOSAR	101	Sanderson et al. (2003)	**13.8**
	Daphnia	EC50 ECOSAR	111	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	70	Sanderson et al. (2003)	
	Algae	EC50 (3 days)	74	Cleuvers (2003)	
	Bacteria	EC50 (15 min)	52.2	Kim et al. (2007)	
	Fish	EC50 (48 h)	35.4	Kim et al. (2007)	
	Daphnia	**EC50 (48 h-mortality)**	**13.8**	**Ferrari et al. (2004)**	
	Diatoms	EC50 (96 h-growth)	31.6	Ferrari et al. (2004)	
	C. dubia	EC50 (48 h)	77.7	Ferrari et al. (2003)	
Diazepam	*Fish*	EC50 ECOSAR	28	Sanderson et al. (2003)	**2**
	Daphnia	**EC50 ECOSAR**	**2**	**Sanderson et al. (2003)**	
	Algae	EC50 ECOSAR	5.5	Sanderson et al. (2003)	
	Invertebrates	EC50	90	Boillot (2008)	

Table 6 (*continued*)

Compounds	Species assayed	Test (endpoint)	Toxicity (mg/004C)	References	PNEC (μg/L)
	Algae	EC50	12	Boillot (2008)	
	Fish	EC50	11	Boillot (2008)	
Fluoxetine	*Fish*	EC50 ECOSAR	1.7	Sanderson et al. (2003)	**0.05**
	Daphnia	EC50 ECOSAR	0.17	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	0.8	Sanderson et al. (2003)	
	Invertebrates	EC50	0.9	Boillot (2008)	
	Algae	EC50	0.05	Boillot (2008)	
	Fish	EC50	2	Boillot (2008)	
Cimetidine	*Fish*	EC50 ECOSAR	571	Sanderson et al. (2003)	**35**
	Daphnia	**EC50 ECOSAR**	**35**	**Sanderson et al. (2003)**	
	Algae	EC50 ECOSAR	40	Sanderson et al. (2003)	
	Daphnia	EC50 (96 h-immobility)	271.3	Kim (2007)	
Ranitidine	*Fish*	EC50 ECOSAR	1076	Sanderson et al. (2003)	**63**
	Daphnia	**EC50 ECOSAR**	**63**	**Sanderson et al. (2003)**	
	Algae	EC50 ECOSAR	66	Sanderson et al. (2003)	
Clenbuterol	*Fish*	EC50 ECOSAR	30	Sanderson et al. (2003)	**2**
	Daphnia	**EC50 ECOSAR**	**2**	**Sanderson et al. (2003)**	
	Algae	EC50 ECOSAR	10	Sanderson et al. (2003)	
Fenoterol	*Fish*	EC50 ECOSAR	20	Sanderson et al. (2003)	**17.5**
	Daphnia	**EC50 ECOSAR**	**17.5**	**Sanderson et al. (2003)**	
	Algae	EC50 ECOSAR	25	Sanderson et al. (2003)	
Terbutaline	***Fish***	**EC50 ECOSAR**	**1.05**	**Sanderson et al. (2003)**	**1.05**
	Daphnia	EC50 ECOSAR	27	Sanderson et al. (2003)	
	Algae	**EC50 ECOSAR**	**32**	**Sanderson et al. (2003)**	
Cyclophosphamide	*Fish*	EC50 ECOSAR	70	Sanderson et al. (2003)	**11**
	Daphnia	EC50 ECOSAR	1795	Sanderson et al. (2003)	
	Algae	EC50 ECOSAR	11	Sanderson et al. (2003)	
Ifosfamide	*Fish*	EC50 ECOSAR	140	Sanderson et al. (2003)	**11**
	Daphnia	EC50 ECOSAR	1795	Sanderson et al. (2003)	
	Algae	**EC50 ECOSAR**	**11**	**Sanderson et al. (2003)**	
Iopromide	*Fish*	EC50 ECOSAR	865,000	Sanderson et al. (2003)	**370,000**
	Daphnia	EC50 ECOSAR	766,000	Sanderson et al. (2003)	
	Algae	**EC50 ECOSAR**	**370,000**	**Sanderson et al. (2003)**	

Compounds with average mass loads of less than 10 mg/1000 inh/d (not reported in Fig. 20) were: acetylsalicylic acid, doxycycline, cefotaxime, salbutamol, aminopyrine, glibenclamide, famotidine, loratadine, clotrimazole, phenazone, tylosil, cyclophosphamide, fenofibric acid, norfluoxetine, paroxetine, estradiol, estriol, ethinylestradiol, simvastatin, gabapentin, valproic acid, oxcarbazepine, fenoprofen, sulfamethazine and phenobarbital.

3.5. Environmental risk assessment of secondary biological effluent

The environmental risk posed by the presence of PhCs in water is still under discussion. Safety threshold values have been defined for a limited number of PhCs, but only in single compound–single organism toxicity studies, meaning that mixture effects have not yet been considered.

Moreover, many compounds themselves have not been extensively studied, and, when available, PhC toxicity data tends to refer only to acute rather than chronic effects.

Table 6 reports the PNEC values defined for 67 out of the 118 PhCs included in this review, the corresponding assayed species, the endopoint and the literature references. Conforming to EC (EC, 2003), each of the reported PNECs is 1000 times lower than the toxicity concentration value found for the most sensitive species assayed, so as to take into account the effect on other, potentially more sensitive, aquatic species to those used in toxicity studies.

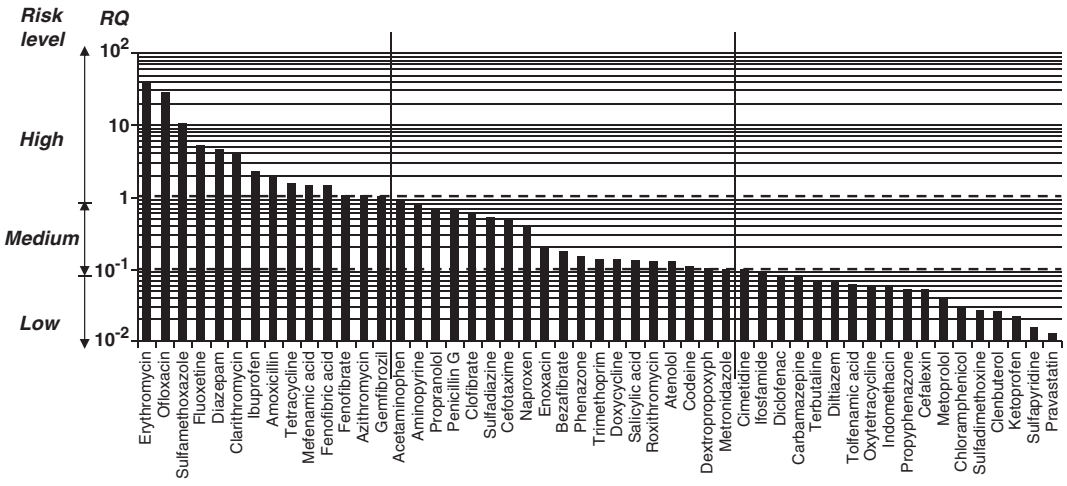


Fig. 21. RQ of the investigated compounds.

An evaluation of the environmental risk posed by PhCs in secondary effluent was carried out by means of the risk quotient (RQ), that is the ratio between the average PhC concentrations measured in the secondary effluent and its corresponding PNEC (EMEA, 2001). Average secondary effluent concentrations are reported in brackets after the name of the compounds in the *x*-axis of Figs. 7–12, and PNEC values are those reported in Table 6.

A commonly used ranking criterion was applied, according to De Souza et al. (2009) and Hernando et al. (2006): RQ<0.1 low risk to aquatic organisms, $0.1 \leq RQ \leq 1$, medium risk; $RQ \geq 1$, high risk. The RQ values were found within the range of 6.8×10^{-6}–37 for the 67 compounds considered; compounds with RQ greater than 0.01 are reported in Fig. 21, in descending order. The dotted lines in the graph represent the thresholds defining the three environmental risk levels: high, medium and low.

As seen in Fig. 21, fourteen compounds pose a high risk: 7 antibiotics (erythromycin, ofloxacin, sulfamethoxazole, clarithromycin, amoxicillin, tetracycline and azithromycin), 2 psychiatric drugs (fluoxetine and diazepam), 2 analgesics-anti/inflammatories (ibuprofen and mefenamic acid) and 3 lipid regulators (fenofibric acid, fenofibrate and gemfibrozil). A medium risk is posed by nineteen compounds: 7 analgesic-anti/inflammatories (acetaminophene, aminopyrine, naproxen, phenazone, salicylic acid, codeine and dextropropoxyphene), 8 antibiotics (penicillin G, sulfadiazine, cefotaxime, enoxacin, trimethoprim, doxycycline, roxithromycin and metronidazole), 2 beta-blockers (propranolol and atenolol) and 2 lipid regulators (clofibrate and bezafibrate). For the remaining 18 compounds included in Fig. 21, the environmental risk is considered low, as is that of the 16 PhCs excluded from the graph due to an RQ of less than 10^{-2} (cimetidine,clindamycin, ranitidine, acetylsalicylic acid, clofibric acid, timolol, norfloxacin, sulfachloropyridazine, fenoterol, cyclophosphamide, ciprofloxacin, lincomycin, nadolol, sulfathiazole, penicillin V, cefaclor, iopromide).

Comparison of Figs. 20 and 21 shows that the top compounds are not the same in the two rankings, with the exception of the two analgesics/anti-inflammatories ibuprofen and mefenamic acid. Compounds of different classes had the highest mass loads: the antihypertensive hydrochlorothiazide, the psychiatric drug carbamazepine, the receptor antagonist cimetidine, the beta-blocker atenolol and 5 analgesics/anti-inflammatories (naproxen, ibuprofen, diclofenac, ketoprofen and mefenamic acid), many of which are administered frequently and/or over long periods of time. In contrast, the highest risk is posed by the 12 compounds cited just above belonging to the groups of antibiotics, lipid regulators and analgesics/anti-inflammatories. This fact confirms the results obtained by other Authors (among them Escher et al., 2011) that high consumption does not mean high risk for the environment.

4. Final considerations and further needs

Most of the municipal WWTPs consist of preliminary, primary and secondary treatments (mainly activated sludge systems) with the final effluent being discharged into a surface water body and often indirectly reused for irrigation purposes or recreational activities. The present review shows that many PhCs are usually present in raw influent at concentrations in the range of 10^{-3}–10^{2} μg/L and even more, and that common WWTPs are not able to efficiently remove all of them. Observed removal efficiencies vary in a wide range for the different compounds, as well as for the same substance, due to the different chemical and physical characteristics of PhCs and to operational conditions (mainly aerobic, anaerobic, anoxic reactors, SRT, pH and water temperature) as discussed above. MBRs seem (only 20 pilot plants were investigated and a limited number of PhCs were tested) to guarantee higher removal efficiencies for most compounds and a better quality of the permeates with respect to CAS.

This review highlights the fact that the occurrence of some PhCs in the secondary effluent discharged into surface water bodies may pose a medium–high (acute) risk to aquatic life. Furthermore, many other compounds, even if their environmental risk was found to be low, are discharged at high daily mass loads, which could contribute to negative effects on aquatic organisms in the long term due to chronic and mixture toxicities.

For these reasons, it would be more prudent to begin monitoring the most frequently and most persistent administered PhCs, as well as those with the highest environmental risk, namely antibiotics (including erythromycin, ofloxacin, sulfamethoxazole, clarithromycin, amoxicillin, tetracycline and azithromycin), psychiatric drugs (like fluoxetine, diazepam and carbamazepine), analgesics/anti-inflammatories (ibuprofen, mefenamic acid, naproxen, diclofenac and ketoprofen) and lipid regulators (fenofibric acid, fenofibrate and gemfibrozil).

From a legislation point of view, it is quite important to note that the Directives concerning the protection of aquatic environments and related organisms are the Water Framework Directive 2000/60/EC (WFD), the daughter Directive 2006/118/EC (GWD) for the protection of groundwater and the daughter Directive 2008/105/EC (PSD) stating the List of Priority Substances (also known as Annex X to WFD) for surface waters and related Environmental Quality Standards (EQSs). Pharmaceuticals are not included among those compounds to be monitored, notwithstanding their occurrence has been documented since more than 20 years in many European countries. The revision of the list of compounds and the subsequent definition of pertinent new EQSs are based on significant risks to or via aquatic environment in compliance with Art. 16 of the WFD.

Bottoni et al. (2010) report that a simplified and pragmatic methodology was developed under the WFD Common Implementation Strategy (CIS), taking into consideration both monitoring data and modelling data. According to these Authors, possible priority pharmaceuticals could be antineoplastics (including tamoxifen and cyclophosphamide), synthetic estrogens and hormones. The inclusion of target PhCs in the EU List of Priority Substances implies the definition of their corresponding EQSs and the necessity to subject to monitoring ambient water, sediment and biota in the different EU countries. In addition further attempts to define prioritisation lists have been made by other Commissions. For instance that by Oslo and Paris Commission (OSPAR) including mainly antibiotics, psychiatric drugs, receptor antagonists, that by Global Water Research Coalition (GWRC, 2008) that defined a high priority level for a group of substances belonging to different classes: carbamazepine, sulfamethoxazole, diclofenac, ibuprofen, naproxen, bezafibrate, atenolol, ciprofloxacin, erythromycin and gemfibrozil. National prioritisation procedures have also taken place and prioritised PhCs based on the potential risk that they are perceived to pose to aquatic environment. In the United Kingdom, 12 compounds were prioritised for targeted monitoring based upon their predicted environmental concentrations, PNECs, and persistence, bioaccumulation and toxic (PBT) properties: mainly analgesics, antidepressants, antibiotics, and antineoplastics (Ashton et al., 2004). In the United States the contaminants candidate to be included into the priority lists are the antibiotic erythromycin and the estrogens ethinylestradiol, estradiol, equilenin, estriol, estrone, mestranol and norethindrone (Richardson and Ternes, 2011). All these attempts provide a good start in focusing efforts, but they should be considered with caution as they are based on acute, principally lethal, ecotoxicological test data and may therefore not include those substances that may be exerting effects following chronic exposure. Occurrence data have to be used not only to confirm the presence of a compound in the aquatic environment, but it is used in combination with relevant ecotoxicol test data to allow the refinement of risk assessments.

For these reasons, further researches are necessary (*i*) to analyse the occurrence of scarcely investigated PhCs in the influent and effluent of municipal WWTPs; (*ii*) to define PNECs for a wider spectrum of compounds, (*iii*) to evaluate the environmental impact of mixtures of different PhCs, (*iv*) to evaluate the chronic effect of authentic PhC mixtures on the aquatic life, (*v*) to evaluate the best end-of-pipe

measures for the existing WWTPs to guarantee better removal of the most persistent compounds, and (*vi*) to suggest source control options to reduce the quantity and variety of PhCs in the water cycle.

Acknowledgements

This work was financially supported by the Technopole Terra&AcquaTech of the University of Ferrara (Funding: POR-FESR 2007–2013).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2012.04.028.

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