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Status of hormones and pain killers in waste water effluents across several European states - considerations for the EU watchlist concerning estradiols and diclofenac

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	Directive 2013/39/EU introducing(i) quality evaluation of aquatic compartments; (ii) the polluter pays principle, (iii) need of innovative wastewater treatment technologies, and (iv) identification of pollution including a list of compounds to be monitored. A watch list of 10 substances was defined by Decision 2015/495. Several recalcitrant chemicals, among them diclofenac and the hormones E2 and EE2 are named. Although some approaches for their removal exist, retrofitting WWTPs with AOPs will not be acceptable as consistent investment at reasonable operational cost. The same is true for membrane technologies, because they lead to higher operation costs that a majority of communities will not accept. Advanced technologies in wastewater treatment like membrane bioreactors (MBR) integrating biological degradation of organic matter with membrane filtration have proven more complete elimination of emerging pollutants. Still, most of the presently applied methods are incapable of removing critical compounds completely. In this opinion paper the state of the art of European WWTPs is reflected, and capacities of single methods are described. Furthermore, the need for analytical standards, risk assessment and economic planning is stressed. The survey concludes that combinations of different conventional and advanced technologies including phytoremediation seem to be most promising to solve the problem of hazardous emerging xenobiotics.
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Status of hormones and pain killers in waste water effluents across several European states – considerations for the EU watchlist concerning estradiols and diclofenac

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1. Abstract

Technologies for wastewater treatment that are normally employed do not sufficiently address the increasing pollution situation of receiving water bodies, especially with the growing use of personal care products and pharmaceuticals (PPCP) in the private household and health sector. The relevance of addressing the problem of organic pollutants was taken into account by the Directive 2013/39/EU that introduced (i) the quality evaluation of aquatic compartments; (ii) the polluter pays principle, (iii) the need of innovative and affordable wastewater treatment technologies, and (iv) the identification of pollution causes including a list of principal compounds to be monitored. In addition, a watch list of 10 other substances was recently defined by Decision 2015/495 on March 20, 2015. On this list, several recalcitrant chemicals, among them the pain killer diclofenac and the hormones E2 and EE2 can be found. Although some modern approaches for their removal exist, such as advanced oxidation steps, retrofitting most wastewater treatment plants with AOPs will not be acceptable as consistent investment at reasonable operational cost. The same is true for membrane technologies despite of the incredible progress that has been made during recent years, because these systems leads to higher operation costs (mainly due to higher energy consumption) so that the majority of communities will not easily accept them. Advanced technologies in wastewater treatment like membrane bioreactors (MBR) that integrate biological degradation of organic matter with membrane filtration have proven a more complete elimination of emerging pollutants in a rather cost and labor intensive technology. Still, most of the presently applied methods are incapable of removing critical compounds completely. In this opinion paper the state of the art of European WWTPs is reflected, and capacities of single methods are described. Furthermore, the need for analytical standards, risk assessment and economic planning is stressed. The survey results in the conclusion that combinations of different conventional and advanced technologies including phytoremediation seem to be most promising to solve the burning problem of polluting our environment with hazardous emerging xenobiotics.

2. Introduction and Demand

Across Europe, most people don´t know where their drinking water comes from, or how big the efforts are to allow the performance of the most normal daily action, namely to open the tap and to consume clean, clear and pure water. Still, it is the extremely high quality of our drinking water that warrants the healthy life we lead. In fact, to provide unpolluted water as a resource for drinking water supply, food production but also other aspects of daily life, will remain one of the major challenges for Europe in the closer future. Novel emergent organic compounds (pharmaceuticals, industrial chemicals, personal care products and others) pose a threat to our water reserves

(Heberer, 2002b; Kasprzyk-Hordern et al. 2008). These anthropogenic substances, often addressed as micropollutants that may adversely affect drinking water quality are most typically polar to semi-polar organic compounds detected at concentrations in the pg/L to µg/L range (Benner et al., 2013). Contamination of drinking water resources (surface water and ground water) with these micropollutants raises important questions related to human health, ecology, and economic impacts (Benner et al., 2013). Among sources that are considered responsible for the occurrence of micropollutants in surface water and ground water, effluents of municipal wastewater treatment plants (WWTP) are frequently pinpointed as most important (Ternes, 1998; Zuccato et al., 2006; Kasprzyk-Hordern et al. 2008). Whereas well-assessed treatment strategies exist for classical issues in WWTP such as removal of biodegradable organic substances, nutrients (phosphorus and nitrogen), detergents and even microorganisms, polar and semi-polar micropollutants are not or only incompletely removed by these technologies. Hence, with the growing number of micropollutants being identified in surface water and ground water, novel remediation and management strategies are needed to provide cost-effective and sustainable treatment solutions across Europe.

Since the majority of all significant waters, lakes and streams are shared between several European countries, the European Union (EU) has to find a common strategy for remediation of micropollutants and to set limits for effluents from WWTP. Furthermore it will be necessary to expand the scope of water protection to all waters, surface waters and groundwater, to achieve satisfactory status for all waters by a set deadline, and to delegate water management to regional authorities based on river catchments. This is in part proposed by the European Water Framework Directive (see below: international conventions and agreements), which has already been implemented in most EU countries.

Among thousands of micropollutants, not everything that can be measured is worth measuring, and not everything worth measuring is measurable. With regard to pharmaceutically active compounds, those to be monitored in natural waters should be related to prescription and non-prescription practices in each country (compare Fig. 1). It is very important to develop a ranking system for prioritizing pharmaceutically active compounds considering the following 4 criteria: a) occurrence (prevalence, frequency of detection), b) highest percentages of excretion c) removal in treatment plants, c) ecological effects (bioaccumulation, ecotoxicity).

From the large number of micropollutants that fit this scheme, diclofenac (2-(2-(2,6-dichloro-phenylamino)phenyl)acetic acid, DCF) and the estrogenic hormones 17β-estradiol (1,3,5(10)-estra-trien-3,17β-diol; E2) and 17α-ethinylestradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-in-3,17-diol; EE2) have recently been included in the EU watchlist (Directive 2013/39/EU) of priority substances (EU, 2013).

Diclofenac is a widely used non-steroidal anti-inflammatory drug used as pain killer prescribed as pills or ointments and among the most frequently detected pharmaceuticals in WWTP effluents, in µg/L concentrations (Verlicchi et al., 2012). E2 is a primary female sex hormone and key regulator of the estrous and menstrual female reproductive cycles, whereas EE2 is a synthetic, bioactive estrogen used in many formulations of combined oral contraceptive pills. Both estrogens are detected in WWTP in the lower ng/L concentrations and are known to cause endocrine disrupting effects in the biota (Forrez et al., 2009). Again, WWTP effluents are considered as main source of estrogens in the environment (Snyder et al. 2001).

Using these three selected micropollutants from the EU watchlist as representatives, the aim of this review is to summarize current problems and solutions in several EU countries and critically evaluate the viability of various treatment methods for the removal of micropollutants from wastewater.

The North Sea Conference on Co-operation in dealing with pollution of the North Sea by oil and other harmful substances (Bonn, 1983), stimulated public awareness to the topic of water quality for the first time. Still, it took almost a decade until the Hague Declaration on the future European Community ground water policy was ratified at the EC Ministerial Meeting on 26.-27.11.91. Another decade went by until the Agenda 21 requested that quantitative and qualitative discharge standards for municipal and industrial effluents should be established and applied by the year 2000. This recommendation included the proposal to revise Directive 76/464/EEC (Dangerous Substances in Water) and the Directive No. 96/61 EC on Integrated Pollution Prevention and Control (IPPC, 1996), as well as Directive 93/793/EEC on environmental risk from chemicals (testing the ecotoxicity of listed priority chemicals). Nowadays, updated European framework legislation promotes the reduction of micropollutants. The ETAP (Environmental Technologies Action Plan) of the European Union claims urgent action for better water quality and protection of our natural resources. High priority is also given to environmentally sound water treatment technologies that will reduce greenhouse gases, recycle materials and provide all partner countries with affordable technologies. The discussion paper on water issues is very specific about novel green technologies to be adopted in this respect (http://europa.eu.int/comm/environment/etap/pdfs/etapwaterissuefr.pdf). Substantial political concern exists that water pollutants have to be monitored and removed. However, our knowledge of xenobiotics control or degradation has hardly gone beyond scratching the surface and confirming the importance of the problem. Finally, the EU enhanced the list of dangerous compounds and put estradiols and diclofenac on the Watchlist (Directive 2013/39/EU). The substances (diclofenac and two hormones: 17β-estradiol (E2) and 17α-ethinyl-estradiol (EE2)) shall be monitored by the EU member states in their surface waters for a maximum of four years. In addition, environmental quality standard values of 100 ng L^{-1} for inland waters and 10 ng L^{-1} for costal water were proposed for diclofenac. Although such political decisions are very helpful to increase the public awareness of water pollution problems, our general behavior towards water protection and water pricing is ambiguous.

3. National inventories

The availability of data on the daily use of pharmaceuticals in the EU is scattered, and incomplete for recent years. A comprehensive view may be possible for the years between 2005 and 2011 where data from several countries can be compared (Fig. 1). Diclofenac (DCF) and 17a-ethinylestradiol (EE2) consumption rates vary greatly between and also within countries. According to the published literature data in different countries around the world (Ternes 1998; Carballa et al., 2005; 2008) the annual consumption of DCF varies between 195 and 940 mg per inhabitant, as for EE2 vary between 20 and 580 µg per inhabitant, respectively. However, in Serbia with population of 7.2 million in 2012, the annual consumption of DCF and EE2 was equal to 8650 and 0.39 kg per year, respectively, while consumption of DFC and EE2 per inhabitant was estimated to be 1197 mg and 50 µg per year per inhabitant, respectively (Radonjić and Šipetić, 2012). In Germany, for DCF and EE2, according consumption quantities of active ingredients in human medicines was estimated 1033 mg and 600 µg per inhabitant per year (SRU, 2007), while DCF consumption rate in Turkey for the years of 2009 and 2013 were 950 and 985 mg per inhabitant per year, respectively (Sari et al., 2014), and 440 mg per caput and year in The Netherlands (Oosterhus et al. 2013).

For the calculation of drugs consumption in several EU countries for 2011 (Table 1) the concept of "Defined Daily Dose" (DDD) was used, i.e. the assumed average maintenance dose per day for a drug used for its main indication in adults expressed as DDD/1,000inhabitant/day, as prescribed by the WHO Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no/). Comparing the consumption data obviously the DCF and EE2 are still among most popular and consumed medicine products.

Figure 1

Supplemental Table 1

Recent analysis of the consumption of DCF and EE2 in three Baltic States for the 2009-2013 period revealed the demand for drugs that affect the musculoskeletal system has increased by 4.9%, the demand for drugs that affect the urogenital system and sex hormones has increased by 9.85%. The sales of diclofenac were equal to 30.3% of all the sales in accordance with ATC subgroup; the sales of EE2 in their subgroup were equal to 11.6% (Baranauskaite and Dvarioniene , 2014).

Occurrence of analgesics and hormones in STP's effluents and surface waters

Various studies over recent years have shown that treated municipal wastewater contributes significantly to water pollution from micropollutants (Hollender et al., 2009; Jelic et al., 2012; Kasprzyk-Hordern et al., 2009; Ternes 1998; Verlicchi et al., 2012). This is a consequence of the increasing number of prescribed medicaments and of the fact that state of the art sewage treatment plants are obviously not designed to remove PPCPs from the wastewater they receive from households and hospitals. DCF, E2 and EE2 have been detected in both, WWTPs (influents and effluents) and surface waters in the range of low µg/L to few ng/L levels (Tab. 1).

One of the first compilations on this topic was a German study detecting diclofenac among 55 pharmaceuticals and 9 of their metabolites in the discharge of 49 sewage treatment plants as well as in their effluents in concentrations of up to several µg/L (Ternes 1998). In the UK, diclofenac was detected in estuaries at concentrations up to 125 ng/l (Thomas and Hilton, 2004). Another more recent study reports that 27 out of 32 pharmaceutical substances and 4 of 5 metabolites were detected in the effluents of European wastewater treatment plants, and that surface water peak values exceeded 1 µg/L (Larsen et al. 2004). During an EU-wide monitoring survey on emerging polar organic contaminants in wastewater treatment plant effluents diclofenac was found at an average concentration of 49.5 ng/L, whilst the highest concentration found was 174 ng/L (Loos et al., 2013a). This pollution in the effluents leads to contamination of surface water as has been proven in several novel studies. Levels of target compounds were in the ng/L range but concentrations of some of them exceed 1 μg/L (including diclofenac) with fairly high concentrations of 1.3 μg L^{-1} and even 20.1 μg L^{-1}, respectively (Petrović et al., 2014), reflecting the consumption of PhACs by the residents of Novi Sad, the second largest town in Serbia. In recent Spanish investigations, DCF seasonal behaviour was also monitored along the El Albujón watercourse, till the Mar Menor Lagoon into the Mediterranean Sea, where even concentrations of 50 ng L^{-1} were detectable (Moreno-González et al., 2014). Analogously, along the Turia river, which flows into the Mediterranean Sea at some kilometers more at north than El Albujón, a very consistent amount of DCF was determined (Carmona et al., 2014). In this case 3500 ng L^{-1} were detected in the water, whereas a contamination of sediments of 100 ng g^{-1} was determined.

The Turia case represents a paradigm of the problem of the impact on human uses of water contaminated by DCF, considering that water obtained after osmotic treatment, then used as “drinkable” water, contained yet a concentration of 18 ng L^{-1} of this pharmaceutical.

Table 1

As for estrogens, concentrations of of 1–500 ng L^{-1} have been recorded in untreated municipal wastewater, with the distribution of concentrations generally following the pattern E1 > E2 > E3 > EE2 (Racz and Goel 2009). Interestingly, concentrations of 1–500 ng L^{-1} have also been reviewed by the same authors in the effluents of wastewater treatment facilities, indicating that elimination of these endocrine substances is insufficient in many if not all treatment systems.

4. Progress in detection and identification

For the monitoring of DCF, EE2 and E2 in water samples pre-concentration is required. Currently, solid-phase extraction (SPE) is the most widely used procedure to extract and concentrate pharmaceuticals and other organic pollutants from environmental samples. In the specific case of DCF, acidification of the aqueous sample is frequently used to facilitate more efficient recovery of the target molecule from natural samples (Tab. 2). When the adopted analytical technique is based on gas-chromatography (GC-ion trap-MS-MS, GC-MS or GC-MS-SIM), derivatization is necessary (methylation, terbutylation, etc) to enable separation and detection. These operations are not necessary when final analysis is performed with LC-MS-MS. In any case, pretreatment and derivatization will enhance the overall difficulty of the analysis, and its final net cost, for the respective further preparative works, without a significant difference in terms of limits of quantification (LOQ). Consequently, and specifically since co-elution occurs, several labs have reconsidered to omit this preconcentration step and begun to search for other solutions.

When analyzing sewage sludge, an additional step is necessary for exhaustive determination of DCF, E2 and EE2. Namely, the first step in pretreatment usually applied involves extraction of the target compounds from solid sample by pressurized liquid extraction (PLE, Radjenović et al. 2009a), microwave assisted extraction (MAE, Cortazar et al. 2005, Rice and Mitra 2007) or ultrasound sonification (US, Gatidou et al. 2007). In addition, an extensive cleaning of the obtained extract to avoid any matrix interference might be used to remove organic and inorganic co-extractives, because they might interfere with analyte separation and detection causing background noise in GC-MS analysis and signal suppression and/or enhancement in LC-MS analysis.

After applying of one of the mentioned extraction techniques (PLE, MAE or US) as the first pretreatment step to solid matrices, the next steps involved are presented in Table 2. Which of the listed methodologies will be chosen depends on the type of analyte and respective techniques available in the laboratory.

In Table 2 the main published procedures for analyzing DCF, E2 and EE2 in environmental water samples are compiled. It becomes clear that for both diclofenac and the estrogens determination by GC-MS necessarily involves an additional derivatization step (e.g. by methylation, tert-butyldimethylsilyl, with N-methyl-N-(trimethylsilyl)trifluoroacetamide, etc.) due to the polarity of the compounds. Determination by LC-MS is indeed simpler and can even be automated provided that an on-line SPE can be used to reach the low detection limits that are frequently required.

Table 2

Another issue worth considering is the presence in environmental aqueous samples, together with target pharmaceutical compounds, of other compounds that are practically linked to the selected targets, namely metabolites and degradation products. The determination of such compounds is not straightforward due to the lack of relevant mass spectrometric data available in LC-MS/MS methods, namely the precursor ion mass, the product ion masses (quantifier ion and qualifier ion) and the collision energy voltage. Therefore, an approach that is not based on the selectivity of the MS/MS mode but that employs high resolution MS (HRMS) allowing the detection in scan mode would be much more beneficial. This is actually implemented in untargeted screening, as described in the next paragraph.

Approaches for target and non-target analysis

The detection and identification of PPCPs in environmental samples can be divided into three categories, namely quantitative targeted analysis employing reference standards, suspects screening without reference standards, and non-targeted screening (Krauss et al., 2010; Kind and Fiehn, 2010; Little et al., 2011). These three categories are also defined as *known, known unknown* and *unknown unknown*, respectively. Quantitative target analysis is the most common approach, in which only a number of previously selected, and often regulated, compounds are determined and the method is only validated for such compounds. These analyses are most often carried out with High Performance Liquid Chromatography (HPLC) or Reverse Phase Liquid Chromatography (RPLC) coupled with MS/MS detection, due to their high selectivity and sensitivity. The disadvantage of MS/MS approaches is that the product ions must be known in advance. Hence, with such a procedure there is lack of information on analyzed samples because only user-defined MS/MS transitions are saved in the method and compounds in the sample that are not specified beforehand remain unknown. Employment of MS/MS techniques for quantitative target analysis has also some drawbacks and limitations, namely (i) methods are typically limited to about 100–150 target compounds depending on chromatographic separation under the constraints of having at least two transitions per compound, (ii) for some compounds only non-specific transitions might occur such as the neutral loss of H_2O or CO_2, which are also common for matrix interferences, (iii) for some analytes, especially those of low molecular weight, only one transition is present. Target analysis employing high resolution MS (HRMS), instead, overcomes these limitations of MS/MS analysis. Virtually all compounds present in a sample can be determined simultaneously with HRMS instruments operating in full-scan mode, making pre-selection unnecessary.

In *suspect screening* analysis (without reference standards, i.e. also without known metabolites) all compounds with a mass-to-charge ratio (m/z) within the defined mass range are detected. Also, MS/MS analysis can be employed providing that the transitions of the suspected compounds are available. When employing HRMS, analytes are examined after the analysis by plotting a narrow-window extracted ion chromatogram of 20–50 mDa. This comprehensive dataset also enables retrospective reanalysis of the sample years after the sample was first analyzed. Reference standards are currently available only for few environmental contaminants, and lack in particular for trans-formation products. Still, compound-specific information for suspects is available, and can be efficiently used in the identification and confirmation process (Moreno-Bondi et al., 2009; Hogenboom et al., 2009). Up to now, practical experience shows that a resolving power of 20,000 to 60,000 is required for most organic pollutants, depending on the complexity of the matrix (Kellmann et al. 2009).

In non-target screening analysis, unknown components in the sample chromatogram are extracted from TIC, using special deconvolution software that detects the ions filtering them out from the background. For this type of experiment, the employment of HRMS(/MS) is reported to be the only effective technique to be used (Krauss et al., 2010; Nurmi et al., 2012; Godfrey and Brenton, 2012). Indeed, a structure proposition for a peak detected by HRMS and MS/MS spectra involves several work intensive data and expert processing steps (Krauss et al., 2010; Nurmi et al., 2012; Kind and Fiehn, 2010; Little et al., 2011, Little et al., 2012). Although the described non-target workflows are often focused on one specific evaluation step, the following key features have emerged: (i) peak detection by exact mass filtering from the chromatographic run; (ii) assignment of an elemental formula to the exact mass of interest; and (iii) a database search of plausible structures for the determined elemental formula. In addition, useful information can be gathered from mass spectra leading to a more effective determination of the elemental composition of the unknown compound. This includes the abundance of natural isotopes which refers to the percentages in which the isotopes of an element are found in natural sources on earth. Such an approach leading to unequivocal assignment of chemical structures taking into account isotopic distribution of ions is defined as employing the spectral accuracy (Wang and Gu, 2010; Amorisco et al. 2013). Several reports focused on how isotope patterns can be used as a tool to help identifying unknowns on various mass spectrometers (Erve et al., 2009; Jiang and Erve, 2012, Godfrey and Brenton, 2012). However, it is evident that non-target screening analysis is incapable of revealing all compounds in the sample, causing possible false negative results. This is due to the inherent nature of LC-MS analysis, since both, chromatography and ionization always exclude some of the compounds. As a very useful evaluation tool for possible candidates, HRMS is ideal when combined subsequently with a powerful structure elucidation technique like NMR (nuclear magnetic resonance spectroscopy, De Laurentiis et al., 2014).

An efficient modern method for both, target and non-target screening analysis is the hyphenation of hydrophilic interaction chromatography (HILIC) with RPLC coupled with high accurate MS, such as TOF-MS. With this, the analyst has a powerful tool for comprehensive and simultaneous analysis of compounds in a wide range of polarity (Rajab et al. 2013).

NMR techniques have enabled incredible progress in non-target analysis, since they complement standard mass spectrometry to yield structural analytical information. 1H-NMR spectroscopy allows detection of bonding states of individual H atoms in aliphatic or aromatic molecules, so that structural isomers can be distinguished. The use of NMR spectroscopy as a method of environmental analysis was only possible after development of cryotechnologies and resolution of > 500 MHz which made the usual enrichment procedures for organic pollutants unnecessary. Today instruments are able to determine molecules in the ng/L range, and two-dimensional NMR techniques deliver structures in the ppb range. But since the costs of such equipment are extremely high, many labs still have to rely on information delivered by classical HPLC-MS or GC-MS and solid phase extraction.

5. Conventional treatment systems and their shortcomings

Conventional municipal wastewater treatment plants (WWTPs) are designed to limit the discharges of organic carbon, nitrogen, phosphorus and pathogens to the aquatic environment. To do so, WWTPs apply a primary, a secondary and an optional tertiary treatment process. During primary treatment, coarse solids are separated from the liquid stream and micropollutants are removed mainly by chemical and mechanical separation. The sorption of micropollutants onto solids depends basically on their physico-chemical properties, such as lipophilicity or acidity. Two types of coefficients have been mostly used to determine the sorption effectiveness: the octanol-water partition coefficient (K_{ow}) and the organic carbon partition coefficient (K_{oc}). Log K_{ow} < 2.5 indicates a low sorption potential, 2.5 < log K_{ow} < 4 indicates a medium sorption potential, while log K_{ow} > 4 indicates a high sorption potential (Rogers, 1996). However, some limitations have been found in literature (Holbrook et al., 2004; Lai et al., 2000) for the applicability of these coefficients to explain the sorption behavior of some micropollutants, because acidity determined by functional groups also plays a significant role in sorption behavior. Therefore, the solid–water distribution coefficient (K_d), defined as the ratio between the concentrations of a substance in the solid and in the aqueous phase at equilibrium conditions, has been proposed as the most suitable parameter (Schwarzenbach et al., 2003; Ternes et al., 2004; Joss et al., 2005). This coefficient takes into account the two main sorption mechanisms absorption (hydrophobic interactions characterized by the K_{ow} value, relevant for neutral compounds) and adsorption (electrostatic interactions related to the substance tendency to be ionized or dissociated in aqueous phase, characterized by the dissociation constant, pKa). At pH above the pK_a phenolic hydroxyl or carboxyl groups dissociate and become negatively charged (Schäfer et al. 2011). DCF, for example, with a pK_a > 4 is negatively charged in municipal WWTP effluents, while E2 and EE2 are still in their neutral form. Table 3 summarizes these properties for the compounds under consideration. It can be observed that the three substances show a medium tendency to sorb onto solids, and consequently, intermediate removal (20-45%) has been obtained during primary treatment (Carballa et al., 2005; Behera et al., 2011).

Table 3

The most common applied secondary treatment in WWTPs is the conventional activated sludge process (CAS), where both organic matter and nutrients are biologically removed. In this step, removal of a parent compound occurs by different mechanisms: a) stripping by aeration; b) sorption to particles or biomass; and c) biotransformation/biodegradation. Stripping is not significant for DCF, EE2 and E2 due to their high molecular mass and therefore low volatility (Radjenovic et al., 2007a). As described in the previous paragraph, sorption to sewage sludge is moderate, and therefore, biological transformation is the most likely mechanism responsible of micropollutants elimination in WWTPs. Although the microbiota developed in WWTPs may have been exposed to a plethora micro-pollutants for a long time, the effective biological removal of these substances is conditioned by singular factors. Some of these factors are micropollutant-related, such as chemical structure or functional groups. In general, linear compounds with short side chains, unsaturated aliphatic compounds and compounds possessing electron donating functional groups are easily degradable (Luo et al., 2014). The biodegradability of organic compounds is commonly classified according to their kinetic reaction rate (k_{biol}). Suarez et al. (2010) have defined four groups of substances according to their biodegradability:

- very highly degradable: $k_{biol} > 5$ L/(g_{SS}·d)
- highly degradable: $1 < k_{biol} < 5$ L/(g_{SS}·d)
- moderate degradable: $0.5 < k_{biol} < 1$ L/(g_{SS}·d)
- hardly degradable: $k_{biol} < 0.5$

From the data compiled in Table 3, only E2 and EE2 can be identified as very highly degradable, while DCF is very recalcitrant. However, it should be considered that these degradation constants are usually determined in lab-scale experiments and the operational conditions in WWTPs might be different. In fact there is evidence that some operating parameters, such as hydraulic retention time (HRT), solid retention time (SRT), redox conditions and temperature may affect micropollutant removal. HRT is the time that allows for biodegradation and sorption (Luo et al., 2014). Micropollutants having slow/intermediate kinetics will experience less effective biotransformation at shorter HRT or increasing loading rates (Fernandez-Fontaina et al., 2012). However, for E2 and EE2, the effect of this parameter is minor. SRT controls the size and diversity of a microbial community. Extended SRT, facilitating the buildup of slowly growing bacteria, such as nitrifying bacteria, will enhance the elimination of micropollutants (Clara et al. 2005a; Suarez et al., 2010; Silva et al., 2012; Luo et al., 2014), but beyond 25–30 days, this parameter is not significant anymore. This influence is clear for E2 and EE2, but contradictory results have been published for DCF. According to the findings of Joss et al. (2005), the elimination rates of DCF did not improve even when extreme SRT (more than 60 days) was applied. In contrast, promoted removal rates for CDF with increasing SRT were reported by Nikolaou et al. (2007), Stasinakis et al. (2010), Falas et al. (2012), Fernandez-Fontaine et al. (2012) and Falas et al. (2013). However, extremely high SRT (> 150 days) is unrealistic in conventional WWTPs with activated sludge process. Regarding redox conditions, different removal efficiencies have been observed for anaerobic, anoxic and aerobic conditions (Joss et al. 2004). Overall, aerobic conditions are preferable for estrogens removal (Silva et al., 2012), while anoxic and anaerobic conditions might be slightly better for DCF (Zwiener and Frimmel, 2003; Vieno and Sillanpää, 2014). Finally, higher temperatures influence positively the removal of micropollutants, as shown for example in Ternes et al. (1999b) when comparing the removal efficiencies of estrogens in a German and a Brazilian WWTP.

To sum up, conventional WWTPs have not been designed for micropollutant elimination, and have therefore only limited capacity to remove DCF, E2 and EE2. During recent years, various studies have demonstrated this shortcoming and pointed out that treated municipal wastewater even contributes significantly to water pollution (see Table 4). In order to minimize micropollutant discharges into the environment, existing wastewater treatment processes must be upgraded with advanced and alternative methods.

Table 4

6. Advanced and alternative methods

Mechanical-Physical methods

Membrane filtration

Microfiltration (MF) and ultrafiltration (UF) are suitable to decrease the concentrations of pharmaceuticals by improved retention of suspended solids in which the more hydrophobic/neutral pharmaceuticals are adsorbed. Hydrophilic substances which are not adsorbed to sludge cannot be retained by MF and UF because of the pore sizes (MF: 100-5000 nm, UF: 10-100 nm) (Joss et al. (2005)). Nanofiltration (NF) and reverse osmosis (RO) have much tighter structures (NF: 1-10 nm) and RO: 0.1-1 nm). In NF and RO membrane processes the rejection of organic micropollutants like DCF, E2 and EE2 can generally be achieved by size exclusion/steric hindrance, adsorption onto membrane and/or charge repulsion (Bellona et al., 2004, Xu et al. 2006). The removal efficiency (Tab. 5) is dependent on properties of the target compound (e.g. molecular weight (MW), molecular diameter (MWd), pk_a hydrophobicity/hydrophobicity (log K_{ow}) and diffusion coefficient) and membrane properties. Key membrane properties affecting rejection are pore size, molecular weight cut-off (MWCO), surface charge (measured as zeta potential), hydrophobicity/hydrophobicity and surface morphology (measured as surface roughness). Additionally, operation conditions like pH value, ionic strength, hardness, the presence of organic matter and membrane fouling influence the rejection of organic micropollutants (Bellona et al., 2008, Xu et al. 2006, Schäfer et al. 2011). Membrane operation conditions as well as hydrodynamic conditions, such as feedwater recovery, concentration polarization and feedwater velocity have been found to influence the rejection of organic micropollutants.

Table 5

In general, if the MW of an organic compound is larger than MWCO of the membrane, the rejection of the compound can be expected to be very high because of steric and electrostatic exclusion. Especially for compounds with a log $K_{OW} < 2$ rejection is governed by MWd compared to the pore size of the membrane. The pH value has a strong influence on the retention of DCF, since the retention of ion species is higher than that of neutral solutes in nanofiltration (Bellona et al., 2004). At lower pH range, where the acidic pharmaceuticals are neutral, larger molecules gave higher retention, because size is the most important parameter in nanofiltration (Urase and Sato, 2007).

Table 6 shows the percentage of rejection determined for DCF, E2 and EE2 by different authors along with the applied type of membrane.

Table 6

A study by Nghiem et al. (2004) observed that, under the presence of organic matter, micropollutant retention (e.g. hormones) was favored. A clear pH dependency was also found by these authors. As the pH value decreases in the water matrix, the amount of humic acids adsorbed on the membrane increased, as well as the adsorption of the endocrine substances. Koyuncu et al. (2008) explained this by the formation of macromolecular complexes, resulting from the association of humic acids with the hormones. This leads to an increase of size and may enhance the size exclusion effect and the adsorption of hormones onto membranes (Silva et al. 2012).

Röhricht et al. (2009) investigated two different types of submerged nanofiltration flat sheet modules for the removal of pharmaceuticals from WWTP effluents. It was shown that DCF was retained up to 60%. At pH 8 DCF (pKa value of 4.15) was deprotonated and could be rejected by the negatively charged membrane surface. This was in accordance with the statement pointed out by Nghiem et al. (2005) indicating that speciation of pharmaceuticals may result in significant change in rejection as function of pH, with much greater retention for ionized, negatively charged molecules. When reverse osmosis was applied after conventional activate sludge-ultrafiltration (CAS)-UF/RO and membrane bioreactor MBR/RO, Sahar et al. (2011) reported relatively similar and high elimination of 95% for DCF in both processes. Despite the highly effective RO treatment, DCF was found in permeates from both units indicating that RO could not completely eliminate this compound and that the additional process was necessary.

One drawback of NF and RO is membrane fouling which may influence the performance of the process as a whole by causing a noticeable decrease in the rejection of organic micropollutants (Ng and Elimelech, 2004).

Special types of membrane filtration are direct contact membrane distillation (DCMD) and forward osmosis (FO) which were investigated by Cartinella et al. (2006) for the rejection of hormones. With these techniques high rejection of over 99.5 % was observed.

Adsorption onto adsorption materials

Over the years, adsorption has been considered one of the most effective methods to eliminate pollutants from contaminated water (Table 7). Adsorption elimination is based on the uptake of pollutants from the aqueous phase onto a solid phase (sorbent). The affinity of a target compound for its sorbent is often quantified by the specific sorption coefficient, representing the ratio of sorbed and dissolved concentrations of a target compound in equilibrium (Silva et al. 2012). Especially activated carbon (AC) is a well-studied sorbent. In Europe the most commonly applied ACs are powdered activated carbon (PAC, 5-50 µm diameters) and granular activated carbon (GAC, 100-2400 µm diameters). Table 7 lists different studies concerning the removal of DCF, E2 and EE2 from aqueous solution and WWTP effluents. Zhang et al. (2007) reported that the adsorption process onto AC is strongly influenced by environmental conditions. The contact time has a major effect on the removal efficiency. Short contact is likely to lead to significantly lowered adsorption efficiency (Luo et al. 2014). Kumar and Mohan (2011) demonstrated that the adsorption capacity from WWTP effluents is maximum at neutral conditions and at temperatures of up to 30 ^{0}C. The sorption of micropollutants onto AC is reduced by the amount of organic matter and other substances, which are also present in the water matrix because they compete for AC adsorption sites (Fukuhara et al. 2006; Kumar and Mohan 2011; Snyder et al. 2007; Zhang and Zhou 2005). Grover et al (2011) showed removal efficiencies for DCF, EE2 and E2 of > 98 % in a full-scale granular activated carbon plant treating WWTP effluent. The efficiency of GAC-based removal technology will decrease over time due to saturation of adsorption site. Therefore reactors based on GAC have to be operated with care (Luo et al. 2014).

Table 7

On the technical scale, PAC is added to WWTP either directly into the activated sludge process or in a subsequent process and needs to be separated from the treated wastewater after application. This can be done by sedimentation under addition of flocculation agents or ultrafiltration or sand filtration (Margot et al. 2013). Those authors reported mean removal efficiency with GAC/UF combination of 69 %. PAC adsorption, with a dosage of 10 - 20 mg/L has been proposed as a more efficient alternative compared to GAC treatment (Boehler et al., 2012; Nowotny et al., 2007; Serrano et al., 2011).

The main advantage of using AC to remove micropollutants is that it does not generate toxic or pharmacologically active products (Rivera-Utrilla et al. 2013). The addition of PAC or GAC could also enhance the removal efficiency of micropollutants during biological treatment. Serrano et al. (2010 and 2011) reported a significant improvement of DCF removal by adding 1 mg/L PAC to an MBR treating municipal wastewater and of 0.5 mg/L GAC to a conventional activated sludge treatment.

Apart from AC several other sorbent materials have been studied to remove DCF, E2 and EE2. Zhang and Zhou (2005) used chitin, chitosan, an ion-exchange resin and a waste-derived carbonaceous adsorbent for the removal of E2, but the sorption capacity was lower than with GAC. Another studied sorbent is steroid-based imprinted polymer (MIP). Different groups studied the adsorption of E2 and EE2 onto MIP but only in aqueous solution and never in wwtp effluent. Joseph et al. (2011) reported good removal efficiency up to 98 % from sea water and brackish water with single-walled carbon nanotubes (CNTs). They recorded that removal efficiency is independent of pH and ionic strength. However, increasing concentrations of co-present organic matter decreases the removal of EE2 by 5-15 %.

Coagulation-flocculation

In general, the coagulation-flocculation process is applied in WWTP to remove particulate matter. For elimination of micropollutants it is inefficient (Matamoros and Salvado, 2013). DCF was removed at a rate of 21.6 % when using $FeCl_3/Al_2(SO_4)_3$ as coagulant in hospital wastewater (Suarez et al. 2009). Dissolved humic acids could enhance its elimination (Vieno et al. 2006). The efficiency of coagulation-flocculation can be influenced by different operating conditions like pH, temperature, alkalinity, presence of divalent cations, and concentration of destabilizing anions (Alexander et al. 2012).

Oxidation processes

Photolysis

Irradiation with ultraviolet light (UV) is widely used in wastewater treatment plants for effluent disinfection before discharging into surface water. UV treatment is also known to transform some micropollutants through light absorption on photoactive groups e.g. photoactive phenolics (Coleman et al. 2004). Two types of photocatalysis are known: a) direct photolysis via direct absorption of light (Rosenfeldt and Linden, 2004) and b) indirect photolysis, when photosensitizers (dissolved organic matter) adsorb the light and generate reactive oxygenated radicals performing the degradation of the target substance (Caupos et al. 2011). Numerous studies describe degradation of DCF, E2 and EE2 in deionized water but also in WWTP effluents up to 100 % due to their high absorption values (Caupos et al, 2011; Rosenfeldt and Linden 2004; Chowdhury et al. 2010; Silva et al, 2012; De la Cruz et al. 2012).

Kolarova et al. (2013) reported that the removal of DCF in UV_{254nm} increases with increasing UV dose. While DCF was eliminated only 47 % at 800 J/m^2, over 98 % were observed at 7200 J/m^2.

Phototransformation has been identified as the important elimination process of DCF in the open environment (Pal et al. 2010). Although the turbidity of wastewater blocks some sunlight, water in the top layers (e.g. in clarifiers) will be well exposed to sunlight irradiation, especially in summer. Therefore, DCF phototransformation will occur with half-life in bright sunlight of less than 1 h. Natural sunlight has also been shown to degrade EE2 (Pal et al. 2010).

Radiation

Similarly, ionizing radiation such as e-beam accelerators (β-rays) and gamma irradiation (γ-rays, ^{60}Co), originally intended for disinfection, are under research for micropollutants degradation. Table 8 lists facilities in Europe performing wastewater treatment by ionizing radiation.

Table 8

The basic differences between these two sources are the dose rate and penetration. Gamma rays are highly penetrating, enable to process a bulk of material. When wastewater is irradiated, organic molecules are oxidized. Such sequence of interaction excites water electronically and some ions, excited molecules and free radicals are formed. In the presence of oxygen in water $H^{\cdot}$-atoms and e^-_{aq} (solvated electrons) are converted into oxidizing species: Perhydroxyl radicals (HO_2) and anions (O_2^-). (HO_2) and (O_2^-) together with OH-radicals initiate degradation of pollutants. Ionizing radiation leads to OH radical formation in water dependent on dose, rate and irradiation time (Borrely et al. 1998; Pikaev, 2000; Getoff, 2002).

The gamma irradiation (^{60}Co) dose required for the elimination of estrogen activity of below 1ng/L has been found about 0.2kGy (Kimura et al., 2007a). Complete decomposition of DCF (50mg/L) in aqueous solutions requires 4.0 kGy (^{60}Co), however, saturation with N_2O decreases the dose to 1.0kGy (Trojanowicz et al., 2012). The sterilization dose of DCF sodium salt, as a pharmaceutical raw material, has been found to be 12.4 kGy (^{60}Co) (Ozer et al., 2013). Homlok et al. 2011 found a complete removal of DCF with 1.0 kGy. When cost is an issue, it is difficult to give a precise price for irradiation systems in advance because of many factors involved: The kind and amount of pollutants in water, their properties (chemical, biological etc), dose-rate to be used, presence of ozone, combined methods of radiation and conventional techniques. In general the costs decrease with increase of treatment capacity and it is possible to say that γ-irradiation costs about four times more than e-beam irradiation because of high cost of ^{60}Co source and the facility (Borrely et al. 1998).

Ultrasonic treatment

Ultrasonic treatment is also described as a method to degrade organic micropollutants. Ultrasonic treatment performs three zones of reaction solution: cavitation bubbles, supercritical interface, and bulk solution (Mendez-Arriga et al. 2008, Naddeo et al. 2010). Mendez-Arriga et al. (2008) and Chiha et al. (2010) described, that hydrophilic and non-volatile compounds were mainly degraded in the bulk solution, whereas hydrophobic, nonpolar and/or volatile compounds react in all three zones. DCF, EE2 and E2 are mainly attacked in bulk solution (Naddeo et al. 2009 and 2010, Güyer et al. 2011). It was found that DCF conversion is enhanced at increased applied power densities, acidic conditions and in the presence of dissolved air (formation of hydroxyl radicals during ultrasonic treatment). They also reported that biodegradability increased after ultrasonic treatment.

Oxidation with single strong oxidation agent

Treatment of WWTP effluents with ozone (O_3) as oxidizer is one of the most studied chemical treatment technologies in Europe. Ozone oxidizes micropollutants directly or indirectly over HO radicals (Gerrity et al., 2011). One of the first studies to remove DCF from wastewater was by Ternes et al. (2003). The authors employed ozone concentrations of 5.0 to 15.0 mg/L to investigate the removal efficiency in WWTP effluents which was > 96%. Magdeburg et al. (2014) described an oxidation efficiency of > 90 % for 9 different micropollutants including DCF by ozonisation of secondary effluent of WWTP using an ozone dose of 0.7 g/g DOC. These removal efficiencies are in the same range as reported by Hollender et al. (2009), Ternes et al. (2003) and Antoniou et al. (2013). Huber et al. (2005b) investigated the removal of estrogen activity by ozone at three different pH values (3, 7, and 11). Estrogenic activity had disappeared at pH 3, but residual activity remained after oxidation at pH 7 and 11, probably due to by-product formation. Suspected sludge particles could lead to higher ozone consumption, which might reduce the efficiency of ozone for DCF, E2 and EE2 (Hernandez-Leal et al. 2011). Recently Antoniou et al. (2013) investigated the required ozone doses for removing pharmaceuticals in wastewater effluents. They normalized the specific ozone dose to the dissolved organic carbon (DOC) of the effluent, which resulted in an applied ozone dose (DDO_3/DOC) ratio of 0.67 for DCF.

During the last years some of WWTP in Switzerland and Germany have been upgraded with ozone oxidation or/and activated carbon adsorption. While in an adsorptive process using PAC or GAC organic micropollutants are removed, ozonation will mainly transform them into –predominantly – unknown oxidation products with unknown toxicity (Joss et al. 2008; Stadler et al., 2012).

One drawback is the fact that oxidation processes do not result in complete mineralization of micropollutants but in the formation of oxidation by-products (transformation products). In general the transformation products have low concentrations as well as insignificant estrogenic and antimicrobial activities compared to the parent compound (Hollender et al. 2009; Reungoat et al.

2011). To further reduce transformation products biological post-filtration over activated carbon filtration or sand can be considered (Luo et al. 2014).

Huber et al. (2005a) investigated the potential of chlorine dioxide (ClO_2) for the oxidation of DCF and EE2 during water treatment (drinking water, groundwater and lake water; not wastewater) because ClO_2 is also used as disinfection agent in water treatment. ClO_2 is a stable free radical that reacts with micropollutants through a one electron transfer and is a highly selective oxidant with respect to specific functional groups like phenolic groups (Huber et al. 2005a). DCF (1 µg/L) was readily oxidized with ClO_2 in 30 min with a dose of 0.95-11.5 mg/L ClO_2 but in lake water only after 60 min. EE2 (11 µg/L) reacted very fast in less than 5 min with 0.1 mg/L ClO_2 in groundwater. There are no studies available for WWTP effluents.

EE2 and DCF degradation were studied under MnO_2 or biogenic produced manganese oxides (BioMnOx) in a synthetic wastewater (Forrez et al. 2009, 2010) verifying removal of up to 80%. At neutral pH, the diclofenac oxidation with BioMnOx was 10-fold faster than with chemically produced MnO_2. The main advantage of BioMnOx over chemical MnO_2 is the ability of bacteria to reoxidize the formed Mn^{2+}, which inhibits the oxidation of DCF. Diclofenac oxidation was proportional to the amount of BioMnOx dosed, and the pseudo first order rate constant k was 6-fold higher when pH was decreased from 6.8 to 6.2. The Mn^{2+} levels remained below the drinking water limit (0.05 mg L-1), thus indicating the efficient in situ microbiological regeneration of the oxidant. These results combined with previous studies suggest the potential of BioMnOx for WWTP effluent polishing, but the technique is not yet used in technical scale.

7. Advanced oxidation processes

Advanced oxidation processes (AOPs) are very effective in the oxidation of numerous organic and inorganic pollutants. AOPs base on the generation of free radicals, mainly the $HO^{\cdot}$ radical, with high oxidizing power, which can successfully attack most organic molecules with elevated reaction constants from 10^6 to 10^9 $M^{-1}s^{-1}$ (Von Sonntag 2008; Huber et al. 2003; Rivera-Utrilla et al. 2013). This makes AOPs superior to treat organic molecules with high chemical stability and/or low biodegradability (Oller et al., 2011). Due to their electrophilic nature $HO^{\cdot}$ radicals oxidize almost all electron-rich organic substances, eventually converting them to carbon dioxide and water. Most AOPs use combination of two different oxidants (e.g. O_3/H_2O_2), oxidant and irridation (e.g. H_2O_2/UV), oxidant and catalyst (e.g. $H_2O_2/Fe^{2+/3+}$ (Fenton)), oxidant and photocatalyst (e.g. H_2O_2/UV/ $Fe^{2+/3+}$ (Photo-Fenton), or oxidant and ultrasonic (e.g. H_2O_2/ultrasonic) (Von Gunten 2003; De la Cruz et al. 2012). Many of these advanced systems have been evaluated in laboratory batch tests and have yet to be applied on technical scale, since there is a lack of good quality data on the mechanisms involved, the influence of operational variables, the reaction kinetics, and reactor design issues. Gerrity et al. (2011) reported high removal efficiency for DCF of > 99 % and of E2 of > 83 % in a pilot scale treatment plant of WWTP effluent with O_3/H_2O_2. Recently, Rivera-Utrilla et al. (2013) and Silva et al. (2012) exhaustively reviewed the literature on the removal of pharmaceuticals from water, summarizing also performances of different water treatment systems including advanced technologies. In the case of DCF, EE2 and E2, some promising technologies have been identified and summarized in Table 4.

In recent years, the electrochemical based AOPs (EAOPs) have gained more attention due to several advantages over normal AOPs (Martínez-Huitle and Ferro, 2006; Sirés et al., 2014; Sirés and Brillas, 2012). The EAOPs are clean technologies that do not use any chemicals during the process. Besides, the operation under mild and versatile conditions, the high energy efficiency and the easy handling are – among others – advantages that distinguish the application of EAOPs (Sirés et al., 2014). The EAOPs can be classified into two groups: (1) Anodic oxidation (AO), where, at the anode surface, *in situ* OH radicals are generated (e.g. boron doped diamon delectrodes (BDD). (2) Electro-Fenton (EF), via *in situ* electrocatalytically generated Fenton's reagent, including different coupling with other photo-, sono- or physio-chemical treatment methods (Oturan and Aaron, 2014). The anode material is a crucial element in an EAOP. Originally, the AO process was conducted with high O_2 evolution overpotential anodes (Brillas and Martínez-Huitle, 2011), such as Pt, Graphite, PbO_2, doped SnO_2, IrO_2 or dimensionally stable (DSA) anodes. An essential feature of the anode material is to inhibit the generation of oxygen molecules and to impose the formation of significant amounts of oxidising agent such as hydroxyl radicals (Comninellis et al., 2008). The previously reported electrode materials are not stable against the reactive species formed on its surface and erosion of the material would be possible (Barrera-Díaz et al., 2014). The boron-doped diamond (BDD) electrode, however, shows an outstanding specification for electrochemical oxidation processes promoting it as a very promising anode material (Fryda et al., 2003; Kraft et al., 2003; Tröster et al., 2004, Urena et al. 2013). The variability in the degradation progress among the water matrices can be explained through competitive reactions with organic and inorganic matter at high concentrations in hard water and WWTP effluents. These substances can affect the availability of oxidative species, leading to a less effective DCF degradation (Wert el al. 2011; Rajab et al. 2013).

Photocatalytic oxidation

Heterogenous photocatalytic oxidation is a method relying on the capability of photocatalysts like titanium dioxide (TiO_2), zinc oxide (ZnO), zinc sulfide (ZnS), ferric oxide (Fe_2O_3), silicon (si), tin oxide (SnO_2) to act as sensitizes for light-reduced redox processes (Silva et al. 2012). TiO_2 is the most widely cited photocatalyst due to its considerable activity, high stability, non-environmental impact and low cost (Augugliaro et al. 2012; Silva et al, 2012).The heterogeneous photocatalysis process using TiO_2 was applied successfully for the removal of DCF, E2 and EE2 by several authors with high removal efficiencies in aqueous solutions also in WWTP effluents. Selected studies are listed in Table 9. Coleman et al (2004) found a selectivity for estrogens EE2 > E2. The removal efficiency of E2 and EE2 increases with increasing pH value (Karpova et al. 2007). A removal of EE2 of 100 % was observed and was not influenced by urea.

All mentioned advanced oxidation processes can transform a variety of organic micropollutants into biodegradable, intermediate compounds. However, these intermediate compounds might potentially be more toxic than the original compounds for the biological system. Hence, a post-biological treatment after oxidation could also be a way to degrade these intermediates (Christensen et al. 2009).

Table 9

Options for Phytoremediation of DCF

Recent reviews have indicated that besides longer SRT and HRT the implementation of wetland plants might improve the performance of older WWTP in small settlements. Recommendations have been made to add lagunar phytoremediation modules to improve the removal of PPCPs even more effectively (Schröder et al. 2007). In such systems, the uptake and removal of DCF and estrogens relies on the biology of green plants, and their accompanying rhizospheric microbial communities, in analogy to mammalian detoxification systems.

In humans many drugs undergo a cascade of different reactions. An initial activation reaction is frequently followed by conjugation with smaller biomolecules like glucuronic acid or sulphuric acid. These modifications of the parent drug increase its solubility and the potential for excretion of active metabolites. The very same mechanisms exist in plants (Schröder and Collins 2002) and it has been demonstrated that they are active against a broad spectrum of xenobiotic compounds. In mechanistic laboratory and greenhouse studies with different plant species (*Armoracia rusticana, Brassica juncea, Hordeum vulgare, Lupinus luteolus, Typha latifolia, Phragmites australis*), the uptake and subsequent detoxification of DCF has recently been demonstrated (Kotyza et al 2010, Huber et al. 2012, Bartha et al. 2014). Since DCF is a weak acid, its uptake in the plant with the transpiration stream is not inhibited, and significant concentrations accumulate in both, roots and shoots of investigated species. Interestingly, the pharmaceutical is attacked by enzymes very similar to mammalian ones. After activation by P450 or peroxidase enzymes, the hydroxylated primary metabolites were conjugated either with glucose, or glutathione, rendering the products more water soluble and non-toxic.

Figure 2

Estradiols

Phytoremediation of ECDs has been investigated in different studies. The removal of 17 β-estradiol and and 17 α-ethinylestradiol from contaminated waters by macrophytes was discussed by Trueman and Erber (2013). The authors studied the uptake of two estrogenic compounds as well as Bisphenol A into the tissues of two *Potamogeton* species. Whereas the amounts of the estradiol compounds in both species were rather low (15,7ng/l) compared to the concentration in the water, the plants took up a considerable amount of Bisphenol A (8,3 µg/g DW).

The use of vertical flow wetlands is a common technique in phytoremediation. Planted with common reed (*Phragmites australis*) these systems have been tested for the removal of endocrine disruptors from wastewaters (Song et al. 2009). The authors reported a maximal removal efficiency of 67.8±28.0 %, 84.0 ±15.4 % and 75.3±17.6 % for E1, E2 and EE2, respectively. In a comparison of different wetland depths, they found the shallowest (7,5 cm) to be the most efficient one to remove EDCs from the waterbody.

Apart from macrophytes, Duckweed (*Lemna* species) and a mixture of algae and cyanobacteria were studied for their capacity to remove ECDs from synthetic wastewater under different conditions in batch experiments. In the presence of Duckweed and algae, effective removal of the estrogens E1, E2 and EE2 from waters was observed, even at ng per liter concentrations (Shi et al. 2010). The accelerated removal of estrogens is probably due to its absorption on the duckweed or algae and subsequent degradation by microorganisms adhering to the plants. However, plant metabolism was not excluded, and Duckweed showed a slightly higher efficiency to remove estrogens than algae.

Generally, for the use of plants in any remediation scenario, the selection of the most suitable species to do the job is crucial (Schröder 2007). This includes knowledge of the plants´ metabolic capacity, their ability to grow under given environmental conditions and favourable milieu (e.g. oxygen, root surface, chemical milieu) for plant associated microorganisms which may contribute to degradation and removal of the pollutants in manifold ways. When using macrophyte species it remains important to remove all plants after remediation to avoid the release of sequestered nutrients and pollutants back in to the system during decomposition. In many cases, phytoremediation may be an appropriate and cost effective way to remove pollutants from aquatic ecosystems.

8. Ecotoxicology and Risk assessment

While compilations on the occurrence and fate of pharmaceutically active compounds and their metabolites in sewage and potable water are increasingly available, and point to the danger of their widespread distribution (Sweetman 2002, Petrović et al., 2014, Škrbić et al., 2014), the environmental effects of their presence alone and in mixtures have so far not been properly addressed (Halling-Sorensen et al. 1998, Daughton 2001, Ternes, 2001, Arnold et al. 2013, Manickum and John 2014, Vieno and Sillanpää 2014, Shore et al. 2014). In this section, the main ecotoxicological issues related to diclofenac and EE2 are summarized; for a wider discussion on the topic, the reader is referred to the accompanying paper on ecotoxicity of micropollutants (Papa et al., in preparation).

1. Pure-compound approach

The objective of an environmental risk assessment (ERA) is to prove, beyond reasonable doubt that the compounds are safe for all natural ecosystems of which it may enter, such as WWTPs, rivers and soil. A compound is judged as having little or no environmental risk if the predicted environmental concentration (PECs) – which is the concentration of the compound expected to be found in the environment – is higher than the predicted no effect concentration (PNEC) – that is, the concentration that causes no adverse effect to the environment. However, the compounds are rarely present alone in the environment, hence, the concentrations of compounds that are asserting similar adverse effects in the environment are usually added for the ERA (Fent et al. 2006). Moreover, since many compounds may be altered prior to or during treatment, and/or in the recipient itself, also potential metabolites (relevant for many pharmaceuticals) and transformation products should be included in the assessment.

The ERA is a tiered process that progresses from using screening-level tests and conservative assumptions to increasingly more realistic assumptions (EC 2003). The PNEC is typically obtained from the lowest effect concentration (LOEC) for the most sensitive species. However, available ecotoxicity data are often limited, especially for metabolites and transformation products. Hence, the traditional ERA, as described by the European Commission Technical Guidance Document (TGD), allows the use of assessment factors to account for the uncertainty in deriving PNEC values based on acute toxicity data and a limited number of species (EC 2003). For biologically active compound such as pharmaceuticals this approach may overlook sub-lethal and subtle subcellular effects that may occur in some species at much lower concentrations during chronic exposure.

Typical PNEC values for diclofenac and EE2 when derived from traditional ERA using acute toxicity data lies in the mg/l range, while chronic histopathological effects have been observed in rainbow trout after 28 days of exposure to 1-5 µg diclofenac /l (Schwaiger et al. 2004, Triebskorn et al. 2004).

The fact that diclofenac also bioaccumulates is also of concern and should be addressed properly (Fent et al. 2006). Kallio et al. (2010) found that the total bioconcentration factors (BCF_{total}) for diclofenac and its metabolites in rainbow trout bile varied between individuals and was roughly estimated to range from 320 to 950.

As for EE2, Caldwell et al. (2008, 2012) proposed a PNEC value of 0.1 ng/l in surface water. It was derived from a species sensitivity distribution using no observed effect concentrations (NOECs) for reproductive effects from 42 papers in 26 species and was determined as the median hazardous concentration at which 5 % of the species tested were affected (HC5,50).

2. Whole-effects approach

Moreover, the approach in the assessment of micropollutants can also be switched from a compounds-oriented to an effects-oriented one, in order to take into account i) unknown/undetected compounds, as metabolites and parent compounds ii) and the mixture effects of substances, either synergistic or antagonistic. Therefore, comprehensive bio-analytical tools can directly measure the specific biological activity of groups of chemicals. This is just the case of EE2: indeed, when assessing its ecotoxicological effects, the main threat is represented by the induced estrogenic activity, i.e. a specific mode of toxic action directly related to all the molecules (then called EDCs: endocrine disrupting compounds) that can mimic, block or interfere with hormonal activities in living organism. In regard to ERA for the receiving water bodies, the main adverse impact related to this kind of biological activity is represented by impaired reproductive performance in wildlife, and especially in fish: levels of 0.1-0.4 ng/l were derived by Jarosova et al. (2014) for safe concentrations of estrogenic equivalents (EEQs) for municipal WWTP effluents. The concept of estrogenic equivalents is used to group all the chemicals able to induce this specific mode of toxic action, and is measured via estrogenic activity assays (Leusch et al., 2010). They are based on the interaction between compounds and estrogenic receptors and can be performed either with cells (E-SCREEN, ER-CALUX, MELN and KBluc assays) and yeast (YES assay).

9. Modelling of diclofenac and hormones

In wastewater treatment plants, mathematical models are routinely used for plant design, optimisation and control. In general, the most commonly used models are derived from the activated sludge models (ASMs) that were developed to predict the degradation of organic carbon, nitrogen and phosphorus (Henze et al., 2000). In recent years, ASM models have been extended to include the degradation of micropollutants, including pharmaceutical compounds such as diclofenac and estrogens such as E2 and EE2 (Lust et al., 2012; Plósz et al., 2012). These models have been developed to primarily include removal mechanisms associated with biotransformation and adsorption, since removal via volatilisation/stripping has been found to be comparatively negligible for these compounds.

In the modelling of biotransformation processes, separate kinetic expressions are typically employed in order to describe both aerobic and anoxic degradation (Joss et al., 2004; Joss et al., 2006). Biotransformation, described by Joss et al. (2004, 2006) through pseudo first-order degradation kinetics, generally occurs at a higher rate aerobically than anoxically, due to the contribution of autotrophic bacteria (i.e. nitrifiers), which often display higher kinetics for pharmaceutical degradation than heterotrophic bacteria. Adsorption and desorption are typically estimated assuming an equilibrium between the dissolved and sorbed concentration of pharmaceutical. This equilibrium is dependent on the suspended solids concentration, which is a parameter (K_D) routinely estimated in literature for pharmaceuticals such as DCF and estrogens.

The ASM-X model developed by Plosz et al. (2012) for DCF (and other pharmaceuticals) incorporates expressions involving both the biotransformation of the micropollutant and its reformation into the parent compound. This is due to the fact that closely related conjugates can also be found in influent wastewaters (typically generated as human metabolites), where diclofenac is then re-formed through biotransformation in the activated sludge process. The biodegradation of DCF is predicted through both direct biodegradation as well as through co-metabolic biodegradation via other soluble substrates present in the wastewater. While sorption and desorption of DCF to the sludge was predicted through the partitioning coefficient (K_D), Plosz et al. (2012) also employed a term to predict the fraction of DCF sequestered in sludge to account for the fact that the sorbed DCF detected in the activated sludge was substantially higher than that predicted by liquid-solid equilibrium.

Models describing the biodegradation of estrogens (estrone (E1), 17β-estradiol (E2) and 17α-ethinyl-estradiol (EE2)) have also been developed (Monteith et al., 2008; Lust et al., 2012), which also predict both their biodegradation and adsorption/desorption to sludge through liquid-solid equilibrium (K_D) coefficients. With respect to biodegradation, since E1 is formed from E2 biodegradation, sequential degradation of E2 to E1 has been incorporated into these models as the biochemical pathway. Formation of conjugated estrogens was also incorporated into the model of Lust et al. (2012).

Recently, the ASM-X model has also been incorporated into the benchmark simulation model (BSM) structure in order to facilitate its integration with plant-wide control strategy scenarios (Snip et al., 2014). This study also proposed a dynamic influent prediction tool for estimating the concentration of e.g. DCF as a function of administration pattern, bioavailability and residence time in the human body.

Some of the main challenges to be addressed by future research in this area include the transformations of these compounds in tertiary treatment processes, such as filtration, UV and ozonation, considering the fact that these processes have been typically found to contribute to a substantial portion of the removal of pharmaceutical compounds. WWTPs effluents, if properly treated, can be reclaimed and reused for determined restricted uses, contributing in this way to the reduction of water pollutants and the pressure over the worldwide water scarcity. Nevertheless, the use of inadequately treated municipal wastewaters for irrigation will definitely raise public health concerns arising from the presence of microorganisms and contaminants of emerging concern. This situation strongly calls for the development of remediation techniques to limit the release of these substances in the environment. It is also evident, that in order to protect resources for future generations, approaches have to be adopted, which will not only preserve the ecosystem but also protect biodiversity. Moreover, further efforts are needed regarding the generation of the associated metabolites from DCF or estrogen biotransformation or oxidation processes, particularly in view of the toxicity that other metabolites may exhibit, often higher than the parent compound itself, and that they may constitute the bulk of the final chemical form that reaches and persists within the environment.

10. Economics

Following the precautionary principle, the European Commission included DCF, estradiol and ethinylestradiol in a priority watchlist. Hence, member states have to ensure the monitoring of such pollutants and specify environmental quality standards to be met according the EU Water Framework Directive. Due to high cost of compliance with this regulation, the pharmaceutical, water industries and many governments are opposed to it. Although high-tech solutions are available all over Europe, their sustainability is usually not achieved, resilience to numerous parameters is questionable, and clear cut evidence is presented in the ETAP papers that these technical solutions are too expensive for many communities. Owen and Jobling (2012) reported that to remove ethinylestradiol from wastewater to comply the proposed legislation, granular activated carbon systems should be implemented in all conventional WWTPs. The investment cost of such system for a town on 250,000 people would be around € 8 million and its operating costs around € 800,000 per year. Hence, wastewater treatment costs will increase significantly which would involve higher water prices. A similar conclusion was drawn by Jones et al. (2007) who concluded that the cost of utilizing drinking water technologies to treat wastewater will likely be really expensive. In particular, it was estimated that for medium and large sized WWTPs, the capital cost of sand filter and membranes exceeded the cost of the basic activated sludge WWTP by £2.63 and £1.5 million, respectively. Moreover, the potential operating costs of the extra treatment processes would be also significantly higher than standard treatment since they would increase by around six times.

It should be noted that the removal of PPCPs not only involves costs but also environmental benefits that can be quantified in monetary terms. But databases to which extent treatment in state-of-the-art municipal waste water treatment plants is capable to achieve zero pollution levels with regard to secondary environmental effects and costs are scarce. In this context, to the best of our knowledge, only Molinos-Senante et al. (2013) quantified the environmental benefits of preventing the discharge of 5 PPCPs (diclofenac, ethinylestradiol, sulafamethoxazole, galaxolide and tonalide) into water bodies. Thus, using the distance function approach, Molinos-Senante et al. (2013) estimated the shadow prices of these 5 PPCPs. They can be interpreted as the economic value of environmental benefits to avoid the discharge of contaminants into environment. In particular, for non-sensitive areas, the shadow prices of the DCF and ethinylestradiol were quantified by 42.20 and 73.73 €/kg whilst for sensitive areas they were 53.47 and 93.76 €/kg, respectively. These figures represent the positive externalities of removing both pollutants from wastewater with highest available standards. For example, the value of 42.20 €/kg means that for each kg of DCF that is removed from wastewater the environmental benefit is quantified by 42.20 €. It should be noted that to estimate the overall benefits from wastewater treatment, not only the value of the shadow prices in €/kg should be considered but also the volume of each pollutant removed in kg/m^3.

11. Concluding remarks

Nearly half of the European countries are facing water stress issues today, both in terms of water scarcity and water quality deterioration, and it is estimated that 20-40% of Europe's available water is being wasted (lack of water saving technologies installed, too much unnecessary irrigation, etc.). In addition, priority and emerging organic pollutants and pathogens are continuously discharged into European rivers and streams, by that compromising valuable ecosystem services and resulting in potentially adverse effects to aquatic organisms. Although concentrations in groundwater are still generally low and an acute toxicological risk for consumers of drinking water has not been identified so far, the contamination of our ground and drinking water reserves has to be avoided.

However, conventional WWTPs are neither specifically designed nor operated to remove residual concentrations of organic pollutants, causing the potential accumulation of such pollutants into receiving water bodies and limiting at the same time the proper water reuse. Thus, emerging contaminants are continuously discharged into European surface waters which are often used as drinking water supplies. This *de facto* potable water reuse is frequent worldwide. In consequence, the potential economic value of this particular water is decreased. It is evident that such a situation strongly calls for the development and improvement of remediation techniques to limit the release of these substances into the environment.

Cleaning highly treated wastewater through an environmental buffer to augment a drinking water supply is a recent practice, which is referred to as intentional indirect potable reuse, which can occur through recharge of unconfined or confined aquifers. It has been demonstrated by several projects that non-potable and potable water reuse can represent a viable option to diversify local water resources while at the same time reducing the demand for conventional freshwater supplies. This is particularly useful in those areas in the EU where water-scarcity situation exist.

The relevance of addressing the problem of organic pollutants was also taken into account by the Directive 2013/39/EU that introduced (i) the quality evaluation of aquatic compartments; (ii) the polluter pays principle, (iii) the need of innovative and affordable wastewater treatment technologies, and (iv) the identification of pollution causes including a list of principal compounds to be monitored. In addition, a watch list of 10 other substances was recently defined by Decision 2015/495 on March 20, 2015. Since these documents were launched recently, there is still a lack of knowledge about the occurrence of many emerging organic pollutants in WWTPs effluents as well as about the efficiency of treatment options. But time is precious. It is urgently required to develop an overall evaluation scheme for indirect potable reuse strategies in order to provide water utilities and national and EU authorities a useful and reliable decision support tool for future investments and implementations.

We have to face the fact that all conventional technologies have failed to alleviate the load of watchlist compounds from our waters. This leads to the urgent demand that treatment facilities across Europe urgently need upgrading to fulfill upgraded water standards, and to keep the end-users healthy. And last but not least, for groundwater, in addition to the requirements of good status, any significant and sustained upward trend in the concentration of any pollutant should be identified and reversed as early as possible.

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Figure

Figure 1: graphical representation of DCF and EE2 consumption levels across the EU.

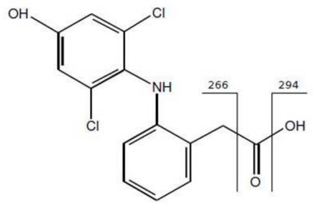
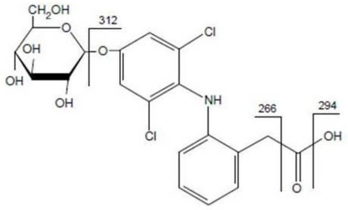
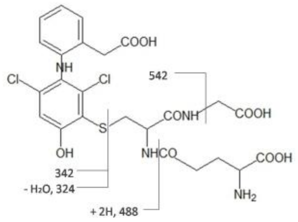
	4´OH-diclofenac (M+H)$^+$ *m/z* 312 → m/z 294 m/z 266
	diclofenac-glycopyranoside (M+H)$^+$ *m/z* 474 → m/z 312 m/z 294 m/z 266
	OH-glutathionyl-diclofenac (M+H)$^+$ *m/z* 617 → m/z 324 m/z 342 m/z 488 m/z 542

Fig. 2: Chemical structures of diclofenac metabolites identified in plants and the characteristic mass transitions obtained in positive ionization mode by LC-MS/MS analysis.

Table 1: Concentrations of pain killers and hormones recorded in the aquatic environment during the last decade (2003-2013). WWTP= waste water treatment plant; WW-E= waste water effluent; SW= surface water; DW= drinking water; GW=ground water.

Compound	Type of water	Conc. (ng/l)	Country	Citation
DCF	WW-E	≤1612	Portugal	Salgado et al. (2010)
	WWTP	4534-38674	Portugal	Salgado et al. (2012)
	WW-I	1020 (in)	Italy	Patrolecco et al. (2013)
	WW_E	507 (out)	Italy	Patrolecco et al. (2013)
	WW-E	5450	Italy	Andreozzi et al. (2003)
	WW-E	250-5450	France, Italy & Greece	Jiskra (2008)
	WW-E	2200	Germany	Letzel et al. (2009)
	WW-E	310-930	Switzerland	Jiskra (2008)
	WW-E	290	UK	Thomas and Hilton (2004)
	WW-E	125	UK	Roberts and Thomas (2005)
	WW-E	99	Switzerland	Tixier et al. (2003)
	WW-E	91	UK	Ashton et al. (2004)
	WW-E	0.14	Finland	Bignert et al. (2013)
	SW	261	UK	Kaspryzk-Hordern et al(2008)
	SW	140	Germany	Letzel et al. (2009)
	SW	94	China	Huang et al. (2011)
	SW	89	Germany	Heberer (2002b)
	SW	16-65	Finland	Bignert et al. (2013)
	SW	35	Finland	Vulliet et al (2011)
	SW	10-16	Italy	Marchese et al. (2003)
	SW	1.6	Italy	Loos et al. (2007)
	SW	4-260	The Netherlands	RIWA 2014
	SW	10-120	Belgium	RIWA 2014
	GW/DW	6	Germany	Heberer (2002b)
E2	WWTP	≤97	Portugal	Salgado et al. (2011)
	WWTP	64	Belgium	Forrez et al. (2009)
	WW-E	15-27	Germany	Carballa et al. (2004)
	WW-E	17	USA	Wright-Walters and Volz (2007)
	WW-E	< 10	Sweden	Bigner et al. (2013)
	SW	9,5	Italy	Pojana et al. (2007)
	SW	9	Italy	Vigano et al. (2008)
	SW	1	Italy (Rome)	Baronti et al. (2000)
	SW	< 1	The Netherlands	RIWA 2014
EE2	WWTP	≤39	Portugal	Salgado et al. (2011)
	WWTP	106	Belgium	Forrez et al. (2009)
	WW-E	< 1	Spain	Carballa et al. (2004)
	WW-E	0.04	Sweden	Bigner et al. (2013)
	SW	11	Italy	Pojana et al. (2007)
	SW	0.04	Italy (Rome)	Baronti et al. (2000)
	SW	< 500	The Netherlands	RIWA 2014

Table 2: Relevant information related to pre-concentration steps and analysis of environmental water samples for diclofenac, E2 and EE2 determination. Costs listed refer to the different analytical options, without considering those related to instrument investment or the possibility, for each method, to be capable of determining several compounds simultaneously (multiresidual analysis). In any case, limiting the determination only to a restricted number of target compounds could be considered a too simplistic approach which might not be useful to fully take advantage of the potentialities of the instrumentation nowadays available.

sample	Preparation steps	Recovery (%)	Analytical technique	LOQ (μg/L)	Analysis time and difficulty[1]	Analysis costs (€/sample)[2]	Reference
Diclofenac							
wastewater influent and effluent	1.Filtration 2. SPE pre-concentration 3. Derivatization	100	GC-MS/MS	0.05	+++	40-60	Carballa et al. 2004, 2005, 2007
raw industrial and municipal wastewater, surface, ground, drinking water	1. Acidification 2. SPE pre-concentration 3. IS addition	55-116	LC-ESI-MS/MS	0.012-0.02	++	30-50	Gros et al. 2006a, 2006b, 2009, 2012; Petrovic et al. 2014
wastewater influent and effluent, groundwater	1. Filtration 2. SPE pre-concentration 3. Derivatization	55-100	GC-MS	0.025	+++	40-60	Ternes 1998,Ternes et al., 2001 and 2003
wastewater influent and effluent, bacins water	1. Acidification 2. IS addition 3. SPE pre-concentration	100	LC/ESI-MS/MS	>0.03	++	30-50	Sacher et al. 2008 Oosterhuis et al 2013
wastewater influent and effluent	1. Acidification 2. IS addition 3. SPE pre-concentration	100	UHPLC-MS/MS	0.05-0.14	++	30-50	Gracia-Lor 2010, 2011
river water, wwtp effluent	1. Addition of deuterated standards 2.Acidification 3. SPE pre-concentration 4. IS addition	99	LC/ESI/MS	0,02	++		Letzel et al. 2009
wastewater influent and effluent	1. Acidification 2. SPE pre-concentration 3. Derivatization	65-85	GC/Ion trap-MS/MS	0.12	+++	40-60	Serrano et al. 2011
river, wastewater influent and effluent	1. Filtration 2. SPE pre-concentration 3. Derivatization	56-112	UHPLC-MS/MS	0.006-0.012	+++	40-60	Huang et al. 2011

E2 and EE2							
surface water and wastewater	1. Filtration (1.5-um) 2. SDB-XC disk extraction 3. SPE (C18 & NH2) 4. HPLC elution 5. Derivatization	88-92	GC/ion trap-MS/MS	0.1-2.4	+++	40-60	Belfroid et al. 1999
wastewater influent and effluent, rivers	1. Filtration (1.5-um) 2. SPE pre-concentration 3. Addition of IS	80-92	LC/ESI-MS/MS	0.008-0.8	++	30-50	Baronti et al. 2000
wastewater influent & effluent, anaerobic digester influent & effluent	1. Filtration (1.5-um) . SPE purif/pre-conc 3. Derivatization	82-84	GC/ion trap MS/MS	1	+++	40-60	Ternes 1998; Carballa et al. 2004, 2005, 2007
synthetic, wastewater influent and effluent, surface waters	1. Filtration (1.5-um) 2. MeOH and IS addition . SPE purif/pre-conc 4. Derivatization	79-100	GC/ion trap MS/MS	3-20	+++	40-60	Quintana et al. 2004
surface water, wastewater influent and effluent	1. Filtration	65-105	LC/LC-MS/MS	0.002-0.003	+++	20-40	Gorga et al. 2013

[1]: +: low, ++: moderate, +++: high

[2]: analysis cost was estimated including the cost of the column (lasting about 500 injections) and SPE cartridge and amortization of instrumentation (lasting five years).

Table 3: molecular properties of the compounds under consideration

Compound	Molecular weight (g/mol)	Molecular width (Å)	Log K_{ow}	pK_a	Log K_d	k_{biol} for CAS L/(g_{ss} d)
DCF	296.2	5.95[f]	4.5-4.8 [a,f]	4.0-4.5[a]	1.2[d]-2.1[g]	≤ 0.1[c]
E2	272.4	5.21[f]	3.9-4.0[e,f]	10.4	2.5-3.5	300-800
EE2	296.4		2.8-4.2[e]	10.5-10.7	2.3-2.8[d]	7-9[b]

[a]Yang et al. (2011), [b]Suarez et al (2008), [c]Joss et al. (2010), [d]Ternes et al. (2004), [e]Schäfer et al (2011), [f]Drewes et al.(2005), [g]Radjenovic et al (2009)

Table 4. DCF, E2 and EE2 concentrations in influent and effluents and the removal efficiency by conventional waste water treatment in Europe since 2002. During secondary treatment, diclofenac had moderate removal rates in different WWTPs in Europe. The removal rates are different, depending on various influences.

Compound/WWTP/Country	Concentration, µg/L		Removal efficiency, %	Reference
	Influent	Effluent		
DCF				
not described, Germany	3.02**	2.51**	17	Heberer (2002b)
Conventional WWTP, France, Greece, Italy	---	0.68**	---	Andreozzi et al. (2003)
Conventional WWTP, UK	---	0.41-0.46	---	Hilton and Thomas (2004)
4 Conventional WWTP, UK	---	0.599* (0.424**)	---	Ashton et al. (2004)
Conventional WWTP, Germany	2,3*	1,6*	30	Quintana and Reemtsma (2004)
three conventional WWTPs (1-3) with preliminary clarification,	WWTP1 (3 samplings): 3.19-4.11	WWTP1 (3 samplings): 1.53-1.68	WWTP1 (3 samplings): 47-62	Clara et al. (2005)
2 aeration tanks, final clarification, Austria	WWTP2: 1.40	WWTP2: 1.30	WWTP2: 7	
	WWTP3: 0.90	WWTP3: 0.78	WWTP3: 14	
Conventional WWTP, Sweden	0.16	0.12	25	Bendz et al. (2005)
pilot scale membrane bioreactor (in 3 sampling periods	3.19-4.11***	2.03-3.46***	-6.6^a – 50.6	Clara et al. (2005)
conventional WWTP, pilot scale membrane or fixed-bed reactor, Switzerland	---	---	20-40	Joss et al (2005)
3 conventional WWTPs in EU with secondary or tertiary treatments	---	---	<5	Reemtsma et al.(2006)
Different conventional WWTP Spain, Belgium, Germany and Slovenia	0.021-0.148***	0.032-1.42***	---	Hernando et al. (2006)
5 conventional WWTP, Croatia	250*	215*	14	Gros et al. (2006b)
	---	0.21-0.49***	---	Rabiet et al. (2006)
Finnland, conventional WWTP	0,42* (0,46**)	0,32* (0,35**)	24	Vieno (2007)
Norway conventional WWTP	295**	259**	13	Thomas et al. 2007
Hospital Ulleval, Norway	784**			Thomas et al. 2007
Hospital Rijkshospitalet, Norway	1550**			Thomas et al. 2007
29 WWTP, municipal and industrial in Bosna-Herzegovina, Croatia, Serbia	0.859*			Terzic et al. (2008)
Conventional WWTP, Sweden, Municipal and hospital wastewater	0.23*	0.49*	-105	Zorita et al. (2009)
WWTP Cilfynydd, Wales, UK: biological treatment-trickling filter beds	0.07	0.12	-71^a	Kasprzyk-Hordern et al. (2008)
7 conventional WWTPs, Spain:			30-100	Gros et al. (2010)
Conventional WWTP, Greece	0,86-2.17***	0.15-1.1*** 0.41*	---	Samaras et al. (2013)
Conventional WWTP, Spain With influent of ww from 4 hospitals and municipal ww	0.0670*	0.043	38	Santos et al. (2013)
Conventional WWTP, Switzerland	1.197 *	1.187*	9	Margot et al. (2013)

8 conv WWTPs, Greece	0.28*	0.11*	70	Kosma et al. (2014)
Conventional WWTP, Spain industrial / municipal ww	0.288	0.309	< 1	Collado et al. (2014)
Conv. WWTP, France a) total nitrification+ post denitrification b) partial nitrification + no denitrification	a) 184* b) 384*	a) 52* b) 171*	a) 72* b) 55*	Mailler et al. (2014)
		0.049*/0.043**		Loos et al. (2013)
E2				
Conv. WWTP, Norway	12**	<3**	75	Thomas et al. 2007
Hospital Ulleval, Norway	28**			Thomas et al. 2007
Hospital Rijkshospitalet, Norway	41**			Thomas et al. 2007
Conventional WWTP, Europe	25,7 * 21.5**	1.9* 1.0**		Janex-Habibi et al 2009
EE2				
Conventional WWTP, Norway	<0.3**	<0.3**		Thomas et al. 2007
Hospital Ulleval, Norway	<0.3**			Thomas et al. 2007
Hospital Rijkshospitalet, Norway	<0.3**			Thomas et al. 2007
Conventional WWTP, France	1.6* 1.0**	0.9* 0.5**		Janex-Habibi et al 2009

[a] increase of the effluent concentration relative to the influent concentration

* mean, ** median, ***min-max

Table 5. Concentrations in influent and effluents and the removal efficiency by advanced biological methods

Treatment process	SRT, d	Removal efficiency, %	Reference
Diclofenac			
Full scale wwtp	14-16	68	Kruglova et al. (2014)
Lab scale SBR	10-12	90	
			Ribeiro et al. (2013)
Lab scale MBR	37	23	Quintana et al. (2005)
Single-house-MBR	> 100	103	Abbeglen et al. (2009)
Lab scale MBR, synthetic ww, HRT 24 h	70	17.3 (mean)	Tadkaew et al. (2011)
E2			
Lab scale MBR, synthetic ww, HRT 24 h,	70	> 99.4	Tadkaew et al. (2011)
EE2			
Single-house-MBR	> 100	77	Abbeglen et al. (2009)
Lab scale MBR, synthetic ww, HRT 24 h	70	93.5 (mean)	Tadkaew et al. (2011)

Table 6: Rejection of DF, E2 and EE2 by membrane filtration.

Compound	Membrane type	Rejection (%)*	Reference
Diclofenac			
	NF	100	Radenovic et al. 2009
	RO	100	Radenovic et al. 2009
	NF	60	Röhricht et al. (2009)
	NF	65	Röhricht et al. (2010)
	MBR/RO	95	Sahar et al. (2011)
E2	RO	83	Kimura et al. (2007)
	NF/RO	90	Ngiem et al. (2005)
	NF	> 99	Weber et al. (2004)
	NF	>95	Yoon et al. (2004)
	RO/NF	high	Drewes et al. (2005)
	NF	77	Bodzek & Duziak (2006)
	DCMD	≥ 99.5	Cartinella et al. (2006)
	NF	100	Koyuncu et al. (2008)
	NF/RF	100	Alturki et al. (2010)
	NF	100	McCallum et al. (2008)
EE2	NF	>99	Weber et al. (2004)
	NF	90	Bodzek & Dudziak (2006)
	NF	60	Yoon et al. (2007)
	NF/RO	99	Alturki et al. (2010)

* under optimal conditions

Table 7: advanced technologies

Sorbent	**Amount of sorbent**	**Removal details**	**Reference**
Diclofenac			
AC	30 mg/L	Activated carbon, P110 Hydraffin, (ultra-pure water), tubular glass reactor (300 mm long and 50 mm, 93% after 20 min	Beltran et al. 2009
PAC	50 mg/L	Pilot scale, natural water with organic matter spiked with 0.1 µg/L, contact time 4 h, 38-46 %	Snyder et al. (2007)
PAC	10-20 mg/L	300 mg/L DCF in surface water PAC, 2 h; 76,7 %	Dai et al. (2011)
PAC	23 mg/L PAC	8, 23, 43 mg/L in MBR effluent, hospital wastewater, 96, 98, 99 %	Kovalova et al. (2012)
PAC/UF	10-20 mg/L	1.13 µg/L± 0.39 WWTP effluent , 10-20 mg/L PAC, 69 %	Margot et al. (2013)
PAC	5-10 mg/L	WWTP effluent; HRT 25-30 min, pilot scale, up to 98 %	Mailler et al (2014)
GAC	Packed	Full scale; > 98 %	Grover et al. (2011)
GAC	Packed	Full scale (empty bed), 15 min contact	Yang et al. (2011)
GAC/activated sludge	0.5 g/L	Addition of GAC to bioreactor, 93 %	Serrano et al. (2010)
PAC/MBR	1 g/L	Addition of PAC to bioreactor, 93 %	Serrano et al. (2011)
MIP	10 mg/L	300 mg/L DCF in surface water , MIP 97.6%	Dai et al. (2011)
E2			
GAC	Packed	Max. adsorption constant: K_d 12,200 mL/g with 24.8µg/L E2 in water K_d 7,988 mL/g with 24.8µg/L E2 in WWTP effluent	Zhang and Zhou (2005)
AC	0.03-1.5 mg/L	Various pore size distributions; Max. adsorption capacity: 67.6 mg/g at 1 µg/L in pure water	Fukuhara et al. (2006)
GAC	Packed	Full scale; 100 %	Grover et al. (2011)
GAC, PAC	Packed, 5 mg/L	Full scale; > 90 % for both materials	Snyder et al. (2007)
MIP		25 %	Meng et al. (2005)
MIP	Packed	95 % from 2 µg/L in deionized water	Le Noir et al. (2007)
MIP	0.5-20 g/L	Dest water, 0.1-1 mg/L E2, 97 %, 15 mg/g	Lai et al. (2010)
MIP	0.25 g/L	90 % after 2 min incubation, 96 % after long equilibrium	DeMaleki et al. (2010)
EE2			
AC	Packed	Highest adsorption at neutral conditions (95 %), 50 µg/L EE2 solution (dest water)	Kumar and Mohan (2011)
GAC	Packed	Full scale; 100 %	Grover et al. (2011)
Single-walled CNT		95-98 %, in sea water and brackish water	Joseph et al. (2011)
Multi-walled CNT		25, 50, 75 µg/L aqueous solution; sorption capacity: 5.6 µg/g	Kumar and Mohan (2012)

Table 8: Major facilities for wastewater treatment by ionizing radiation (Borrely et al. 1998)

Country	Radiation Source	Energy (MeV)	Power (kW) Activity (kCi)	Purpose	Dose (kGy)
Austria	EBA	0.5	12.5	TCE, PCE removal	0.2-2.0
Germany	^{60}Co	1.25	135	Disinfection of sludge	2.0-3.0

EBA - Electron Beam Accelerator

TCE - trichloroethylene

PCE - tetrachloroethylene, perchloroethylene

Table 9: Advanced methods and removal efficiency of DCF, E2 and EE2

Method	**Initial concentration**	**method, removal efficiency**	**Authors**
DCF			
$FeCl_3/Al_2(SO_4)_3$	14-18 µg/L (municipal wastewater) 10-18 µg/L 10-18 µg/L	coagulation-flocculation; 70% $FeCl_2$ / 68%$Al_2(SO_4)_3$, with aluminium polychloride, 50% flotation with low fat wastewater 12°C, 25%; 25°C, 40% flotation with high fat wastewater 22°C, 25%; 25°C, 48%	Carballa et al. 2005
$FeCl_3/Al_2(SO_4)_3$	Municipal wastewater	coagulation-flocculation, 21.6 %(mean)	Suarez et al 2009
UV-A	15 mg/L (deionized water)	50 mL cylindrical quartz glass UV-reactor; photocatalytic treatment 1500 W xenon arc lamp (750 W/m^2) 100 % in 1 h	Calza et al. 2006
UV-A	10 mg/L (deionized water)	350 mL laboratory scale photoreactor; 9 W UV-A lamp at a fluence 0.69 kWh/m^2, TiO_2, 85% after 240 min	Achilleos et al., 2010
UV_{254nm}	0.518 µg/L (wwtp effluent)	10 min, 100 %	De la Cruz et al. 2012
$UV_{200\text{-}800\ nm}$	9.24 mg/L (deionized water)	Low and medium pressure: 97-98%	Lekkerkerker-Teunissen et al. 2012
UV_{254nm}	0.858 µg/L(MBR effluent hospital ww)	800, 2400, 7200 J/m²; 47%, 88 %, >98 %	Kovalova et al. (2013)
UV/ H_2O_2	2.8 mg/L	LP-Hg lamp (2.51 x 10^{-6} E/s) [H_2O_2] 5 and 10 mM, pH 7.8, T = 298 K; 100 % in 2 min	Andreozzi et al. (2003)
UV/H_2O_2	1 mM (296 mg/L) solution with double glass-distilled water	UV/H_2O_2 oxidation, 17 W low-pressure mercury monochromatic lamp, annular reactor (0.420 L); complete in 10 min	Vogna et al., 2004
UV-A/ TiO_2/H_2O_2	(synthetic wwtp effluent)	UV-A: 2.8 x 10^{-6} E/s, [TiO_2]: 0.1 g/L, [H_2O_2]: 100 mg/L; Fixed bed reactor	Pablos et al. 2013
$UV_{200\text{-}800\ nm}$/ H_2O_2	9.24 mg/L (deionized water)	Low and medium pressure, [H_2O_2]: 5-10 mg/L, 97-98 %	Lekkerkerker-Teunissen et al. 2012
UV_{254nm} / H_2O_2	0.518 µg/L (wwtp effluent)	10 min, [H_2O_2]: 50 mg/L, 100 %	De la Cruz et al. 2012
UV_{254nm}/Fenton (Photo-Fenton)	0.518 µg/L (wwtp effluent)	10 min, UV_{254nm}, [Fe^{2+}]: 5 mg/L, [H_2O_2]: 25-50 mg/L, 100 %	De la Cruz et al. 2012
UV_{254nm}/ H_2O_2/Fe UV_{254nm} / H_2O_2	0.49-1.3 µg/L (WWTP effluent) 0.49-1.3 µg/L (WWTP effluent)	[H_2O_2]: 20-30 mg/L, [Fe^{2+}]: 2 mg/L: 99-100 % [H_2O_2]: 20-30 mg/L, 99-100 %	De la Cruz et al. 2013
radiation	0.1-1 mM	0.1-1 mM DCF: few kGy doses sufficient. 0.1mM DCF - complete degradation with 1 kGy dose	Homlok et al. 2011

radiation	50mg/L	100 % with 4.0 kGy dose (^{60}Co), or with 1.0kGy, when saturated with N_2O	Trojanowicz et al., 2012
radiation	DCF sodium salt	12.4 kGy (^{60}Co)	Ozer et al., 2013
Ultrasonic	2-5 mg/L (deionized water)	pH (3.5–11), power density (25-100 W/L), TOC removal of 19 % after 60 min	Naddeo et al. 2009
Ultrasonic	30 µM DCF (deionized water)	pH 3, frequency: 861 kHz, 90 min sonication in presence of 8.9 mM reactive zero-valent iron (ZVI), 0.01 mM reactive divalent iron (DVI) and 0.001 mM non-reactive iron superoxide nanoparticles (NPI) were 22%, 43% and 30%, respectively	Güyer et al. 2011
O_3	1.3	[O_3]: 5-10 mg/L , > 96%	Ternes et al. 2003
O_3	1 mM (296 mg/L) solution with double glass-distilled water	[O_3]: 5 mg/L semi-batch glass reactor (1.090 L); almost completely after 10 min	Vogna et al., 2004
O_3	10 µg/L	K_{O3} =6.8 x 10^5 $M^{-1}s^{-1}$ [O_3]: 0.016 mg/L, 100%,	Sein et al.2008
O_3	200 mg/L (MilliQ water)	ozonation, 1L batch reactor; almost completely after 30 min	Coelho, et al. 2009
O_3	0.015 (WWTP effluent)	Technical scale; [O_3]: 5 mg/L, > 90% in 15 min	Sui et al. 2010
O_3	0.858 µg/L(MBR effluent hospital wastewater)	[O_3]: 4.2, 5.8, 7 mg/L; 100 % for all three O_3 concentrations	Kovalova et al. (2013)
O_3	1 µg/L (WWTP effluent)	[O_3]: 0.5-12.0 mg/L	Antoniou et al. 2013
O_3	1.13 µg/L± 0.39	5.7 mg/L ozone dosage, technical scale; wwtp effluent, 94 %	Margot et. al. 2013
O_3	1 µg/L (WWTP effluent)	[O_3]: 0.5-12 mg/L, 100 %	Antoniou et al. (2013)
ClO_2	1 µg/L (ground & surface water)	[ClO_2]: 0.95-11.5 mg/L, 30-60 min, 100 %	Huber et al. 2005a
O_3/H_2O_2	0.165 (average) WWTP effluent	Pilot scale; [O_3]: 5 mg/L; [H_2O_2]: 3.5 mg/L; > 99 %	Gerrity et al. 2011
O_3/UV-A/TiO_2	30 and 80 mg/L (ultrapure water and WWTP effluent)	cylindrical borosilicate glass photo-reactor (0.45 m height and 0.08 m inside diameter), 100 % within 6 min	Aguinaco et al. 2012
O_2/UVA/TiO_2 O_3/UVA/TiO_2	10^{-4}M/L solution in MilliQ water	cylindrical borosilicate glass photo-reac-tor (0.45 m height, 0.08 m diameter); ozonation, almost completely after 7 min O_2/UVA/TiO_2, 90% after 10 min O_3/UVA/TiO_2, 95% after 10 min	Garcia-Araya et al. 2010
Fenton	0.518 µg/L (WWTP effluent)	30 min, [Fe^{2+}]: 5 mg/L, [H_2O_2]: 25-50 mg/L, 24 %	De la Cruz et al. 2012

Sonolysis TiO_2/sonolysis	50 mg/L (deionized water)	300 mL batch reactor; sonolysis, 90% after 60 min; sonolysis, TiO_2 catalyst, 84% after 30 min; sonolysis, SiO_2 catalyst, 80% after 30 min; sonolysis, TiO_2 and SiO_2 catalysts, 80% after 30 min	Hartmann et al. 2008
BDD/Si	175 mg/L (deionized water)	150 mL batch reactor pH 6.5 50 mA/cm^2: 95.1 % after 360 min 100 mA/cm^2: 98.9 % after 360 min 300 mA/cm^2: 100 % after 300 min 450 mA/cm^2: 100 % after 200 min	Brillas et al. 2010
BDD/Nb	300 mg/ L (bidistilled water)	Batch reactor 100 mL; [Na_2SO_4]=0.1 Surface area electrode: 6 cm; 42 mA/cm^2; 99.8% within 600 min	Vedenyapina et al., 2011
BDD/Ti	150 mg/L	Batch reactor; pH 6.5; current densities=10, 15 and 20 mA/cm; Higher DCF decay achieved at current density of 15 mA/cm^2. Higher current density lead to oxygen evolution and less efficiency.	Coria et al., 2014
BDD/Nb	50 µM (deionized water, hard tap water, WWTP effluent)	Batch-reactor, 3L, 3.5 A, 100 % after 15 min in deionized water, in 20 min in hard tap water, in 30 min in WWTP effluent	Rajab et al., 2013
pulsed corona discharge	5 mg/L (tap water)	Reactor (solution volume – 55 mL); 100 % after 7 min	Dobrin et al. 2013
magnetic nano-scaled catalyst cobalt ferrite/oxone	33.77 µM (deionized water)	250 mL glass bottle; 100 % in 15 min	Deng et al. 2013
PdFe	32 mM (bidistilled water)	plated elemental iron (PdFe), anoxic condition, batch experiment 80% within 10 min, 100% after 2 h	Ghauch et al. 2010
Fe^0 based trimetallic system	32 µM (bidistilled water)	anoxic condition, batch experiment PdNiFe, 100% after 1 h PdCuFe, 80% after 1 h NiPdFe, 80% after 1 h	Ghauch et al. 2011

E2			
O_3	0.5-5 µg/L (WWTP effluent)	[O_3]: ≥ 2mg/L, 90-99 %	Huber et al 2005b
UV	5 µM (deionized water)	LP-UV, MP-UV, reduction of estrogenic activity lower relevant concentrations	Rosenfeldt et al. 2006
UV//H_2O_2	5 µM (deionized water)	LP-UV + 5 mg/L H_2O_2; > 90 % MP-UV+ 5 mg/L H_2O_2; > 90 %	Rosenfeldt et al. 2007
UV-A/TiO_2	500 µg/L (deionized water)	[TiO_2]: 10 mg/L Degradation efficiency increases with increasing pH value	Karpova et al 2007
UV-A/TiO_2	10 µg/L (distilled water)	55 min for 100 %, 24 min for 90 %	Coleman et al. 2004
O_3/H_2O_2	0.003 (average) WWTP effluent	Pilot scale; [O_3]: 5 mg/L; [H_2O_2]: 3.5 mg/L; > 83 %	Gerrity et al. 2011
BDD/Si	500 µg/L (distilled water)	500 mL batch reactor pH 6 12.5 mA/cm^2: 100 % after 40 min 25 mA/cm^2: 100 % after 40 min	Murugananthan et al. 2007
EE2			
O_3	4 µmol/L (natural water)	[O_3]: 1.5-7.5 µmol/L, removal strongly depends on pH value	Huber et al. 2003
O_3	0.5-5 µg/L(WWTP effluent)	[O_3]: ≥ 2mg/L, 90-99 %	Huber et al 2005b
ClO_2	1 µg/L (ground water)	[ClO_2]: 0.1mg/L, < 5 min, 100 %	Huber et al. 2005a
MnO_2	5 mg/(L d) 40 mg/(L d)	93% 75 %	Forrez et al. 2009
Biologically produced MnO_2	40 mg/(L d)	57%	Forrez et al. 2009
UV-A/TiO_2	10 µg/L (distilled water)	50 min for 100 %, 27.5 min for 90 %	Coleman et al. 2004
Ultrasonic/O_3		Ultrasonic ozonation (US/O_3) & photocatalytic ozonation (PC/O_3) under differrent conditions involving supplied ozone dose, pH value and humic acid (HA) concentration of the effluent, ultrasonic radiation power & photocatalyst dose. < 13.3% removal rate for EE2	Zhou et al. 2015

Supplemental Data

Table 1. Annual DCF and EE2 consumption in several EU countries. Databases and publications from 2005 to 2013 have been considered.

Country	DCF DDD 100 mg		EE2 DDD 25 µg		Reference
	DDD/1000 inhab/day	mg/inhb/year	DDD/1000 inhab/day	µg/inhb/year	
Austria	21	768	54.5	500	Kreuzinger et al. 2004
Estonia	13.1	480	24.2	220	*Estonian State Agency of Medicines 2013*
Finland	4.2	154	2.2	20	Alder et al. 2006
France	6.9	255	n.d.	n.d.	Alder et al. 2006
Germany	28.2	1033	66	600	SRU, 2007
Italy	4.3	160	15.9	150	http://www.epicentro.iss.it/farmaci/OsMed.asp
Lithuania	20.5	750	12.2	111	*Estonian State Agency of Medicines 2013*
Latvia	23.9	870	11.4	104	
Netherlands	12	440	n.a.	n.a.	Oosterhus et al. 2012
Norway	11.5	420	38.7	353	http://www.norpd.no/Prevalens.aspx
Poland	14.7	540	22.9	210	Alder et al. 2006
Portugal	10.1	370	6.0	55	INFARMED 2012
Serbia	34.7	1260	6.67	60	Radonjic and Sipetic 2012
Spain	14.4	541	22.9	210	Carballa et al. 2008
Sweden	10.6	390	29.2	266	http://www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel
Turkey	26.9	985	n.a.	n.a.	

Supplementary Material
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