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**Towards an innovative combined process coupling
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3 **1 Towards an innovative combined process coupling biodegradation and photo-oxidation for the**
4 **removal of pharmaceutical residues**
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1 **Abstract**

2 **BACKGROUND:** Occurrence of pharmaceutical compounds in wastewater has become a major concern
3 for human health and the environment. Therefore, it is challenging to improve the conventional
4 wastewater treatment to remove these compounds. Coupling a biological treatment with an advanced
5 oxidation technology has been widely studied in the literature, but only sequential associations of the
6 two processes have been used. This study proposes an innovative concept based on a real integration of
7 the photocatalytic oxidation process in a continuous recycling loop on a membrane bioreactor. The role
8 of the oxidation is not here to completely degrade pharmaceuticals, but to oxidize them moderately to
9 increase their biodegradability so that they can be eliminated by the biological process.

10 **RESULTS:** Preliminary experiments on oxidation process indicated that a flux density of 5 W.m^{-2} was
11 sufficient to increase biodegradability and decrease toxicity of a cocktail of 3 pharmaceuticals. Then
12 performances of a 20-L continuous membrane bioreactor treating wastewater with 7 pharmaceuticals,
13 without and with pre-oxidation at 5 W.m^{-2} were compared. Pre-oxidation has increased the global
14 removal for some recalcitrant pharmaceuticals (from 3 to 47 % for diclofenac and for 1 to 44 % for
15 furosemide) without affecting neither the removal of carbon, nitrogen and phosphorous by activated
16 sludge neither the removal of already highly removed pharmaceuticals.

17 **CONCLUSION:** This work proves the feasibility and interest of the innovative concept of a continuous
18 hybrid process coupling a photocatalytic oxidation process and a membrane bioreactor for the treatment
19 of pharmaceuticals in wastewater, with a low cost and size.

20 **Key words:** membrane bioreactor, photocatalytic oxidation, micropollutants, pharmaceuticals, hybrid
21 process, wastewater treatment

22 **Introduction**

23 In the last three decades, an increasing number of research papers have reported the presence of
24 pharmaceutical compounds (PhCs) in almost all water bodies, including surface waters, ground water,
25 seawater but also drinking water, at range from ng.L^{-1} to mg.L^{-1} all around the world.^{1,2,3} European Union
26 (EU) monitoring found diclofenac as the most common polar pharmaceutical in natural waters.⁴ Other

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3 1 molecules - such as sulfamethoxazole, gemfibrozil, atenolol, naproxen, propranolol, ibuprofen, etc. - were
4
5 2 commonly found in the aquatic environment.⁵ Carbamazepine, an antiepileptic drug, was also frequently
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7 3 detected in groundwater and surface water.^{5,6} Pharmaceuticals have become one of most important class of
8
9 4 emerging organic micropollutants since they are persistent and bioactive compounds that could affect
10
11 5 aquatic organisms even at very low concentrations.^{1,3,6,7} Main source of pharmaceutical pollution in the
12
13 6 environment comes from wastewater treatment plants (WWTP) effluents, mainly composed by domestic
14
15 7 and industrial wastewaters but also receiving hospital or elderly house effluents which are released
16
17 8 untreated to the sewage grid.^{1,3,8-10} Due to their intrinsic characteristics of high polarity and stability, most
18
19 9 of PhCs are not removed by conventional activated sludge (CAS) in WWTP.^{2,3,5,7} They are consequently
20
21 10 continuously released into the aquatic surfaces and their increasing occurrence has become a major
22
23 11 environmental and human health concern. Membrane bioreactors (MBRs) have shown a higher efficiency
24
25 12 than CAS in removing many pharmaceuticals due to longer sludge retention time and higher suspended
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27 13 solids that favor higher biodiversity and promote stability against high load variations.^{5,8} However, some
28
29 14 pharmaceuticals remain poorly biodegraded even by MBR, including carbamazepine (CBZ) which is one
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31 15 of the most biorecalcitrant drug.^{2,5}
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34 16 To improve the removal efficiency of pharmaceutical compounds, coupling the biological treatment with
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36 17 complementary technologies including adsorption on activated carbon, membrane separation processes or
37
38 18 advanced oxidation processes (AOP) have been studied.^{1,11-13} Contrary to the two first technologies that
39
40 19 only consist in a phase-transfer of micropollutants, AOP could efficiently respond to the problem posed by
41
42 20 biorecalcitrant drugs due to their ability to non-selectively degrade micropollutant molecules.¹⁴⁻¹⁶ Recent
43
44 21 works have shown that AOP can significantly reduce effluent toxicity, increase biodegradability or allow
45
46 22 mineralization of many molecules: pesticides, industrial products even at high concentrations¹⁷, but also
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48 23 pharmaceutical emerging residues at lower concentrations.^{15,16,18-21} With these considerations, AOPs could
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50 24 be used as a pre-treatment of biological processes in order to increase biodegradability of the pollutants or
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52 25 as a post-treatment in order to degrade the micropollutants not completely removed by the biological
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54 26 process. These different combinations have been recently reviewed for emerging contaminants in
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56 27 wastewater.^{1,5,20-25} It appears that AOP could be ineffective as a pre-treatment, due to the complexity of the
57
58 28 wastewater matrix characterized by a high concentration of biodegradable compounds and very low
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1 concentration of the targeted micropollutants²⁵. That is why most frequent combinations of
2 biological/advanced oxidation processes reported in the literature concern a biological step followed by
3 AOP such as ozonation, photo-Fenton or heterogeneous photocatalysis oxidation with TiO₂.^{1,5,22}
4 Nevertheless, formation of oxidation intermediates more toxic than the parent compounds may occur
5 depending on the applied conditions.^{11,22,24,25}

6 Thus, this study aims to propose an innovative concept based on an effective integration of a biological
7 process and a AOP, in which AOP is placed in a continuous recirculation loop on the biological process
8 (Figure 1). The objective of the AOP is not a complete mineralization of the biorecalcitrant molecules, but
9 a moderate oxidation to increase their biodegradability in order they could be removed by the biological
10 process. This hybrid process would intensify the biological one thanks to the synergetic effect of the two
11 processes. A MBR has been chosen as biological process since it is more efficient for pharmaceutical
12 removal and less sensitive to high load variation⁵. Among AOP, heterogeneous photocatalysis with TiO₂,
13 one on the most studied oxidation process,^{15,26} has been selected as it can be driven by solar radiation and
14 so reduce costs and environmental impacts of the process.¹³

15 The main objective of this paper was to assess the feasibility and performance of this integrated system for
16 the treatment of pharmaceutical micropollutants in wastewater. Three pharmaceuticals widely investigated
17 in the literature: ibuprofen (IBU), diclofenac (DCF) and carbamazepine (CBZ) have been first selected as
18 model molecules with high, moderate and low biodegradation potential respectively. Then, four additional
19 molecules among the most frequently found in wastewater from retirement homes¹⁰ have also been added:
20 furosemide (FUR), levetiracetam (LEV), amylnmetacresol (AMY) and paracetamol (PAR). To demonstrate
21 the feasibility of this hybrid system, this work was divided into two distinct steps. First, preliminary
22 experiments were conducted on a continuous photo-oxidation process alone with the aim to determine the
23 best oxidation conditions (flux density) that make the effluent biodegradable (Figure 1, experiment ②).
24 Then, a 20L-MBR was operated in a continuous mode to treat first wastewater without oxidation (with
25 native molecules) as a reference (Figure 1, experiment ①) and then an effluent previously oxidized with
26 the optimal conditions (Figure 1, experiment ③). Carbon, nitrogen, phosphorous and pharmaceutical
27 removal performances as well as effluent toxicity using *Zebra fish* as model organism were investigated.

1 **Material and methods**

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6 2 **Pharmaceuticals.** IBU, DCF, CBZ, FUR, AMY, LEV, PAR were purchased from Sigma–Aldrich
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8 3 (purity >98%). Stock solutions were prepared at concentration of 10 mg.L⁻¹ per compound. All solutions
9
10 4 were prepared in ultrapure water (> 17.5 mΩ.cm) stored at 4°C and used within one month.

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12 5 **Photo-oxidation reactor experiments.** Based on a plan-type model configuration illustrated in Figure 2,
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14 6 the experimental setup is built of a continuous photoreactor running under controlled flow rate (Q) and
15
16 7 irradiated thanks to a panel of LEDs.²⁷ The photo-reactor is a parallelepiped window (4) with a width of
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18 8 10 cm, a length of 15 cm and a thickness of 1 cm. A plate of transparent PMMA UV radiation (90%) is
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20 9 fixed to transmit radiation coming from the LEDs. The LED panel (5) is included in a closed chamber
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22 10 to isolate it from any external light source. The UV flux density (I) can be modulated between 1 and 110
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24 11 W.m⁻². A multi-channel peristaltic pump (Watson Marlow 205 CA) (1) feeds the photoreactor with
25
26 12 continuous flow rate (Q = 5 mL.min⁻¹) of the solution to be oxidized. A previously optimized
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28 13 concentration of 2 g.L⁻¹ of TiO₂ was added in the solution.¹⁸ To ensure homogeneous distribution of the
29
30 14 photocatalyst, the photo-reactor is connected to a 0.25 L recirculation loop system (2) thanks to a
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32 15 variable-speed centrifugal pump (Cole-Palmer Instruments) (3). In this way, the photoreactor runs as a
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34 16 continuous stirred tank reactor. Oxidized samples were taken at least 60 minutes after switch on the
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36 17 LED panel in order to be sure that the steady state was reached.

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39 18 In the first part of this work, preliminary oxidation experiments were performed with IBU, DCF and
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41 19 CBZ - single or in cocktail - solutions at 10 mg.L⁻¹ in distilled or tap water. Several flux densities (2; 5;
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43 20 10; 20 and 40 W.m⁻²) were tested. Other operating conditions such as flow rate (Q), pH and temperature
44
45 21 were kept constant. Samples of oxidized solutions were taken for biodegradability, toxicity and
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47 22 micropollutant concentration measurements.

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50 23 Then, photo-oxidation at 5W.m⁻² of 15 L of a solution containing all the studied pharmaceuticals (IBU,
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52 24 DCF, CBZ, FUR, AMY, LEV and PAR) in tap water at a concentration of 4.5 mg.L⁻¹ each, was
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54 25 performed. This solution was then diluted before being treated by the membrane bioreactor.

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56 26 **Membrane bioreactor experiments.** A laboratory-scale MBR with a working volume of 20 L (Figure
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58 27 3) was equipped with a Rushton turbine (200 rpm) and temperature, dissolved oxygen and pH probes.
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60 28 A membrane module consisted of a ceramic tubular Membralox® (MF) membrane with surface area of

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3 1 0.0055 m² and pore size of 0.2 μm (Pall Exekia, France) was located in an external loop. The tangential
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5 2 velocity in the membrane was set to 4 m.s⁻¹. At initial time, the bioreactor was seeded with an activated
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7 3 sludge from a real WWTP (Castanet-Tolosan, France) with a total suspended solids (TSS) concentration
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9 4 of 2 g.L⁻¹. Then, the MBR was continuously fed with a synthetic wastewater and permeate flowrate was
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11 5 set to 10 L.d⁻¹ (HRT = 48 h). The synthetic wastewater was composed of peptone (640 mg.L⁻¹), meat
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13 6 extract (440 mg.L⁻¹), K₂HPO₄ (28 mg.L⁻¹), NaCl (7 mg.L⁻¹), CaCl₂ (16 mg.L⁻¹), MgSO₄ (8 mg.L⁻¹),
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15 7 NH₄Cl (100 mg.L⁻¹) and NaOAc (80 mg.L⁻¹) diluted in tap water, corresponding to a chemical oxygen
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17 8 demand (COD) of 1000 mg.L⁻¹, a total nitrogen (TN) content of 120 mg.L⁻¹ and a total phosphorous
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19 9 (TP) content of 10 mg.L⁻¹. pH was maintained at 7.2. Cycles of 3 min aeration (dissolved oxygen of 4.5
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21 10 mg O₂.L⁻¹) / 30 min without aeration allowed aerobic / anoxic conditions for nitrification and
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23 11 denitrification steps.²⁸ A part of activated sludge (1 L) was daily removed from the bioreactor to maintain
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25 12 sludge retention time (SRT) at 20 d. Experiments were carried out in two phases: 15 days without
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27 13 addition of pharmaceuticals (Phase I), then 15 more days by adding micropollutant solution (Phase II).
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29 14 This micropollutant solution consisted in a cocktail of the seven native pharmaceuticals (IBU, CBZ,
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31 15 DCF, LEV, AMY, PAR, FUR at a concentration feeding of 40 μg.L⁻¹ each) for the first campaign
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33 16 (MBR_1). For the second campaign (MBR_2), the same pharmaceutical cocktail was previously
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35 17 oxidized at 5 W.m⁻² by the photoreactor before feeding the membrane bioreactor. For each campaign,
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37 18 samples of the feeding solution, membrane permeate, purge and mixed liquor were taken every two days
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39 19 at the end of the anoxic phase to be characterized (TSS, VSS, COD, TN, NH₄⁺, NO₂⁻, NO₃⁻). During
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41 20 phase II, adequate volume of permeate were also sampled every three days for pharmaceutical
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43 21 concentration quantification and once a week for toxicity measurement. All the samples were collected
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45 22 in 20 mL glass vials and were frozen at -18°C until analysis.

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49 23 ***Physicochemical characterization of wastewater.*** A 20 mL sample were centrifuged at 13,500 g during
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51 24 15 min and supernatant was analyzed by means of HACH Kits. The parameters and corresponding
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53 25 HACH Kits were: Chemical Oxygen Demand (COD) (LCK 314 and LCK 514), Total Nitrogen (TN)
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55 26 (LCK 338), NH₄-N (LCK 303 or LCK 301), NO₂-N (LCK 341), NO₃-N (LCK 340), Total Phosphorous
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57 27 (TP) (LCK 350).

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3 1 **Sludge characterization.** The concentrations of Total Suspended Solids (TSS) and Volatile Suspended
4 Solids (VSS) were measured according to standard methods 2540D and 2540E.²⁹

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7 3 **Biodegradability assay.** Biodegradability of micropollutant solution (pharmaceutical cocktail or
8 oxidized pharmaceutical cocktail) was determined using biological oxygen demand (BOD₂₈) (OECD
9 301)³⁰ based on oxygen amount required by an activated sludge to metabolize micropollutants during
10 28 days. BOD₂₈ was measured tanks to a respirometry apparatus (OxiTop C, WTW). Flasks were
11 prepared in duplicate with mineral solution³⁰ and either sample (S) or distilled water to measure
12 endogenous respiration (ER) of sludge or a solution of glucose and glutamic acid³⁰ for activity control
13 of the activated sludge. Volume of mineral solution and sample were adjusted according to their COD
14 concentration³⁰. Activated sludge came from the WWTP of Castanet Tolosan (France) and was
15 inoculated, after washing three times with distilled water, at a final concentration of 0.05 g.L⁻¹.
16 Biodegradability of micropollutant solution was expressed as a percentage of oxygen depletion relative
17 to their COD concentration:

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$$\text{Biodegradability (\%)} = \frac{\text{BOD}_{28}^{\text{S}} - \text{BOD}_{28}^{\text{ER}}}{\text{COD}} \quad (\text{Eq. 1})$$

32
33 15 where BOD₂₈^{ER} is measured in endogenous respiration flask and BOD₂₈^S is the value of sample flask.

34
35 16 **Analysis of pharmaceuticals.** Water samples were unfrozen the same day of the analysis. Samples from
36 the MBR experiment were filtered through 0.22 nylon filters to remove particulate matter. Then, aliquots
37 of this water were collected in chromatographic amber vials. For high concentrations, a dilution of 1/100
38 was performed in water. Liquid chromatography coupled to tandem mass spectrometry (LC-
39 MS/MS, TQD, Waters, Mildford, USA) was used for pharmaceutical analysis.³¹ Drugs were measured
40 under positive electrospray ionization (ESI+), except for ASP and FUR that were detected in negative
41 electrospray ionization (ESI-). Chromatographic separation was performed using a Synergy Polar-RP
42 column (250 mm x 4.6 mm, particle size 4µm, Phenomenex, Torrance, USA). The mobile phases were a
43 binary mixture with 0.1% of formic acid in acetonitrile (A) and 0.1% formic acid in water (B). Gradient
44 elution started at 10% A, increasing to 70% A in 20 minutes and to 100% in 5 minutes, held for 7 minutes
45 and returned to initial conditions after 3 minutes. The analysis run time was 35 minutes. Flow rate was
46 set at 0.4 mL.min⁻¹. Sample tray was maintained at 5°C. 10 µL of the sample were directly injected into
47 the LC-MS/MS system. All data were acquired and processed using Masslynx v 4.1 software (Waters).
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3 1 Two MS/MS transitions were used to monitor each compound and for confirmation their ion ratios were
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5 2 evaluated. Quantification was done using the most abundant transition. External standard calibration
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7 3 was used to calculate the concentration of pharmaceuticals. The system was linear over the range 0.01-
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9 4 2.5 ng.µL⁻¹ (R²>0.99) for all compounds. Compounds were efficiently recovered with the direct
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11 5 injection analysis (from 69 to 117%).

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13 6 **Toxicity assay.** The procedure previously reported by Raldúa et al. (2008)³² with minor modifications
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15 7 was followed. Embryos from wild type zebrafish were obtained by natural mating and maintained in
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17 8 fish water [reverse-osmosis purified water containing 90 µg.mL⁻¹ of Instant Ocean (Aquarium Systems,
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19 9 Sarrebourg, France) and 0.58 mM CaSO₄·2H₂O] at 28.5°C on a 12 h light:12 h dark cycle. Zebrafish
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21 10 embryos were transferred to 48-well microplates (1 larva per well) each well containing 1 mL of media,
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23 11 and exposed from 6 hpf to 120 hpf. 24 embryos were used for each condition. Viability of embryos was
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25 12 checked at 24, 48 and 120 h. Dead embryos or malformations were reported as endpoints at the end of
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27 13 the experiment. All procedures were conducted in the animal facility of CID-CSIC in accordance with
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29 14 institutional guidelines under a license from the local government (agreement number 9027) and
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31 15 approved by the Institutional Animal Care and Use Committee. Water samples were kept frozen at -20°C
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33 16 until toxicological analyses. Firstly range finding test were conducted to determine the optimal dilution
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35 17 to achieve mortalities in initial samples lower or closer to 100% but greater than 50%. Then all samples
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37 18 were assayed at the dilution having the greater number of responses (≤100%) across treatments. Samples
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39 19 were diluted using zebrafish water. Dilutions ranged from no dilution (x 1) to 1/16.. CBZ alone did not
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41 20 produce embryotoxic effects in zebrafish at 10 mg.L⁻¹, thus this drug alone was not assayed. Each trial
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43 21 has a control with zebrafish water and the assay was considered valid if mortality (arrest or embryo
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45 22 malformation) in controls was < 5%.

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49 23 **Removal performance calculations.**

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51 24 Performance of pollutants (COD, N, P) or pharmaceutical removal for both MBR and photo-oxidation
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53 25 processes were assessed with global removal efficiencies (RE), calculated as follow:

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$$RE (\%) = \frac{(C_{IN} - C_{OUT})}{C_{IN}} \quad (\text{Eq.}$$

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58 27 2)

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3 1 Where C_{IN} and C_{OUT} are the concentrations of the pollutants or pharmaceuticals in the inlet and outlet of
4
5 2 the processes. For MBR process, C_{OUT} is the concentration in the permeate.
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8 **Results and discussion**

10 **Photocatalytic experiments**

11 *Photo-oxidation of separate pharmaceuticals*

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15 6 Constant operating conditions with a flux density fixed at $I = 10 \text{ W.m}^{-2}$ were used to oxidize solutions
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17 7 containing IBU, DCF and CBZ alone at 10 mg.L^{-1} . Figure 4.a presents the removal efficiency of
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19 8 pharmaceutical photo-oxidation when molecules were oxidized separately. Different behaviors have
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21 9 been observed depending on the molecules: photo-degradation varied from 12% for CBZ, which was
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23 10 the most resistant to oxidation up to 39 % for IBU, which was the most sensitive to oxidation in these
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25 11 experimental conditions. These results confirm that degradation rate depends on the catalyst / molecule
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27 12 pair.¹⁸ Indeed, heterogeneous oxidation mechanism begins with mass transfer from the solution to the
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29 13 catalyst. Since pollutants can only be photo-degraded close to in catalyst surface, which is site of radical
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31 14 production, interactions between pollutant and catalyst are driven by physicochemical characteristics of
32
33 15 both molecules (hydrophobicity) and solution (salinity, pH, organic matter content). The impact of the
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35 16 oxidation on biodegradability of these 3 molecules can be seen on Figure 4.b. The biodegradability
36
37 17 of CBZ and DCF was zero both before and after photo-oxidation, despite the efficiency of the oxidation
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39 18 process to reduce CBZ and DCF concentrations. It seems that DCF, CBZ and their oxidized
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41 19 transformation products could not be used or transform by activated sludge microorganisms in the
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43 20 conditions used for the biodegradability test. On the contrary, oxidation of DCF solution decreased its
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45 21 toxicity (Figure 4.c) indicating that oxidation transformation products seemed less toxic for the
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47 22 environment even if their could not be biodegraded in the tested conditions. Concerning IBU, its
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49 23 biodegradability before oxidation was quite high (~70%) and increased up to 83% after oxidation,
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51 24 probably due to the higher biodegradability of its oxidation products coupling with a toxicity divided by
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53 25 two after oxidation (Figure 4.c). These first results show the positive effect of the photo-oxidation at I
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55 26 = 10 W.m^{-2} on the biodegradability and toxicity of the three selected micropollutants.
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27 *Cocktail effect on oxidation efficiency*

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3 1 The same constant operating conditions with a flux density fixed at $I = 10 \text{ W.m}^{-2}$ were applied on a
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5 2 solution containing a cocktail of CBZ, DCF and IBU at an initial concentration of 10 mg.L^{-1} each. When
6
7 3 in cocktail, the three pharmaceuticals were more recalcitrant to oxidation as photodegradation efficiency
8
9 4 varied between 1 and 5 % (Figure 4.d). This could be due to competition phenomena between the
10
11 5 molecules and their byproducts on catalyst surfaces that strongly limit photodegradation rate. However,
12
13 6 despite the lower photodegradation, the biodegradability of the oxidized cocktail was quite the double
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15 7 of the non-oxidized cocktail (Figure 4.e) and toxicity decreased by 60% (Figure 4.f). Even if they are
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17 8 not well explained by the literature, synergetic effects between native molecules as well as photo-
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19 9 oxidation products clearly influence their impact on living beings, as it can be observed with
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21 10 biodegradability and toxicity tests.

22 23 24 11 ***Influence of flux density on DCF, IBU and CBZ cocktail***

25
26 12 Photo-oxidation experiments were then conducted with the cocktail of DCF, IBU and CBZ, at a
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28 13 concentration of 10 mg.L^{-1} each, with different flux densities (2; 5; 10; 20 and 40 W.m^{-2}). Overall, the
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30 14 photodegradation removal efficiency (Figure 5.a) increased with the flux density. For DCF, that was the
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32 15 most sensitive to photo-oxidation in these conditions, photo-oxidation removal efficiency increased
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34 16 from 0 to 10 W.m^{-2} and seemed to stabilize for higher flux densities.

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36 17 Biodegradability and toxicity of the oxidized solutions also depends on the applied flux density (Figure
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38 18 5.b). Significant increase was observed for biodegradability until 5 W.m^{-2} . Above this flux density,
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40 19 biodegradability level was quite constant around a maximal value of 40%. A higher biodegradability
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42 20 was linked to a lower toxicity. Indeed, toxicity decreased when flux density increased and stabilized was
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44 21 around 15%. This demonstrates that photo-oxidation allows to increase the biodegradability of the
45
46 22 pharmaceutical solution while reducing its toxicity in the tested conditions. Besides, an increasing the
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48 23 flux density above 5 W.m^{-2} does not improve significantly this biodegradability. Thus, with the objective
49
50 24 to couple photo-oxidation step with a biological treatment, a flux density value of 5 W.m^{-2} was selected
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52 25 to oxidize a synthetic wastewater before its treatment by a membrane bioreactor

53 54 55 56 26 **Membrane Bioreactor experiments**

57 58 27 ***Biological treatment of non-oxidized pharmaceuticals***

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3 1 As a reference, the 20-L membrane bioreactor experiment (MBR_1) was performed in a continuous
4
5 2 mode to treat a synthetic wastewater containing seven micropollutants frequently detected at the outlet
6
7 3 of retirement homes (IBU, DCF, CBZ, LEV, AMY, PAR, FUR) at concentration of $40 \mu\text{g.L}^{-1}$ each
8
9 4 (Figure 1- Experiment 1). These pharmaceuticals were added in the synthetic wastewater after a first
10
11 5 stage of stabilization of the biological process without pharmaceutical addition. Table 1 summarizes the
12
13 6 sludge characteristics and the carbon, nitrogen and phosphorous removal efficiencies before (phase I)
14
15 7 and after (phase II) addition of the pharmaceuticals. As can be seen, pharmaceutical addition had little
16
17 8 impact on MBR running, excepted for nitrogen removal, which was higher after the addition of the
18
19 9 micropollutants. This could be due to a longer adaption time needed to nitrifying biomass to be efficient
20
21 10 rather than micropollutant addition. Indeed, before spiking with pharmaceuticals, NH_4^+ concentration in
22
23 11 permeate was about 25mg.L^{-1} at the beginning of the experiment and decreased to 6mg.L^{-1} after 15
24
25 12 days of running which correspond to the time of micropollutant addition. However, nitrogen removal
26
27 13 was limited by the denitrification step as a concentration of NO_3^- in permeate was between 30 and 50
28
29 14 mg.L^{-1} all along the experiment. This limited impact of native pharmaceutical compounds on COD and
30
31 15 TN removal has been often reported in the literature for several pharmaceuticals³³. Only in some studies
32
33 16 dealing with high concentration of antibiotics, a decrease in denitrification step was observed.^{34,35} To go
34
35 17 further in comprehension, pharmaceutical apparent removals in continuous MBR are reported in Table
36
37 18 2. Three molecules (IBU, PAR, AMY) were highly removed ($> 70\%$) by the activated sludge, one
38
39 19 (LEV) was moderately removed (between 30 and 70 %) and the other three (DCF, CBZ, FUR) were
40
41 20 poorly removed ($< 30\%$). For CBZ, apparent removal was negative due to poor biodegradability and
42
43 21 possible accumulation in MBR.⁵ This behavior has already been observed in CAS or MBR for the
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45 22 treatment of real effluent and could be explained by the inflow of pharmaceuticals in the conjugated
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47 23 form that are transformed into the original compounds during treatment.³³ For IBU, DCF, CBZ and
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49 24 PAR, the apparent removal efficiencies are in the range of those reported in the literature for MBR
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51 25 experiments (Table 2).^{5,37-39} For FUR removal, only two papers were found,^{38,39} so the comparison with
52
53 26 literature should be done with care. To our best knowledge, removal efficiencies in MBR have never
54
55 27 been reported before for LEV and AMY. As CBZ, FUR and DCF were poorly biotransformed, coupling
56
57 28 of the MBR with the photo-oxidation process is of great interest for global removal of these molecules.

1 **Biological treatment of oxidized pharmaceuticals**

2 A second MBR experiment (Figure 1- Experiment ③), called MBR_2 experiment, was performed in the
3 same conditions as MBR_1 experiment except that pharmaceutical solution was previously oxidized at
4 5 W.m⁻² (Figure 1- Experiment ②). As for MBR_1, pre-oxidized pharmaceuticals were added after a
5 stage of 15 days without drug supply. As for native pharmaceuticals, no significant difference was
6 observed between the two phases (Table 1). This result is promising since feeding MBR with the
7 oxidized solution did not impact its global removal performances in terms of carbon, nitrogen or
8 phosphorous. Besides pre-oxidation of the pharmaceutical solution at 5 W.m⁻² seems to affect positively
9 the removal of the selected pharmaceuticals. Indeed, considering the MBR performance alone (Table 2
10 /MBR_2), when the pharmaceutical cocktail has been pre-oxidized at 5 W.m⁻², apparent removal
11 increased for DCF, FUR and LEV. Molecules already highly biodegraded in MBR_1, maintain their
12 high removal efficiency. Only CBZ removal remained negative. These results are in agreement with the
13 increased of biodegradability observed above and the lower toxicity of the effluent. By focusing on pre-
14 oxidation, a slight decrease was observed in concentrations of the parent compound, corresponding to
15 removal efficiencies ranging from 0 % for FUR up to 36 % for PAR (Table 2/Oxidation), as well as a
16 decrease in toxicity from 15 ± 3 % before oxidation to 0 % after oxidation. This could increase the
17 biodegradability of the oxidized solution as previously observed for the cocktail of IBU, DCF and CBZ
18 at higher concentration and so decrease the potential negative impact on sludge. Removal efficiencies
19 of the oxidation / MBR combination reported in Table 2 (Oxidation + MBR_2) were calculated as
20 follow:

$$21 \quad RE_{OX + MBR_2} (\%) = RE_{OX} + (1 - RE_{OX}) \cdot RE_{MBR_2} \quad (\text{Eq. } 3)$$

23 For all pharmaceuticals, removal efficiency increased with addition of the oxidation step comparing to
24 MBR alone (MBR_1). Thus flux density of 5 W.m⁻² was enough to improve the biodegradation of the
25 selected pharmaceuticals by MBR without changing its performance of wastewater treatment. This
26 result validates the feasibility of the concept described in Figure 1 of coupling a MBR with a photo-
27 oxidation process. A higher removal performance for the less degraded molecules (DCF, CBZ and FUR)

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3 1 is expected with the continuous coupling of the two processes since continuous recirculation in the
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5 2 photo-oxidation process will generate several oxidation/biodegradation cycles.
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8 **Conclusion**

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11 4 The concept of coupling in one process, a biological treatment by a MBR and a photo-oxidation process
12
13 5 has been proven for the treatment of pharmaceuticals in wastewater. A flux density of 5 W.m^{-2} was
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15 6 sufficient to improve the removal of most of the selected pharmaceuticals by a MBR without changing
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17 7 its performance in carbon, nitrogen and phosphorous treatment. Particularly, global removal (oxidation
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19 8 + MBR) of some recalcitrant compounds such as DCF or FUR, and in a lesser extend CBZ were
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21 9 improved comparing with the MBR without oxidation step. The observed decrease in toxicity of the
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23 10 treated pharmaceutical solutions corroborates pharmaceutical removal and indicates negligible toxicity
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25 11 of the by-products formed. Comparing with a sequential association of biological process and photo-
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27 12 oxidation process usually described in the literature, this innovative concept is expected to be more
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29 13 compact and less expensive and is very promising for an efficient removal of pharmaceuticals in
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31 14 wastewater.
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For Peer Review

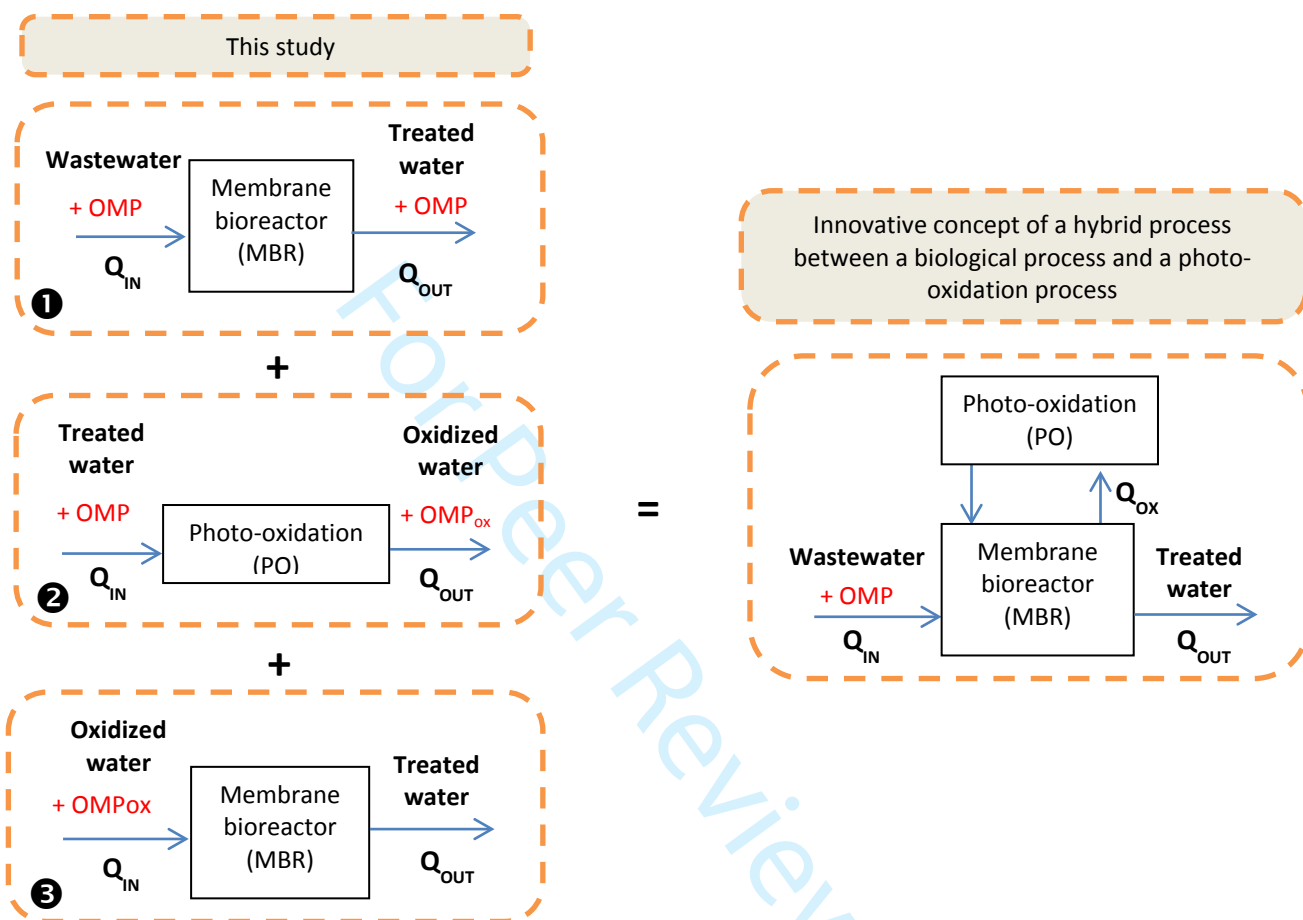
Table 1. Comparison of mean values of sludge characteristics of continuous MBR before and after addition of native pharmaceuticals (MBR_1) or pre-oxidized pharmaceuticals (MBR_2) during 15 days. (Pharmaceuticals: IBU, DCF, CBZ, LEV, AMY, PAR and FUR at 40 $\mu\text{g}\cdot\text{L}^{-1}$ in synthetic wastewater). TSS: total suspended solid; VSS: volatile suspended solid; COD: chemical oxygen demand; TN: total nitrogen; TP: total phosphorous.

	MBR_1		MBR_2	
	Native pharmaceutical addition		Pre-oxidized pharmaceutical addition	
	Before adding micropollutants	After adding micropollutants	Before adding micropollutants	After adding micropollutants
TSS ($\text{g}\cdot\text{L}^{-1}$)	3.2 \pm 0.2	4.4 \pm 1	2.9 \pm 0.1	3.3 \pm 0.3
VSS/TSS (%)	75 \pm 4	74 \pm 7	77 \pm 6	75 \pm 8
COD removal (%)	89.2 \pm 2.2	89.2 \pm 1.7	90.9 \pm 0.8	92.9 \pm 1
TN removal (%)	12.3 \pm 5.8	23.6 \pm 5.7	41.5 \pm 6.2	38.2 \pm 4.1
TP removal (%)	99.8 \pm 0.1	99.8 \pm 0.1	99.8 \pm 0.1	99.8 \pm 0.1

Table 2. Mean apparent removal efficiencies in continuous MBR for a cocktail of pharmaceuticals without pre-oxidation (MBR_1) or with pre-oxidation at a flux density of 5 W.m⁻² (MBR_2)

		IBU	DCF	CBZ	FUR	AMY	LEV	PAR
Without pharmaceutical pre-oxidation	MBR_1 (Figure 1. Exp. ①)	97 ± 6 %	12 ± 10 %	< 0 %	1 ± 30 %	100 ± 0 %	46 ± 27 %	98 ± 3 %
	Literature range	73/100 ^{5,37,38}	0.2/87 ^{5,37}	-42/51 ^{5,37,38}	65 ^{38,39}	Not found	Not found	>95 ^{5,37}
With pharmaceutical pre-oxidation	Oxidation (Figure 1. Exp. ②)	nd	3%	7%	0%	10%	8 %	36%
	MBR_2 (Figure 1. Exp. ③)	nd	45 ± 13 %	< 0 %	44 ± 9 %	74 ± 10 %	84 ± 2 %	97 ± 5 %
	Oxidation + MBR_2 (Figure 1. Exp. ② + ③)	nd	47%	3%	44%	79%	85 %	98%

Figure 1. Experiments of this study (on the left) to demonstrate the feasibility of an innovative hybrid process coupling a MBR and a photocatalytic oxidation process (on the right) for an efficient removal of pharmaceutical micropollutants. OMP = organic micropollutants; OMP_{ox} = oxidized micropollutants; Q = flow rate; IN = inlet; OUT = outlet; OX = oxidized



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3 1 **Figure 2.** Scheme of the photoreactor consisting of a window (4) and a UV panel (5). The flow rate is
4 2 controlled by a peristaltic pump (1). A centrifugal pump (3) allows to feed the loop of recirculation
5 3 (2).

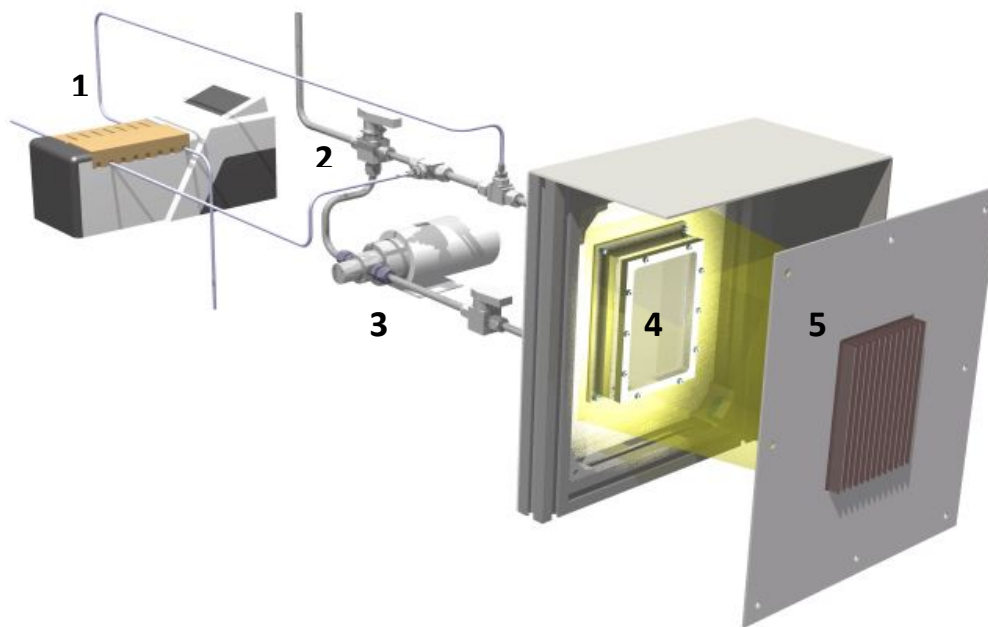


Figure 3: Scheme of the continuous 20-L membrane bioreactor (MBR). Experiments were carried out in two phases: during the first phase (phase I) the MBR was fed only with synthetic wastewater without micropollutant and during the second one (phase II) a cocktail of micropollutants was added together with the synthetic wastewater.

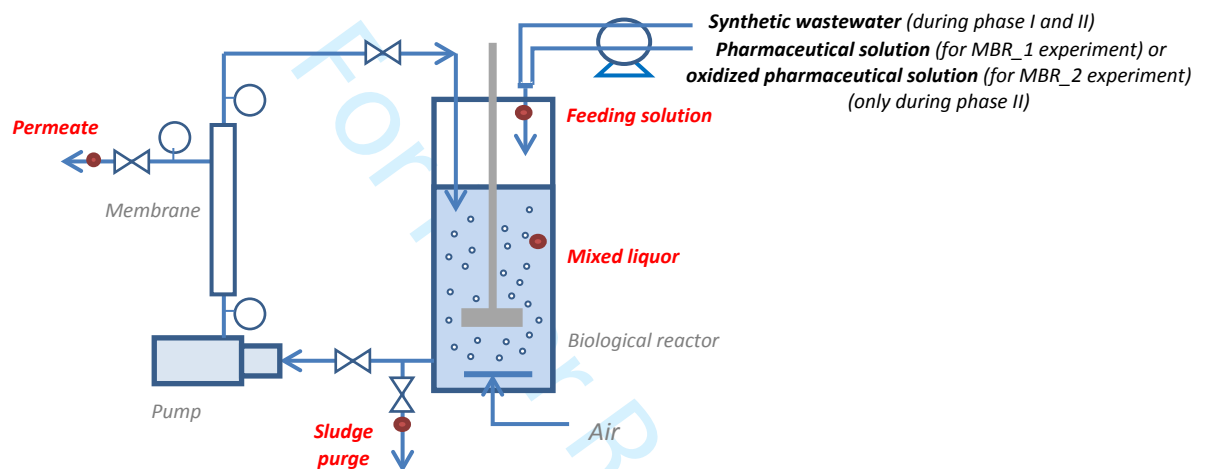
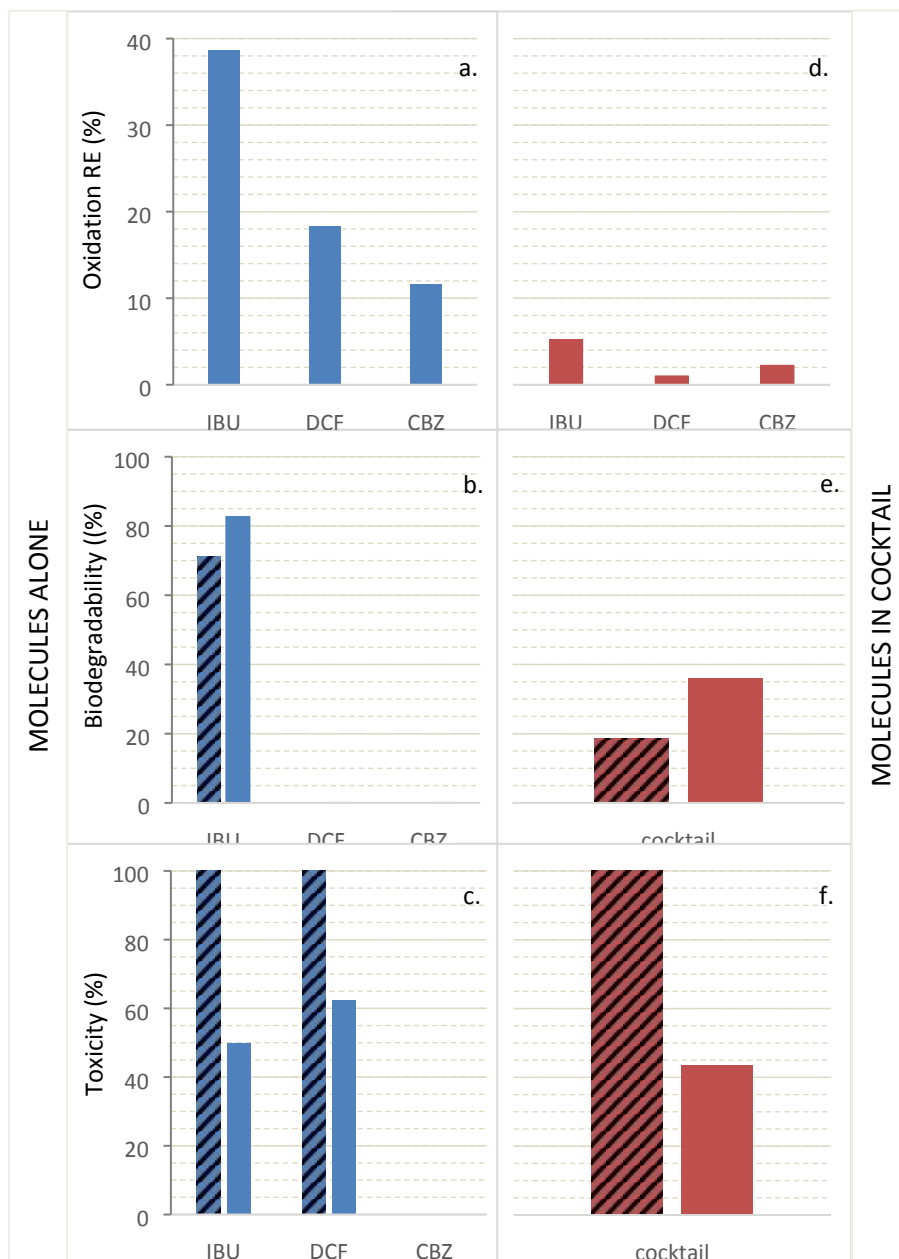


Figure 4. Photo-oxidation removal efficiency (RE), biodegradability and toxicity for IBU, DCF and CBZ alone (left) or in cocktail (right) at 10 mg.L⁻¹ (▨ before oxidation; ■ after oxidation at I = 10 W.m⁻²)



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1 **Figure 5:** Effect of flux density (I) on photo-oxidation removal efficiency of IBU (◆), DCF (■) and CBZ (▲), biodegradability (○) and toxicity (×) of a cocktail solution of IBU, CBZ and DCF at 10 mg.L⁻¹ each

