Comprehensive Evaluation of Non-Catalytic Wet Air Oxidation as a Pretreatment to Remove Pharmaceuticals from Hospital Effluents

*Valérie Boucher [a], Margot Beaudon [a], Pedro Ramirez [b], Pascal Lemoine [b], Kalyssa Volk [c], Viviane Yargeau [c], Pedro A. Segura [a, *]*

[a] Department of Chemistry, Université de Sherbrooke, Sherbrooke, Canada

[b] Centre de transfert technologique en écologie industrielle (CTTÉI), Sorel-Tracy, Canada

(CTTÉI), Sorel-Tracy, Canada

[c] Department of Chemical Engineering, McGill University, Montréal, Canada

KEYWORDS

advanced oxidation processes; micropollutant; emerging pollutants; techno-economic analysis; toxicity; bioassays

The final version of this paper was published in *Environmental Science: Water Research & Technology:*

Boucher V., Beaudon M., Ramirez P., Lemoine P., Volk K., Yargeau V., Segura P. A. (2021) Comprehensive Evaluation of Non-Catalytic Wet Air Oxidation as a Pretreatment to Remove Pharmaceuticals from Hospital Effluents. *Environmental Science: Water Research & Technology*. doi: 10.1039/D1EW00203A

ABSTRACT

Removal of pharmaceuticals from wastewater using chemical processes is a promising solution to mitigate pollution in drinking and surface waters. Non-catalytic wet air oxidation (WAO) is a highly efficient advanced oxidation process that uses air and water at high temperatures and pressures to remove high concentrations of organic compounds from various wastes without use of catalysts. However, the elimination of pharmaceuticals in hospital wastewater with a low organic content by WAO has not yet been sufficiently studied. The objective of the present study was to evaluate both the efficiency and costs of WAO treatment to remove pharmaceuticals present in hospital effluents. First, a laboratory-scale WAO batch unit was used to optimize oxidation temperatures and residence times to achieve high elimination of ten pharmaceuticals of interest in spiked deionized water. Then, optimal conditions were applied to treat hospital wastewater effluents. Results showed that even at low chemical oxygen demand values (< 600 mg O_2 L^{-1}), WAO at 290 °C with 15 min residence time removed between 95.0 % and 99.1 % of the target compounds spiked at 10 µg L^{-1} in hospital wastewater. Acute toxicity bioassays using the crustacean *Daphnia magna* and the bacterium *Aliivibrio fischeri* showed that the toxicity of hospital wastewater increased after WAO treatment due to the generation of transformation products. However, since the intended use of WAO is as pretreatment for hospital effluents before municipal water treatment, it is not yet clear if WAO treated effluents could affect bacteria in activated sludge. The study included a techno-economic analysis to evaluate capital expenditures (CAPEX) and operational expenditures (OPEX) of an industrial-scale WAO unit to remove pharmaceuticals from the wastewater effluent of a local hospital. This analysis demonstrated that CAPEX for an 86 L min^{-1} WAO industrial-scale unit was $ 2.35 M (in Canadian dollars), while OPEX was $ 1.09 M, which corresponds to a relative price of $ 27 per m^3. Initial investment for the WAO unit might be reduced by up to 44 % by employing a preconcentration unit to increase the effluents' chemical oxygen demand in smaller volumes which could also make the process autothermal while reducing WAO's operating expenses by more than 20%.

1. Introduction

Over the past few decades, the occurrence of pharmaceuticals in the aquatic environment has been an increasing cause for concern. A growing number of studies have shown that these micropollutants may have adverse effects on aquatic biota[1-5], microbiota[6] and possibly on human health [4, 7 8]. Another reason to be concerned by pharmaceuticals is that the presence of antibiotics in water bodies, even at low concentrations, could contribute to the dissemination of antibiotic resistance in the environment [6, 9-11].

Pharmaceutical consumption has increased in the last decades because of diverse factors such as aging and increase of the population, changes in clinical practices, discovery of new pharmaceuticals, etc. [12]. For example, between 2000 and 2015, the Organisation for Economic Co-operation and Development (OECD) countries almost quadrupled their consumption of cholesterol-lowering drugs and nearly doubled their consumption of antihypertensives, antidiabetic, and antidepressant drugs [13]. Thus, several drugs that may present adverse effects for the environment are used more and more frequently. For those reasons, the European Union, the United States, the United Kingdom, and Canada have applied environmental risk assessments to human pharmaceuticals or issued recommendations in order to protect the environment from the potential deleterious effects of these compounds [14, 15].

Pharmaceuticals enter the aquatic environment principally via municipal wastewater as they are primarily excreted via urine and feces, either unchanged or as metabolites [16]. Hospitals are considered a major contributor to this problem and indeed, Oliveira*, et al.* [17] reported that their contribution to the content in pharmaceuticals and personal care products of municipal wastewater can be as high as 59 %. In many cases, hospital effluents have higher concentrations of pharmaceuticals than municipal wastewater [18], and they are also known to be an important source of antibiotics and antibiotic resistance genes in the environment [19, 20]. Therefore, hospital effluents can contribute significantly to the occurrence of pharmaceuticals in sewage. For instance, a study in Italy showed that, in average, between 11 % to 67 % of the concentrations of 16 pharmaceuticals found in a municipal influent of a city with a population of 120000 came from the effluents of one hospital with 900 beds [21]. Depending on the size of the hospital and the composition of its effluents, treating hospital wastewater before they reach wastewater treatment plants seems a viable option to reduce inputs of pharmaceuticals in the aquatic environment [21]. Also, adding an on-site hospital wastewater treatment could be beneficial in slowing down the development of antibiotic resistance in microorganisms. Such treatment could be beneficial for both the environment and society where, in OECD countries, an additional US$10000 to 40000 is spent by hospitals to treat a patient infected by antibiotic-resistant microorganisms [13].

To enhance the removal of pharmaceuticals during wastewater treatment, several tertiary treatments have been proposed, such as advanced oxidation processes (AOP) [22]. Unlike secondary treatment processes, AOP remove organic contaminants by oxidation through the generation of hydroxyl radicals (•OH), which are strong oxidants known to be effective against a wide range of organic pollutants [22]. Among the diverse AOP used for removing pharmaceuticals from wastewater, wet air oxidation (WAO) remains one of the least studied up to date.

WAO uses water near but below the critical point of water (374 °C and 218 atm) combined with an oxidant, usually air, to oxidize organic compounds. In these conditions, organic compounds are

broken down into smaller structures by a series of oxidation reactions set out by the presence of dissolved oxygen [23]. WAO is effective to degrade organic compounds and removal rates often above 99 % have been reported for diverse contaminants such as benzene and xylene [23], polycyclic aromatic hydrocarbons, chlorinated solvents, chlorophenols, and malathion [24]. WAO is also considered a green process because there are no emissions of NO_x, SO_2, HCl, dioxins or furans [23, 25] and unlike other AOP it does not require addition of hazardous and costly reagents such as peroxide or ozone [25].

Mineralization of organic compounds is not practically achievable by WAO as the main oxidation product formed, acetic acid, is refractory to further oxidation [25, 26]. This water treatment process is suitable for effluents heavily loaded with organic matter, more precisely for effluents that are too diluted to be incinerated but too concentrated and toxic for biological treatment [25, 27]. For those reasons, WAO is used as a pretreament to improve biodegradability of toxic effluents [25]. Moreover, WAO tends to become autothermal as this highly exothermic process requires little external energy input for chemical oxygen demand (COD) values above 20000 mg O_2 L^{-1} [28]. In that regard, WAO is an interesting alternative to incineration which might require a high energy-consuming dehydration stage.

In the past years, a considerable amount of research has focused on catalytic wet air oxidation (CWAO) to reduce energy demands in the WAO process [29]. However, some catalysts used in CWAO can be costly, e.g., noble metals such as iridium, platinum and ruthenium. Additionally, these catalysts are also easily poisoned by matrix components which makes them inadequate for industrial-scale applications [29]. Non-noble catalysts have been developed for CWAO (e.g., oxides of copper, cesium, manganese and titanium) but they often suffer from instability issues and leach from reactors [25]. More studies on non-catalytic WAO for the removal of pharmaceuticals are needed since its performance as pretreatment for wastewater effluents with low COD, such as hospital waters, remains yet unknown. Previous studies have analyzed the performance of WAO or CWAO for the treatment of pharmaceutical industry wastewater [23, 30, 31] but the removal of pharmaceutical compounds in hospital wastewater by WAO has not yet been studied. Moreover, comprehensive evaluations of pharmaceutical removal from wastewaters taking into account performance and costs [32, 33] as well as toxicity [34], for others AOP has been published in the last years but none has been reported for WAO.

For those reasons, the objective of the present work was to determine if non-catalytic WAO could be applied efficiently and economically as a pretreatment to eliminate pharmaceuticals from hospital effluents before being sent to the municipal sewer system. To accomplish these aims, a series of tests with a batch WAO reactor without adding catalysts was conducted to find the optimal oxidation temperature and residence time for a quasi-total elimination of 10 target pharmaceutical compounds in both spike deionized water and hospital wastewater. These experimental results allowed then the calibration of the CAPEX-OPEX estimation model for a proposed industrial-scale unit under optimal reaction conditions. Additionally, bioassays were performed to consider potential changes in toxicity of hospital wastewaters. This study thus represents a complete evaluation of WAO for hospital wastewater treatment.

2. Materials and methods

2.1 Chemicals and reagents

All pharmaceuticals (acetaminophen, gabapentin, quetiapine, pregabalin, carbamazepine, diclofenac, sulfamethoxazole, trimethoprim, cetirizine and baclofen) were purchased from Sigma-Aldrich Canada (Oakville, ON). Methanol (MeOH), acetonitrile (ACN), water and formic acid were Optima LC/MS grade and were obtained from Fisher Canada (Ottawa, ON).

Stock solutions of each pharmaceutical were prepared in MeOH or water at 1000 mg L^{-1}. Stock solutions prepared in water or MeOH were stored, respectively, at 4 °C and -20 °C. The solutions were renewed at least every six months.

2.2 Selection of target pharmaceuticals

The hospital selected for this study is located in the province of Québec, Canada. It has 166 beds and serves a population of about 51000. To identify which pharmaceuticals should be targeted for WAO removal studies, a risk quotient was calculated for the most consumed compounds according to the hospital's inventory. Since the risk of a compound is determined by both exposure and hazard, the risk coefficient used here includes ecotoxicological and hospital pharmaceutical consumption data.

To evaluate potential exposure, the mass of pharmaceuticals (in kg) rejected in wastewater was calculated using pharmaceutical consumption data for a 9-month period (March 5 to December 9, 2017) obtained from the hospital. The information received contained the number of units and mass of the active ingredients for each pharmaceutical in the hospital's inventory. Percentages of pharmaceuticals excreted unchanged, found in DrugBank [35] or product monographs, were used to estimate the mass of each pharmaceutical discharged in the hospital effluents. Finally, concentrations of pharmaceuticals in the hospital effluents were calculated using an average daily water consumption per bed (420.8 L) in Québec [36].

To determine hazard for each compound, median lethal concentration (LC_{50}) data (in mg L^{-1}) for *Daphnia magna* after 48 h of exposure were obtained using the Ecological Structure Activity Relationships (ECOSAR) Predictive Model, a free software maintained and developed by the United States Environmental Protection Agency [37]. In a recent benchmarking study of five predictive models used for estimating aquatic toxicity of organic chemicals, ECOSAR ranked second, with an accuracy of 61%. Its main advantages over the top ranked model were ease of use, free access and speed [38].

Equation 1 below describes how the risk quotient was calculated:

$$Risk\ quotient = \frac{Estimated\ concentration\ of\ pharmaceutical\ in\ hospital\ effluent}{LC_{50}\ Daphnia\ magna\ 48h} \quad \text{(Eq.1)}$$

2.3 Sampling and preparation of hospital wastewater for quantification of target pharmaceuticals

Samples of hospital effluents were collected at a discharge point from the hospital to municipal sewers on three different dates (February 8, June 26, and June 27, 2019). First, suspended particles in wastewater samples were removed using 1.2 µm pore size hydrophilic glass fibre filters and then 0.45 µm pore size hydrophilic mixed cellulose ester membrane filters both made by MilliporeSigma (Burlington, MA). Then, the pH of samples was adjusted to 6.5 with NaOH 0.1 N or HCl 0.1 N and disodium ethylenediaminetetraacetate dihydrate (200 mg L^{-1}) was added to improve extraction recoveries. Samples were divided in 6 subsamples of 200 mL each and the target analytes were spiked into the subsamples at different concentrations (0, 25, 50 and 75 µg L^{-1}) according to the standard additions method. Next, the subsamples were extracted by solid-phase extraction. The cartridges used were Strata-X-CW polymeric weak cation exchangers (Phenomenex) with a particle size of 33 µm, a sorbent mass of 200 mg and a cartridge volume of 6 mL. Before extraction, cartridges were conditioned by adding successively 5 mL of ACN-MeOH (1:1 *v/v*) and then 5 mL of water at pH 6.5. After loading the subsamples, cartridges were washed with 2×5 mL of water at pH 6.5. If analysis could not be done the same day, cartridges were dried, wrapped in aluminum foil and stored at -20 °C until analysis. Elution was performed with 2×2.5 mL 5% NH_4OH in ACN-MeOH (1:1, v/v). Eluates were evaporated under a gentle nitrogen flow and then reconstituted to 400 µL with H_2O-MeOH (92:8 *v/v*) prior to analysis by liquid chromatography-triple quadrupole mass spectrometry (LC-QqQMS).

2.4 WAO tests with spiked deionized water samples

WAO experiments with spiked deionized water samples were performed in a batch reactor model Cellule 2646 1000 made by TOP Industrie (Vaux-le-Pénil, France). The reactor has a volume of 150 mL and can withstand pressures and temperatures of up to 300 bar and 350°C, respectively. For each test, a fixed volume of spiked water is added to the reactor, then air is purged with nitrogen to create an inert atmosphere. The heating system is then set at the desired temperature and once this value is reached, a fixed amount of air (compressed to 140 bar) is injected to initiate the oxidation process. A diagram of the reactor is shown in Figure 1.

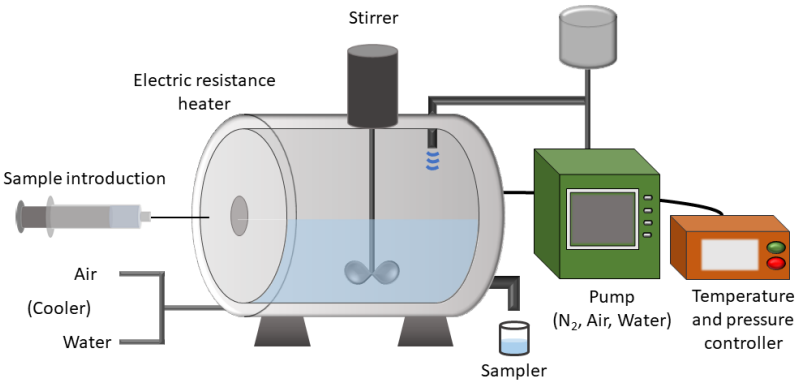

Figure 1. Diagram of the WAO setup used in this study.

This study performed nine different tests to optimize WAO operating conditions, first, a temperature range test where samples were taken at eight different temperatures between 100 °C and 300 °C and then, three tests at 200 °C, 250 °C and 300 °C where samples were taken at eight different times between 5 min and 60 min of residence time. Finally, three tests at 27°C 5, 290°C, and 300 °C with 20 min residence time and two tests at 260 °C and 275 °C with 30 min residence time were performed. For these optimization tests, initial concentration of each target pharmaceutical was 1500 µg L^{-1}. After completing the tests, samples were refrigerated at 4 °C until analysis by LC-QqQMS to measure the percentage removal of target pharmaceuticals.

2.5 WAO tests with spiked hospital wastewater samples

WAO tests with samples collected on January 27, 2020, were performed with a HA1001 model batch reactor manufactured by TOP Industrie, a slightly different reactor that the one described in the previous section. This reactor has a volume of 530 mL and can withstand higher pressures and temperatures (450 bar and 5000°C, respectively) than the previous reactor. Also, it is more suited for complex matrices such as wastewater since it has a titanium coating which is much more robust and tolerant to corrosion.

For each test, a sample volume of 150 mL was spiked with a concentrated pharmaceutical mixture to have the desired concentration (1500 µg L^{-1} or 10 µg L^{-1}) and then introduced in the reactor; air is purged with nitrogen to create an inert atmosphere. A heating ramp (3 °C min^{-1} beginning at 60 °C) was then applied until reaching the target temperature and right after this, air (compressed to 140 bar) was injected in the reactor to start oxidation. WAO tests were performed at fixed values of temperature and residence times and at the end of the test, samples were collected and then frozen to -20 °C until analysis. Treated samples did not require further preparation and were injected directly into the LC-QqQMS instrument after thawing.

2.6 Analysis by liquid chromatography-triple quadrupole mass spectrometry

Quantification of the target pharmaceuticals was performed by LC-QqQMS. Two instruments were used and most of the samples were quantified using a LC-QqQMS instrument consisting of a Quattro Premier mass spectrometer coupled to an Acquity ultra-performance liquid chromatograph, both manufactured by Waters (Milford, MA). The other LC-QqQMS instrument used was a Xevo TQ-S micro, also manufactured by Waters.

For both LC-QqQMS systems, chromatographic conditions were identical. The column was an Acquity UPLC HSS T3 (2.1×50 mm, 1.8µm) from Waters. The mobile phase was constituted of 0.1% formic acid in H_2O as solvent A and 0.1% formic acid in MeOH as solvent B and its flow rate was 0.5 mL min^{-1}. Wash solvents for the needle and the injection port are 900 µL of eluent A and 300 µL of eluent B. The elution gradient was: at initial time, 3% of solvent B; at 1 min, 3% B; at 13 min, 65% B, at 15 min, 67% B, at 16 min, 100% B; at 20 min, 100% B; at 21 min, 5% B; at 25 min, 5% B. The injection volume was 20 µL in full loop mode.

For both systems LC-QqQMS, mass spectrometry conditions were identical except for multiple reaction monitoring (MRM) transitions (Tables SI-1 and SI-2, Supplementary Information). Ionization was done by electrospray in the positive mode (ESI+). ESI source parameters were: source gas N_2, flow rate 0.5 mL min^{-1}; capillary voltage 1 kV; source temperature 150°C; desolvation temperature 500 °C; cone gas flow 50 L h^{-1}. Analysis was done in the MRM mode. Masslynx software was used for data acquisition and QuanLynx software was used for all the data processing. The mean smoothing method was used for integration of MRM peaks. Method performance and quality control information are found in the Supplementary Information (Tables SI-3, SI-4, and SI-5 as well as Section SI-1.2)

2.7 Toxicity bioassays

Two bioassays, the first based on immobilization of the crustacean *Daphnia magna* after 48 h of exposure and the second on the inhibition of bioluminescence of the bacterium *Aliivibrio fischeri* after 5 min of exposure were carried out to measure changes in sample toxicity before and after various levels of WAO treatment.

The acute immobilization bioassay using *D. magna* was based on the OECD Guideline 202 [39] and it was carried employing the Daphtoxkit F magna microbiotest from EBPI (Burlington, ON). In this microbiotest, neonates are obtained from ephippia instead of stock cultures. Median effective concentrations (EC_{50}) are determined by fitting the percentage of immobilized daphnids after 48 h as a function of the volume percentage of the test sample with a dose-response model. Additional details on the protocol are found in the Supplementary Information (Section SI-1.3)

The *A. fischeri* acute bioluminescence inhibition bioassay was performed using the ISO 11348-1:2007 method as a basis and following the testing procedures provided with the testing kit. Briefly, acute toxicity was measured with a testing kit purchased from EBPI containing all necessary solutions and reagents to perform the assay. Toxicity was determined by the decrease in bioluminescence from *A. fischeri* and was measured by the Microtox M500 analyzer (Strategic Diagnostics Inc.) in light intensity. The light intensity values used to determine 20% effective concentrations (EC_{20}) were measured after 5 minutes of incubation time. Toxicity results are presented as volume percentage of the sample required to cause an effect in 20% of the luminescent bacteria. Additional details on the protocol are found in the Supplementary Information (Section SI-1.4).

2.8 Techno-economic analysis

The techno-economic analysis was based on an industrial WAO system for the treatment of hospital waters by using a semi-theoretical methodology developed by the Centre de transfert technologique en écologie industrielle (CTTÉI) [40]. This methodology uses experimental results of COD and elimination of pharmaceuticals in a batch reactor to estimate a plausible reaction performance at industrial scale in continuous mode. Then, a process flow diagram is generated

with Prosim version 3.6, a process simulation software developed by ProSim Inc. (Labège, France). The related process simulation is calibrated with the estimated performance. Then, the mass and energy balances calculated with the simulation results feed the capital expenditures (CAPEX) and operational expenditures (OPEX) models allowing a first economic assessment of the process. It is worth noting that this is an early-study assessment with a great price deviation that can only be narrowed with further detailed engineering studies. Figure 2 shows the process flow diagram of the proposed WAO process for pharmaceutical degradation in Prosim.

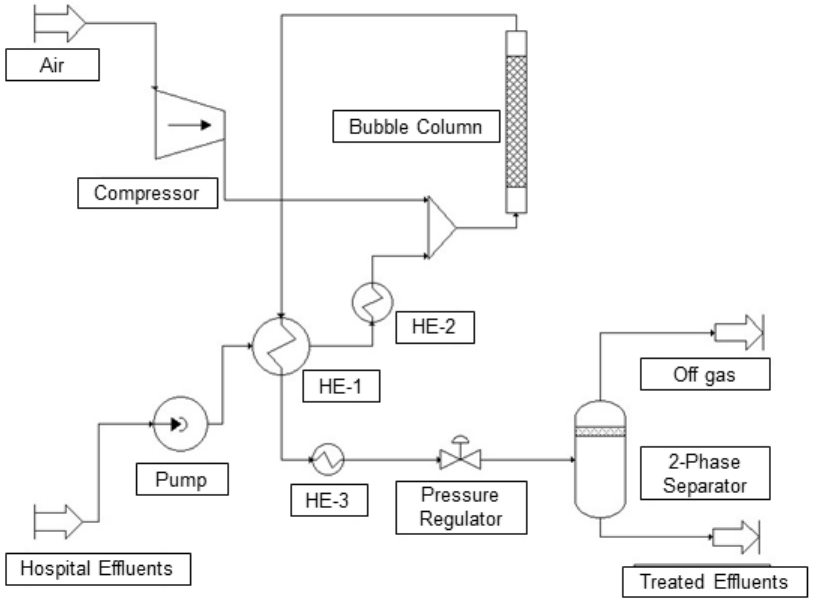

Figure 2. Process flow diagram for removal of pharmaceuticals in hospital wastewater using a continuous WAO reactor.

First, a liquid pump increases the pressure of the hospital water stream to approximately 90 bar, avoiding excessive vaporization inside the reactor. Then, HE-1, a tube and shell exchanger that uses the heat released by the exothermic reaction, increases the temperature of the liquid stream to 265 °C. HE-2, an exchanger that uses either electrical power or natural gas, provides the additional heating requirement to obtain a stream at 290°C and 90 bar, which are the optimal temperature and pressure settings for this specific WAO process. Simultaneously, a compressor allows the injection of air at the bottom of the bubble column reactor while ensuring a bubble regime flow with a uniform distribution of oxygen through the liquid phase [31]. The process simulation model considers a moderate factor of 1.1 for the excess of air, an assumption to be validated through pilot testing in a further project stage. Next, the treated water stream flows from the top of the column to HE-1 to heat the inlet liquid stream. After then, HE-3, an exchanger such as a vapour-compression refrigeration device, decreases the temperature of the treated water stream below 50°C followed by a pressure regulator that allows to stock the treated water and air mixture inside an atmospheric separator. Finally, the offgas is released to the atmosphere while the treated water stream is sent to the municipal wastewater station for further treatment.

The experimental plan included eight preliminary kinetic tests with several residence times at a temperature of 290 °C according to optimization results. The assumptions for the process simulation and the CAPEX-OPEX model are presented in Table 1 and 2. These assumptions were based on local data and the optimization of the WAO process using the lab-scale batch units described previously. Costs of materials and labour were estimated with Prosim's Economic Evaluation Tool which includes theoretical equations for the price of equipment. In addition, the parameters of that module were adjusted according to data from WAO equipment manufacturers.

Table 1. Process simulation assumptions for the estimation of the CAPEX-OPEX for the removal of pharmaceuticals in hospital wastewater by WAO.

Parameters	Assumption	Comments
Flow rate	86 L min^{-1}	In the province of Quebec, the water consumption per hospital is estimated between 420.8 and 4665.8 L day^{-1} per bed [36]. The value used in the model corresponds to the lower range of expected flow rate for a local hospital with 166 beds.
Total COD in hospital waters	1400 mg O_2 L^{-1}	Maximum COD value for typical hospital effluents according to literature [41, 42]
Total pharmaceutical concentration	150 µg L^{-1}	Assuming a conservative value of about 15 µg L^{-1} for each of the ten target pharmaceuticals. Such value is conservative considering that concentrations higher than 50 µg L^{-1} have been detected in hospital effluents for single pharmaceutical [17].
Excess air factor	1.10	Presumption of satisfactory performance of an industrial bubble column with this excess factor; to be validated with pilot testing.
Reaction conditions (Temperature and residence time)	290 °C and 15 min	Optimal conditions for temperature and residence time obtained from the results of WAO experiments described in the present study.
Operating pressure	87 bar	Pressure capable of limiting the vapour fraction in the column to 5 %.
Organic load reduction	80% - 100%	According to COD reduction and removal of pharmaceuticals observed in the present study.
Model molecules	Glucose and acetaminophen	Glucose was chosen to model the organic load and acetaminophen for the pharmaceutical content given their availability in the software's thermodynamic database.
Thermodynamic model	Non-random two-liquid (NRTL)	Accurate model for non-ideal liquid mixtures [43].

Table 2. CAPEX-OPEX assumptions for the removal of pharmaceuticals in hospital wastewater by WAO. Currency is in Canadian dollars (CA$).

Parameters	Assumption	Comments
Methodology	Functional modules +/- 50 %	Preliminary price estimates (order of magnitude) from early studies and without engineering drawings.
Operating time	7920 h per year	24 h per day - 330 days per year - 35 days for maintenance.
Project life	15 years	To estimate the depreciation cost.
Exchange rate	1.5 CA$ per EUR	Currency conversion needed as available price models are in euros.
Power fees	CAD 0.05 per kWh	Local power utility fee for industries.
Natural gas fees	CAD 0.25 per m^3	Average market price of natural gas in Québec taken from a 2019 market survey.
Labour	Technician: CA$ 40 per h Engineer: CA$ 70 per h	Labour fees taken from a 2019 market survey from CTTÉI. This study considers three technicians at 1/3 of the time and one engineer at ¼ of the time.
Materials	Conventional steel (low pressure and clean fluids). Stainless steel (high pressure and dirty fluids). No corrosion resistance required due to low chloride content in tested samples.	
Other data	Duty free: no importation costs included. Estimates for a temporary (early) civil construction.	

3. Results and discussion

3.1 Selection of compounds

The consumption list of pharmaceuticals from the selected local hospital initially contained 70 different compounds for a total of 170.71 kg consumed between March 5 to December 9, 2017 (Table SI-6, Supplementary Information). From this list, metabolization percentages were used to estimate the amount of each pharmaceutical present in the hospital effluents. After that, only the top 25 compounds were considered, since the other compounds represented less than 1 % of the total mass discharged by the hospital. Estimated concentrations of excreted pharmaceuticals in the effluents (Table SI-7 Supplementary Information) were then divided by the median lethal concentrations (LC_{50}) for *Daphnia magna* to determine risk quotients with Eq. 1 (Table 3). Unfortunately, some compounds were eliminated from the risk coefficient list due to technical reasons. For example, phenytoin and metformin, which were ranked among the top 25 compounds with high-risk quotients, were rejected due to inadequate LC-QqQMS method validation for these compounds. Some compounds were also removed for lack of metabolism or ecotoxicological data, e.g., docusate. Finally, four compounds (carbamazepine, diclofenac, sulfamethoxazole and trimethoprim) were added to the list in order to compare the results with previous studies on elimination of pharmaceuticals by other AOP. The ten compounds selected are presented in Table 3.

Table 3. Target pharmaceuticals selected according to their risk quotient. Carbamazepine, diclofenac, sulfamethoxazole and trimethoprim were added for comparison purposes.

Pharmaceutical	Type	Consumed mass (kg)	Excreted mass (kg)	LC_{50} [a] (mg L^{-1})	Risk Quotient ($\times 10^{-6}$)
Acetaminophen	Analgesic	105.22	3.16	63.3	2600
Baclofen	Muscle relaxant	0.045	0.04	5070	0.39
Carbamazepine	Anticonvulsant	N.A.	N.A.	14.1	N.A.
Cetirizine	Antihistaminic	0.039	0.02	3410	0.36
Diclofenac	Anti-inflammatory	N.A.	N.A.	25.8	N.A.
Gabapentin	Antiepileptic	1.84	1.84	4340	22
Pregabalin	Analgesic	1.48	1.45	7200	11
Quetiapine	Antipsychotic	1.70	0.08	9.49	470
Sulfamethoxazole	Antibiotic	N.A.	N.A.	6.43	N.A.
Trimethoprim	Antibiotic	N.A.	N.A.	6.38	N.A.

[a] Values predicted by ECOSAR software. N.A.: Not available.

3.2 Quantification of target pharmaceuticals in hospital wastewater

Results of the quantification of target pharmaceuticals in hospital effluents are shown in Figure 2. Only five out of the ten selected compounds were present at least one of the three collected samples. Baclofen, carbamazepine, gabapentin and pregabalin were not quantified in any samples, even if their limits of quantification (LOQ) were relatively low, 5.4 ng L^{-1}, 1.7 ng L^{-1}, 6.4 ng L^{-1}, and 26 ng L^{-1}, respectively (Table SI-4). Unfortunately, acetaminophen could not be quantified in the samples using the standard additions method. The concentration of the target pharmaceuticals varied substantially between both compounds and sampling times. For example, quetiapine and sulfamethoxazole were only observed in the sample collected on February 8th. On the other hand, diclofenac was not observed in that sample but was observed on those collected on June 26th and June 27th with a difference of ≈ 48 ng L^{-1} between these two days. As for trimethoprim, it was detected on both February 8th and June 27th samples, but with a difference of ≈ 80 ng L^{-1}. Such high variability in concentration data is in agreement with a previous study on pharmaceuticals in hospital effluents in Italy, showing differences of more than 50 % between summer and winter values for some compounds and less than 5 % for others [25]. Results obtained were also compared to a study of several hospital effluents in the United Kingdom [17] and another study that took place in Italy [21]. In those studies, concentration ranges for diclofenac (3 to 530 ng L^{-1}), trimethoprim (68 to 1800 ng L^{-1}) and quetiapine (10 to 60 ng L^{-1}) were of same order of magnitude as the values reported in Figure 3. However, sulfamethoxazole was about 30 to 300 times more concentrated in United Kingdom study (900 to 6500 ng L^{-1}) compared to the present study. Also gabapentin was detected at concentrations of up to 90780 ng L^{-1}. Such disparities may be explained by pharmaceutical consumption differences, e.g., sulfamethoxazole was not part the hospital's inventory. Water consumption in Québec, the United Kingdom and Italy could also explain the results: Québec water consumption is between 420.8 L day^{-1} and 4665.8 L day^{-1} per bed [36] while in the United Kingdom it is between 530 L day^{-1} and 1138 L day^{-1} and in Europe between 500 L day^{-1} and 1000 L day^{-1} [44]. Finally, its also possible that the sampling point chosen was not representative of the hospital total pharmaceutical use.

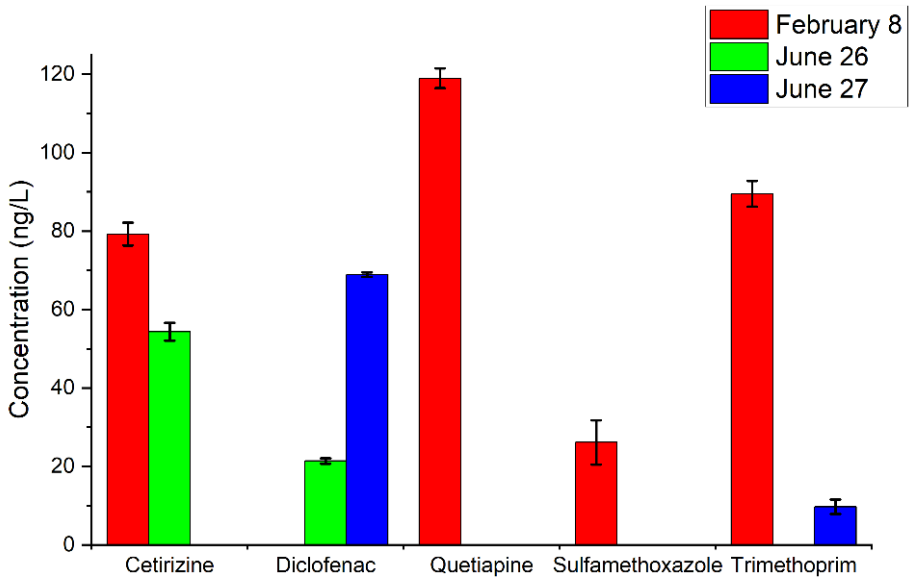

Figure 3. Quantification of the target pharmaceuticals in hospital wastewater in three grab samples collected in three different days in 2019 (*n*=1). Length of error bars represents the uncertainty of the concentration determined with the standard additions method [45].

3.3. Optimization of WAO

3.3.1. WAO tests with spiked deionized water

Residence time and oxidation temperature were optimized to achieve maximum percentage removal of the ten target pharmaceuticals by WAO treatment. At first, an exploratory test was conducted to identify an effective oxidation temperature range in a single run (Figure 4). For this test, each compound was spiked at 1500 µg L^{-1} in deionized water. Addition of oxidant (air) was carried out at room temperature and samples were taken at selected temperatures during the heating process. Figure 4 shows that significant removals (> 90%) were observed around 200 °C for acetaminophen, baclofen, diclofenac, gabapentin, and pregabalin. However, removals were < 70 % for carbamazepine, sulfamethoxazole, quetiapine, cetirizine, and trimethoprim. At 300 °C, elimination of at least 90% was achieved for all compounds.

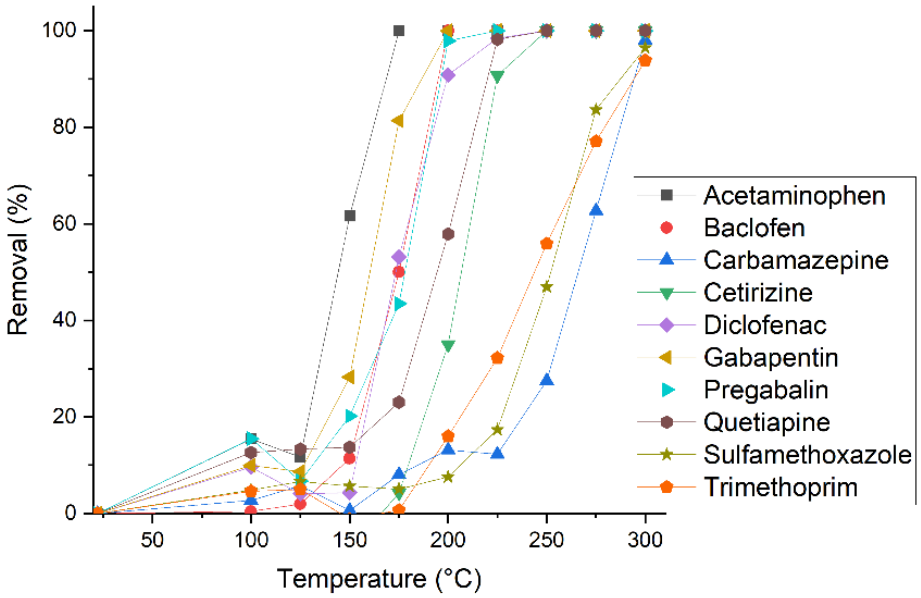

Figure 4. Removal by WAO of the target pharmaceuticals during the exploratory temperature range test (n=1). Compounds were spiked at 1500 µg L^{-1} in deionized water.

Three other trials were performed to evaluate the effect of the residence time (maximum 60 min) on the removal percentage at temperatures between 200 °C and 300 °C. Results are shown in Figure 5. The removal observed at 0 min is not caused by oxidation, since the oxidant (air) is yet to be added, but by thermal decomposition [46] or hydrolysis [28] that could take place during the heating period.

Results in Figure 5 show that carbamazepine, sulfamethoxazole and trimethoprim are more resistant than gabapentin and diclofenac to WAO treatment. At both 200 °C and 250 °C, degradation of carbamazepine, sulfamethoxazole and trimethoprim is < 75%, even after 60 min, while removal of gabapentin and diclofenac is > 80% before addition of oxidant. At 300 °C, almost complete removal (concentrations were < LOQ) for all compounds were observed after only 20 min.

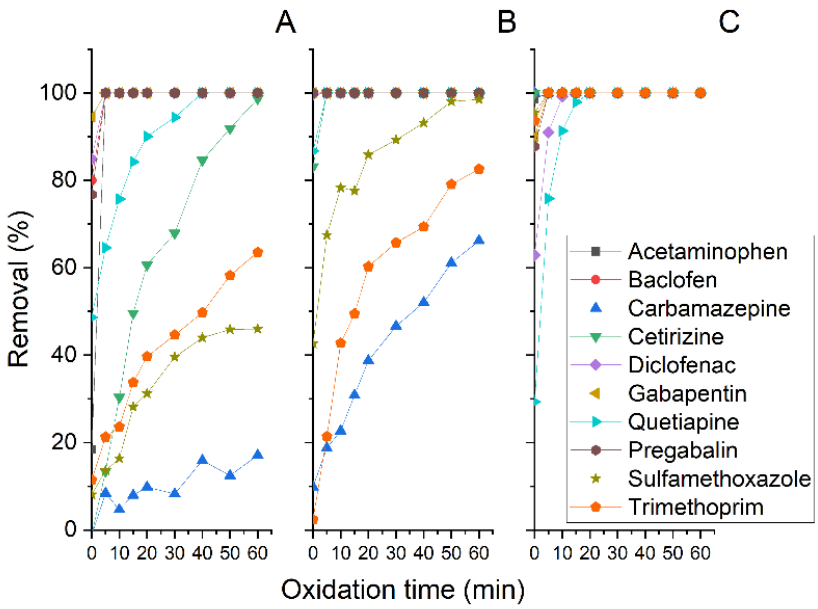

Figure 5. Removal by WAO of target pharmaceuticals spiked at 1500 µg L^{-1} each in deionized water at A: 200°C; B: 250°C and C: 300°C. For each temperature *n*=1.

In an attempt to decrease WAO operating conditions of temperature and residence time, five conditions (275 °C, 290 °C, 300 °C with 20 min residence time; 260 °C, 275 °C with 30 min residence time) were selected. Results in Figure 6A show that removal at 275 °C was relatively low for carbamazepine (76 %) and trimethoprim (68 %); however, results for those two compounds at 290 °C (≥ 93%) were comparable to those obtained at 300 °C (≥ 97%). Figure 6B shows that a longer residence time at 275 °C improved slightly both carbamazepine (86%) and trimethoprim (77%) removal percentages. Therefore, an oxidation temperature of 290 °C and a residence time of 20 min were selected as optimal WAO conditions. It is worth noting that most compounds were degraded with subcritical water (> 260 °C) without oxidant. Nonetheless, WAO seems necessary to ensure the degradation of both resistant compounds (carbamazepine and trimethoprim).

Additionally, we hypothesize that most transformation products may only be removed completely after addition of oxidant. Experiments are under way to test this hypothesis.

Comparison between results of the present study and removal percentages obtained with other AOP demonstrated that WAO gives equivalent or better removals for some of the tested pharmaceuticals [47]. For example, ozonation can remove completely carbamazepine, diclofenac, sulfamethoxazole and trimethoprim from Milli-Q water using ozone doses lower or equal to 4.5 mg L^{-1} [48]. Treatment with UV radiation (540 mJ cm^{-2}) and H_2O_2 (6 mg L^{-1}) of ultrapure water spiked with sulfamethoxazole, trimethoprim and diclofenac removed 91 %, 68 % and 99 % of those compounds, respectively [49]. Ozonation combined with sonolysis (20 kHz) was able to remove spiked diclofenac (94 %), sulfamethoxazole (61 %) and carbamazepine (56 %), from distilled water. However removal efficiencies decreased in mixed solutions containing the three pharmaceuticals [50]. Nevertheless, it is difficult to evaluate the suitability of these AOP methods to

remove pharmaceuticals since information on performance and costs at industrial scales is not often reported.

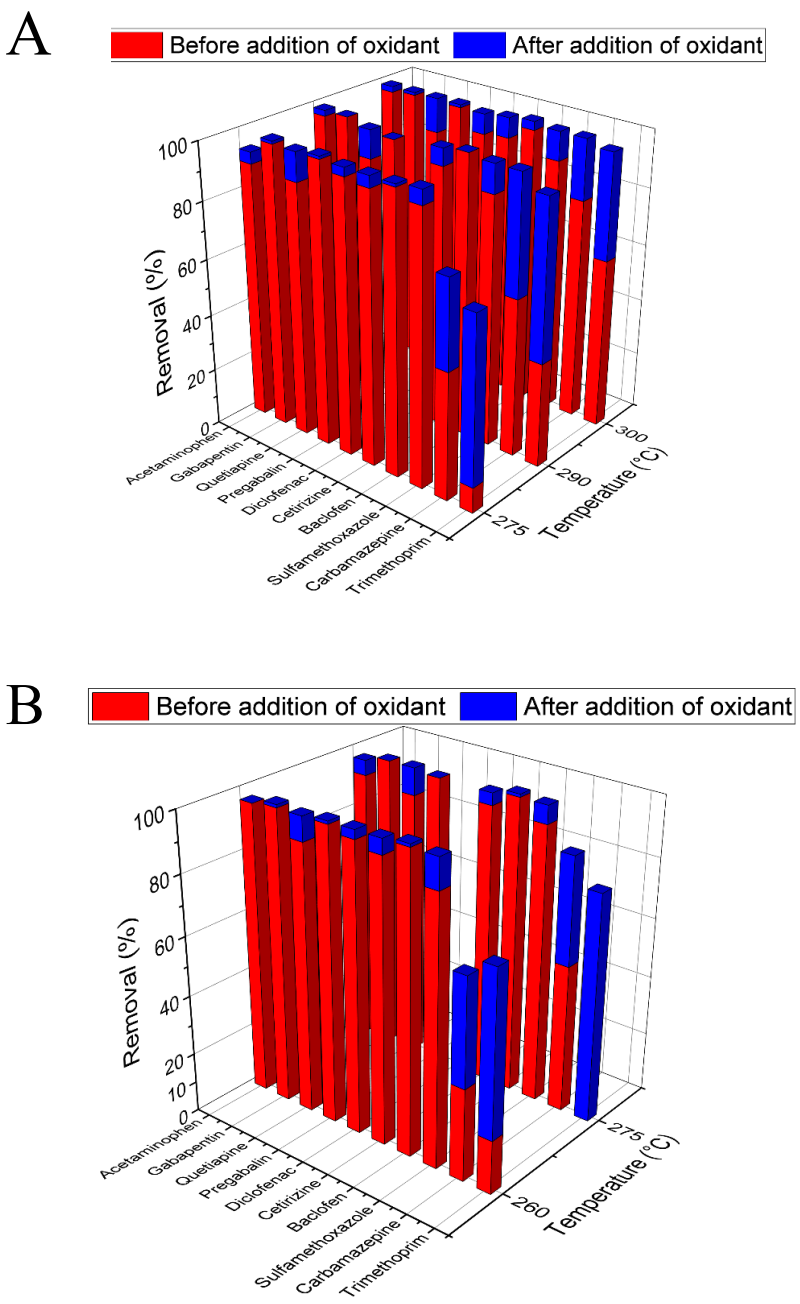

Figure 6. Optimization of WAO temperature at A: 20 min and B: 30 min residence times using a mixture of target pharmaceuticals spiked in deionized water at 1500 µg L^{-1} each. Data for pregabalin at 275 °C did not pass quality control tests and were rejected. For each temperature, n=1.

3.3.2. WAO treatment of spiked hospital effluents

To validate the optimized conditions performance experiments were conducted on real hospital wastewater samples. Based on quantification results of target pharmaceuticals in the hospital effluent (Figure 4), it was decided to spike each compound at 1500 µg L^{-1} (same concentration used for optimization trials) in the sampled wastewater. Tests at 290 °C were carried out with residence times of 20 min (*n*=2) and 15 min (*n*=1), respectively. Table 4 shows that removal percentages obtained with a residence time of 15 min were comparable to those generated with 20 min. Thus, according to those results, the final optimal WAO conditions for target pharmaceuticals removal were a temperature of 290 °C and a residence time of 15 min. The two tests at 20 min also demonstrated that WAO removal reproducibility was high. For all compounds, except trimethoprim, removal differences were less than 3 percentage points.

Table 4. Removal of pharmaceuticals in hospital wastewater by WAO at 290 °C with different conditions in duplicate experiments. Pharmaceuticals were spiked at 1500 µg L^{-1} in all cases except indicated otherwise.

Pharmaceutical	15 min [a] (%)	20 min [a] (%)	High COD [b] (%)	High COD, spiked at 10 µg L^{-1} [b] (%)
Acetaminophen	98.6	98.5; >99.4	99.4; >99.4	95.3; 99.0
Baclofen	99.1	98.8; 99.9	99.5; 99.7	95.2; 99.0
Carbamazepine	92.7	96.9; 99.8	99.6; 99.7	95.0; 99.0
Cetirizine	99.3	99.5; 99.9	99.5; 99.6	95.2; 99.1
Diclofenac	98.8	98.6; 99.9	99.5; 99.8	95.2; 98.9
Gabapentin	98.9	98.8; 99.8	99.5; 99.7	95.2; 99.0
Pregabalin	99.5	99.3; 99.9	99.5; 99.8	95.0; 99.0
Quetiapine	96.0	95.8; 99.4	99.2; 99.6	99.1; 95.2
Sulfamethoxazole	98.8	98.5; 99.9	99.6; 99.6	95.1; 99.0
Trimethoprim	85.9	86.3; 99.9	99.6; 99.6	95.0; 98.9

[a] COD = 573 mg O_2 L^{-1}, [b] COD = 1400 mg O_2 L^{-1}, residence time = 15 min. Note: The 15 min experiment was performed only once.

3.2.3. Effect of initial chemical oxygen demand on removal

According to Boillot*, et al.* [51] COD of a hospital effluent can vary up to about 800% within the same day. Then, to study the possible interference of other organic compounds in pharmaceutical removal in hospital waters by WAO, the test samples were spiked with each compound at 10 µg L^{-1} or 1500 µg L^{-1} and glucose was added to raise the initial COD value to 1400 mg O_2 L^{-1}, a realistic high limit found in hospital effluents [41, 42].

The results in Table 4 show that, except for carbamazepine and trimethoprim, all the pharmaceutical compounds are effectively removed from the hospital wastewater samples regardless the initial COD; in fact, elimination rates lie above 95 % at all conditions of residence time and initial organic and pharmaceutical concentration. However, when analyzing

carbamazepine and trimethoprim results, the results show a slight tendance towards better removal rates at higher initial COD that need to be confirmed by further experimental studies.

3.2.4. Effect of initial pharmaceutical concentration on removal

Pharmaceutical concentrations in hospital wastewater are much lower than 1500 μg L^{-1}. For that reason, hospital wastewater samples were spiked with each compound at a lower concentration of 10 μg L^{-1}, closer to reported values in other hospital effluents [18, 21, 52]. Glucose was also added to raise the initial COD value to 1400 mg L^{-1}. Results of WAO with optimized conditions (Table 4) showed a slight performance decrease in average of 3 percentage points with a lower initial pharmaceutical concentration. Since such difference is close to the observed WAO removal reproducibility, it is possible that the high variability of pharmaceutical concentrations found in hospitals effluents does not influence the WAO treatment performance under similar COD conditions.

3.4. Toxicity bioassays

Toxicity bioassays provide an overview of possible changes in the overall toxicity of hospital wastewater samples due to treatment. In AOP, multiple oxidation products of pharmaceuticals are usually formed [47, 53] and they can be, in some cases, more toxic than the parent compound. For example, ozonation of bezafibrate, diclofenac and fenoprofen generated unknown transformation products that increased the toxicity of the samples towards bioluminescent bacteria[54]. The same effect was observed by Klamerth*, et al.* [55] when removing atrazine, diclofenac, carbamazepine and ketorolac from effluent wastewater by photo-Fenton process; toxicity towards bioluminescent bacteria increased after about 20 min of treatment time. Few studies have successfully identified the transformation products responsible for such increase in toxicity since many compounds are generated simultaneously and synergistic effects could be observed. A study by Dirany*, et al.* [56] found that 3-amino-5-methylisoxazole, p-benzoquinone and possibly short-chain carboxylic acids explained a fraction of the toxicity observed when treating sulfamethoxazole spiked water by electro-Fenton. A paper by Le*, et al.* [57] also identified 2-hydroxy-4-(N-acetyl) aminophenol, 1,4-benzoquinone, benzaldehyde and benzoic acid as toxic oxidation products generated by electro-Fenton treatment of acetaminophen solution. In WAO, if residence times are long enough, small carboxylic acids are usually observed [23]. However no studies have investigated the effect of WAO treatment on the toxicity of deionized water spiked with pharmaceuticals or hospital wastewater samples.

3.4.1 *D. magna* toxicity bioassays

Results of *D. magna* toxicity bioassays (Figure 7, red bars) show, as expected, that untreated samples have low toxicity or no measurable toxicity since target pharmaceuticals predicted acute toxicity at relatively high concentrations (14 to 7200 mg L^{-1}, Table 3). For hospital wastewater, an EC_{50} equal to (72 ± 28) % *v/v* was measured. This value indicates that 72 % *v/v* of that sample

caused the immobilization of half of daphnids exposed to the sample for 48 h. However, after WAO treatment, an increase in toxicity was observed in both types of samples.

For the spiked deionized water samples, after 10 min of WAO treatment, an EC_{50} equal to (18 ± 3) % *v/v* was measured, and a slightly higher toxicity was observed at 25 min of WAO treatment [EC_{50}=(13.0 ± 0.8) % *v/v*]. Such changes in toxicity could be explained by the formation of oxidation products more toxic to *D. magna* than the parent compounds during the WAO treatment. The same effect has already been observed in other types of AOP treatment, as mentioned earlier.

For the hospital wastewater samples, EC_{50} at 48h of exposure increased from (72 ± 28) % *v/v* to (39± 12) % *v/v* after 10 min residence time and did not change significantly up to 25 min of residence time [EC_{50}= (31 ± 11) % *v/v*]. Interestingly, toxicity of treated hospital wastewater was always lower than the toxicity of the spiked deionized water. This suggests that the presence of relatively high concentrations of target pharmaceuticals in the spiked deionized water allowed the generation of high enough concentrations of oxidation products to produce a toxic effect. Hospital wastewater should contain numerous pharmaceuticals but as shown in Figure 3, their concentrations should not be particularly high. Also, other types of organic compounds found in these effluents (e.g., primary metabolites) could be readily oxidable thus forming lesser amounts of toxic oxidation products. Future studies will focus on the nature and origin of these transformation products and their link with the observed toxicity.

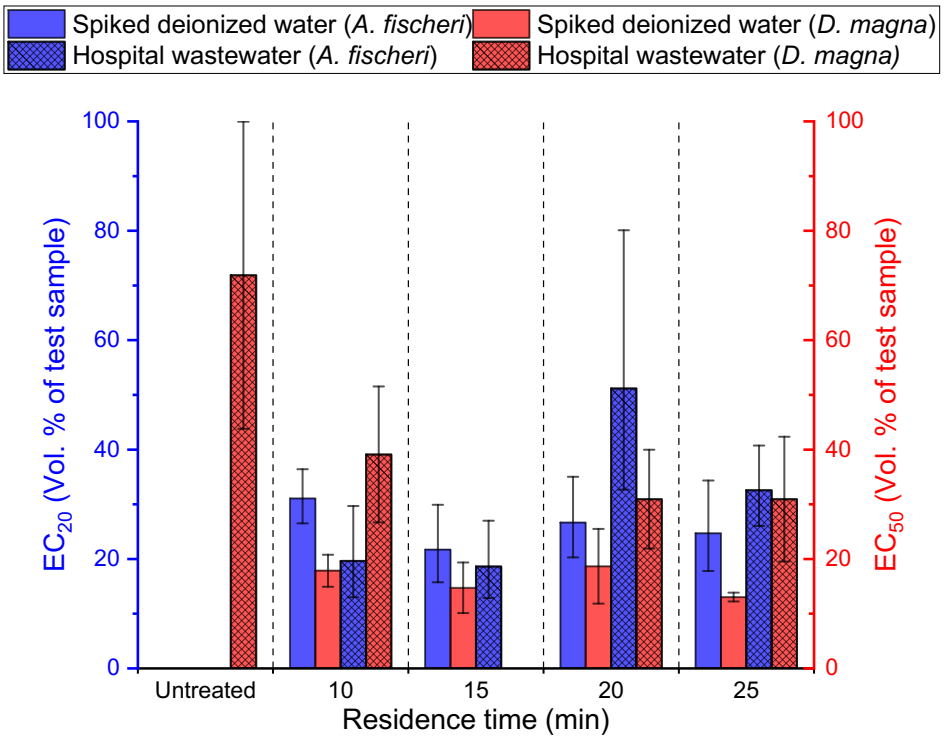

Figure 7. Effect of residence time of spiked deionized water and hospital wastewater on the *D. magna* EC_{50} and the *A. fischeri* EC_{20} measured at 48 h and 5 min, respectively. For both sets of data, length of error bars represents the 95 % confidence interval. For only one sample (hospital wastewater treated for 15 min) the fitting failed and no EC_{50} could be calculated for *D. magna.*

3.4.2 *A. fischeri* toxicity bioassays

To complement the *D. magna* toxicity bioassay, acute toxicity tests were conducted using the bioluminescent bacterium *A. fischeri*. Results of the acute toxicity bioassay (Figure 7, blue bars) showed that both the untreated wastewater and spiked deionized water had no measurable toxicity. The volume percentage value reported for the other samples, represents the percent of the sample required to inhibit the bioluminescence of 20% of the bacteria (EC_{20}). The trends of the measured EC_{20} are similar to the EC_{50} reported for *D. magna*, and further support the formation of toxic transformation products during WAO treatment. For both types of water, the treated samples were more toxic than the untreated ones, but the toxicity does not appear to change significantly with the residence time. A few differences were also observed between the results of both bioassays. The most important was that, unlike the *D. magna* bioassay, the *A. fischeri* bioassay could not generate EC_{50} values. Such outcome can be explained by the sensitivity of both bioassays. It has been reported that the acute bioassay based on *D. magna* is more sensitive than the one based on *A. fischeri* towards organic compounds [58, 59]. In one study it was reported that differences of sensitivity between these two methods can be of a factor of up to 3000 [58].

Nevertheless, while WAO generated toxic oxidation products towards *D. magna* and *A. fischeri*, the intended use of WAO is as a pretreatment for hospital wastewaters, not as a final treatment prior to discharge into the aquatic environment. Considering that the WAO effluent would be sent to a municipal wastewater treatment plants for further treatment, the toxicity towards daphnids is less relevant in that context. It is, however, unknown if the toxicity of the WAO treated waters observed on *A. fischeri*, might suggest possible effect on the bacteria in the activated sludge treatment step. To our knowledge, WAO succeeds in transforming non-biodegradable compounds into compounds more biodegradable by conventional wastewater treatment methods [60]. Therefore, by using WAO as pretreatment for hospital wastewater, the transformation products generated by WAO could be removed by secondary treatment in municipal wastewater plants.

3.5. Techno-economic analysis

3.5.1. Process Simulation

Table 5 summarizes the mass and energy balances for the selected WAO unit based on the assumptions listed in Table 4 and a flow rate of 86 L min^{-1}. A more detailed version of this table is available in the Supplementary Information (Table SI-8).

3.5.2. CAPEX – OPEX

CAPEX-OPEX estimations for an 86 L min^{-1} WAO unit are shown in Table 6. The total CAPEX of the project is CA$ 2.35×10^6 which includes equipment procurement and installation. The annual OPEX is CA$ 1.09×10^6 that corresponds to a relative price of CA$ 27 per m^3. The equipment costs account for almost 46 % of the total initial investment while labour expenses account for 41% of the total operation costs; hence, equipment costs and labour expenses are plausible targets for cost optimization.

Regarding labour, project managers can explore human resources strategies such as personnel reassignment or outsourcing; this lies out of the scope of this work though. On the other hand, equipment costs usually decrease with lower inlet feeds as do OPEX. However, to decrease the inlet flow rate of hospital wastewater, the process setup must include an additional unit that concentrates the total chemical oxygen demand (COD) from the hospital effluent before sending it to the WAO unit such as reverse osmosis or ultrafiltration [61]. Thus, a sensitivity analysis to estimate CAPEX and OPEX for the WAO unit (excluding the required concentration stage) as a function of the inlet flow rate was performed. The definition of a suitable concentration unit and its subsequent pricing remain the subject of further studies.

Table 5. Mass and energy balance for a WAO unit of 86 L min^{-1}

Mass balance		
	Effluent	**Treated effluent**
Total flow (kg h^{-1})	5188	5195
Total flow (L min^{-1})	86	87
COD (mg L^{-1})	1400	280
Acetaminophen concentration (µg L^{-1})	150	≈ 0
Energy balance		
Total electricity consumption (MWh $year^{-1}$)		1049
Heat consumption (GJ $year^{-1}$)		1484
Energy balance (GJ $year^{-1}$)		2533
Proportion electricity/heat (%)		41% / 59%

Table 6. CAPEX-OPEX for a WAO unit of 86 L min^{-1}

Capital Expenditures (CAPEX)	
Item	**Cost (CA$)**
Studies and project management	250 000
Process equipment	1 075 000
Setup and Installation	775 000
Temporary civil works	250 000
Total	2 350 000
Operating Expenditures (OPEX)	
Item	**Cost (CA$)**
Electricity	52 500
Natural gas	35 000
Maintenance	72 500
Labour	450 000
Plant overhead	320 000
Depreciation	160 000
Total expenses	1 090 000
Annual treated volume (m^3)	41 000
OPEX per m^3	27

The results of the sensitivity analysis are illustrated in Figure 7 based on the parameters of the concentration unit indicated in Table SI-9 (Supplementary Information). These results show that CAPEX is about twice as sensitive to inlet flow rates as OPEX for this case of study; for instance, when comparing cases of 86 L min^{-1} and 5 L min^{-1}, CAPEX decreases by 44 % while OPEX decreases only by 20 %. This is explained by the fact that air plays a crucial role in OPEX estimations as the total COD remains unchanged regardless of the concentration factor; therefore, air compression expenses remain the same for all scenarios considered. This sensitivity analysis excluded the CAPEX and OPEX related to the preconcentration unit as those estimations should follow a selection between alternatives such as reverse osmosis or ultrafiltration. However, when considering a moderate concentration factor of 3.5 and thus a flow rate of 25 L min^{-1}, a realistic cost optimization would provide a CAPEX of CA$ 1.77×10^6 and an OPEX of CA$ 9.60×10^5 for the WAO unit, which corresponds to a relative OPEX of CA$ 8 per m^3 (including CAPEX depreciation). This latter value is closer to the OPEX per cubic metre of other AOP treatments that have been proposed previously for similar applications as in the present study such as a membrane biological reactor followed by UV/H_2O_2 treatment (US$ 2.94 per m^3, equivalent to about CA$ 3.61 per m^3)[33]. However, the estimation of CA$ 8 per m^3 for WAO must be validated by future studies on the preconcentration of hospital effluents.

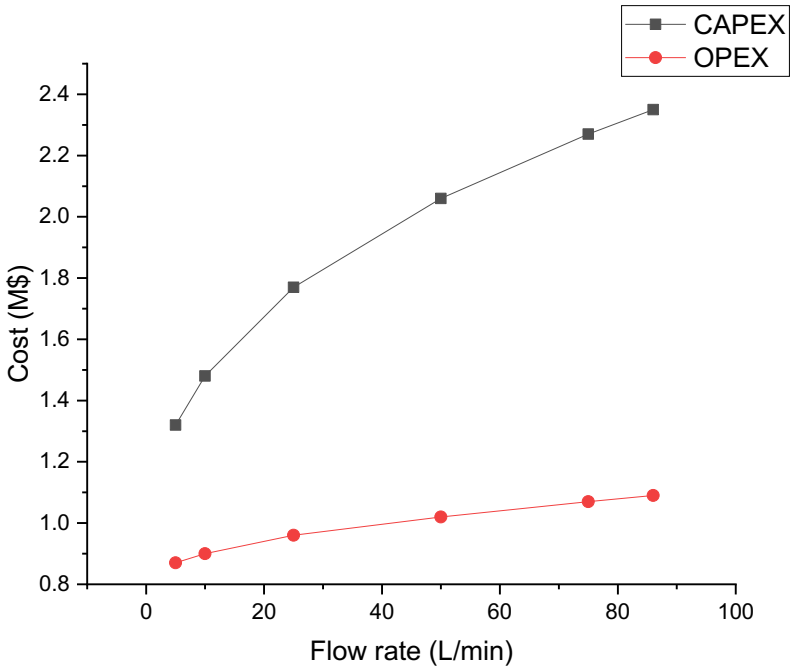

Figure 7. Sensibility analysis of CAPEX – OPEX to the inlet flow rate for the WAO process.

4. Conclusion

Results showed potential for the application of WAO to eliminate pharmaceuticals from hospital wastewater and thus prevent their release into municipal wastewater and minimize their presence

in surface waters. Reduction of environmental loads of these substances is essential to avoid long-term deleterious effects on public health, aquatic ecosystems and water quality. As shown by the techno-economic analysis, WAO demands a high energy consumption leading to high operating expenses; however, this project's sensitivity analysis demonstrated that the CAPEX and OPEX would decrease by using a preconcentration unit since it will reduce the volumetric capacity of the unit as well as decreasing the need for an external energy flow. Moreover, the excess heat that might be released under this alternative approach could contribute to the profitability of operations.

The performed bioassays showed that the toxicity of samples treated by WAO increased with treatment time, suggesting that toxic transformation products were formed. However, in the context of using WAO as a pretreatment to municipal wastewater treatment, this residual toxicity might be removed during treatment at the wastewater treatment plant. The WAO process to remove recalcitrant compounds thus remains a promising approach for pretreatment of hospital wastewater. Future research should focus on coupling a preconcentration unit to WAO to reduce costs, the reduction of toxicity of treated effluents and the identification and quantification of transformation products generated by WAO.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We would like to thank: the Centre Intégré de Santé et de Services sociaux de la Montérégie-Est (CISSSIE) for providing useful pharmaceutical consumption data, the Conseil de recherches en sciences naturelles et en génie du Canada (CRSNG) for their financial help and Synergie Santé Environnement (SSE) for their help in communicating the results and in connecting the collaborators of this project. We also thank Cassandra Guérette for drawing the diagram of the WAO unit (Figure 1).

Credit author statement

Valérie Boucher: Conceptualization, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – Original Draft
Margot Beaudon: Investigation, Writing – Original Draft
Pedro Ramirez: Software, Formal analysis, Writing – Original Draft, Writing – Review & Editing
Pascal Lemoine: Funding Acquisition, Resources, Supervision, Writing – Review & Editing
Kalyssa Volk: Investigation, Writing – Original Draft
Viviane Yargeau: Writing – Review & Editing, Supervision
Pedro A. Segura: Conceptualization, Funding Acquisition, Methodology, Resources, Supervision, Writing – Review & Editing

REFERENCES

1. E. K. Matich, N. G. C. Soria, D. S. Aga and G. E. Atilla-Gokcumen, Applications of metabolomics in assessing ecological effects of emerging contaminants and pollutants on plants, *J. Hazard. Mater.*, 2019, **373**, 527-535.

2. K. Noguera-Oviedo and D. S. Aga, Lessons learned from more than two decades of research on emerging contaminants in the environment, *J. Hazard. Mater.*, 2016, **316**, 242-251.

3. M. Vasquez, A. Lambrianides, M. Schneider, K. Kümmerer and D. Fatta-Kassinos, Environmental side effects of pharmaceutical cocktails: what we know and what we should know, *J. Hazard. Mater.*, 2014, **279**, 169-189.

4. A. Khan, H. Aziz, N. Khan, M. Hasan, S. Ahmed, I. Farooqi, A. Dhingra, V. Vambol, F. Changani and M. Yousefi, Impact, disease outbreak and the eco-hazards associated with pharmaceutical residues: a Critical review, *Int. J. Environ. Sci. Technol.*, 2021, 1-12.

5. Y. Huot, C. A. Brown, G. Potvin, D. Antoniades, H. M. Baulch, B. E. Beisner, S. Bélanger, S. Brazeau, H. Cabana, J. A. Cardille, P. A. del Giorgio, I. Gregory-Eaves, M.-J. Fortin, A. S. Lang, I. Laurion, R. Maranger, Y. Prairie, J. A. Rusak, P. A. Segura, R. Siron, J. P. Smol, R. D. Vinebrooke and D. A. Walsh, The NSERC Canadian Lake Pulse Network: A national assessment of lake health providing science for water management in a changing climate, *Sci. Total Environ.*, 2019, **695**, 133668.

6. I. B. Gomes, J.-Y. Maillard, L. C. Simões and M. Simões, Emerging contaminants affect the microbiome of water systems—strategies for their mitigation, *npj Clean Water*, 2020, **3**, 1-11.

7. E. Touraud, B. Roig, J. P. Sumpter and C. Coetsier, Drug residues and endocrine disruptors in drinking water: risk for humans?, *Int. J. Hyg. Environ. Health*, 2011, **214**, 437-441.

8. G. Kaushik and M. A. Thomas, The potential association of psychoactive pharmaceuticals in the environment with human neurological disorders, *Sustain. Chem. Phar.*, 2019, **13**, 100148.

9. S. A. Kraemer, A. Ramachandran and G. G. Perron, Antibiotic pollution in the environment: from microbial ecology to public policy, *Microorganisms*, 2019, **7**, 180.

10. L. Sandegren, Selection of antibiotic resistance at very low antibiotic concentrations, *Upsala J. Med. Sci.*, 2014, **119**, 103-107.

11. J. Bengtsson-Palme and D. J. Larsson, Concentrations of antibiotics predicted to select for resistant bacteria: proposed limits for environmental regulation, *Environ. Int.*, 2016, **86**, 140-149.

12. T. P. Van Boeckel, S. Gandra, A. Ashok, Q. Caudron, B. T. Grenfell, S. A. Levin and R. Laxminarayan, Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data, *Lancet Infect. Dis.*, 2014, **14**, 742-750.

13. OECD, *Health at a Glance 2017: OECD Indicators*, OECD Publishing, Paris, 2017. Available at: https://www.oecd-ilibrary.org/content/publication/health_glance-2017-en.

14. D. Lee and K. Choi, Comparison of regulatory frameworks of environmental risk assessments for human pharmaceuticals in EU, USA, and Canada, *Sci. Total Environ.*, 2019, **671**, 1026-1035.

15. H. Islas-Flores and L. M. Gómez-Oliván, in *Ecopharmacovigilance: Multidisciplinary Approaches to Environmental Safety of Medicines*, ed. L. M. Gómez-Oliván, Springer International Publishing AG, Cham, Switzerland, 2017, pp. 95-118.

16. C. G. Daughton and I. S. Ruhoy, Environmental footprint of pharmaceuticals: the significance of factors beyond direct excretion to sewers, *Environ. Toxicol. Chem.*, 2009, **28**, 2495-2521.

17. T. S. Oliveira, M. Murphy, N. Mendola, V. Wong, D. Carlson and L. Waring, Characterization of pharmaceuticals and personal care products in hospital effluent and waste water influent/effluent by direct-injection LC-MS-MS, *Sci. Total Environ.*, 2015, **518**, 459-478.

18. L. H. Santos, M. Gros, S. Rodriguez-Mozaz, C. Delerue-Matos, A. Pena, D. Barceló and M. C. B. Montenegro, Contribution of hospital effluents to the load of pharmaceuticals in urban wastewaters: identification of ecologically relevant pharmaceuticals, *Sci. Total Environ.*, 2013, **461**, 302-316.

19. W. P. Rowe, C. Baker-Austin, D. W. Verner-Jeffreys, J. J. Ryan, C. Micallef, D. J. Maskell and G. P. Pearce, Overexpression of antibiotic resistance genes in hospital effluents over time, *J. Antimicrob. Chemother.*, 2017, **72**, 1617-1623.

20. E. Szekeres, A. Baricz, C. M. Chiriac, A. Farkas, O. Opris, M.-L. Soran, A.-S. Andrei, K. Rudi, J. L. Balcázar and N. Dragos, Abundance of antibiotics, antibiotic resistance genes and bacterial community composition in wastewater effluents from different Romanian hospitals, *Environ. Poll.*, 2017, **225**, 304-315.

21. P. Verlicchi, M. Al Aukidy, A. Galletti, M. Petrovic and D. Barceló, Hospital effluent: investigation of the concentrations and distribution of pharmaceuticals and environmental risk assessment, *Sci. Total Environ.*, 2012, **430**, 109-118.

22. F. S. Souza, V. V. Da Silva, C. K. Rosin, L. Hainzenreder, A. Arenzon, T. Pizzolato, L. Jank and L. A. Féris, Determination of pharmaceutical compounds in hospital wastewater and their elimination by advanced oxidation processes, *J. Environ. Sci. Heal. A*, 2018, **53**, 213-221.

23. L. Y. Zou, Y. Li and Y.-T. Hung, in *Advanced Physicochemical Treatment Technologies*, eds. L. K. Wang, Y.-T. Hung and N. K. Shammas, Humana Press, Totowa, NJ, 2007, ch. 13, pp. 575-610.

24. M. Dietrich, T. Randall and P. Canney, Wet air oxidation of hazardous organics in wastewater, *Environ. Prog.*, 1985, **4**, 171-177.

25. M. Kumari and A. K. Saroha, Performance of various catalysts on treatment of refractory pollutants in industrial wastewater by catalytic wet air oxidation: A review, *J. Environ. Manage.*, 2018, **228**, 169-188.

26. J. Levec and A. Pintar, Catalytic wet-air oxidation processes: A review, *Catalysis Today*, 2007, **124**, 172-184.

27. A. Tungler, E. Szabados and H. A. M., in *Wastewater Treatment Engineering*, ed. M. Samer, IntechOpen, 2015, pp. 153-178.

28. V. S. Mishra, V. V. Mahajani and J. B. Joshi, Wet air oxidation, *Ind. Eng. Chem. Res.*, 1995, **34**, 2-48.

29. S. K. Bhargava, J. Tardio, J. Prasad, K. Föger, D. B. Akolekar and S. C. Grocott, Wet oxidation and catalytic wet oxidation, *Ind. Eng. Chem. Res.*, 2006, **45**, 1221-1258.

30. W. Zhan, X. Wang, D. Li, Y. Ren, D. Liu and J. Kang, Catalytic wet air oxidation of high concentration pharmaceutical wastewater, *Water Sci. Technol.*, 2013, **67**, 2281-2286.

31. S. Collado, L. Garrido, A. Laca and M. Diaz, Wet oxidation of salicylic acid solutions, *Environ. Sci. Technol.*, 2010, **44**, 8629-8635.

32. C. Echevarría, C. Valderrama, J. Cortina, I. Martín, M. Arnaldos, X. Bernat, A. De la Cal, M. R. Boleda, A. Vega and A. Teuler, Techno-economic evaluation and comparison of PAC-MBR and ozonation-UV revamping for organic micro-pollutants removal from urban reclaimed wastewater, *Sci. Total Environ.*, 2019, **671**, 288-298.

33. M. J. da Costa Fonseca, J. R. P. da Silva, C. P. Borges and F. V. da Fonseca, Ethinylestradiol removal of membrane bioreactor effluent by reverse osmosis and UV/H2O2: A technical and economic assessment, *J. Environ. Manage.*, 2021, **282**, 111948.

34. C. Baresel, M. Ek, H. Ejhed, A.-S. Allard, J. Magnér, L. Dahlgren, K. Westling, C. Wahlberg, U. Fortkamp and S. Söhr, Sustainable treatment systems for removal of pharmaceutical residues and other priority persistent substances, *Water Sci. Technol.*, 2019, **79**, 537-543.

35. D. S. Wishart, Y. D. Feunang, A. C. Guo, E. J. Lo, A. Marcu, J. R. Grant, T. Sajed, D. Johnson, C. Li and Z. Sayeeda, DrugBank 5.0: a major update to the DrugBank database for 2018, *Nucleic Acids Res.*, 2018, **46**, D1074-D1082.

36. Centre des technoligies de l'eau, *Guide méthodologique d'audit de l'usage de l'eau en milieu institutionnel - Annexes*, Gouvernement du Québec, 2nd edn., 2014. Available at: https://www.cteau.com/wp-content/uploads/2016/03/Annexes-ABCDEFGH-version-Mai-2014.pdf.

37. U.S. Environmental Protection Agency, Ecological Structure Activity Relationships (ECOSAR) Predictive Model, https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model, version 2.0).

38. F. Melnikov, J. Kostal, A. Voutchkova-Kostal, J. B. Zimmerman and P. T. Anastas, Assessment of predictive models for estimating the acute aquatic toxicity of organic chemicals, *Green Chemistry*, 2016, **18**, 4432-4445.

39. Organisation for Economic Co-Operation and Development, *Test No. 202: Daphnia sp., Acute Immonilisation Test, In: OECD Guidelines for the Testing of Chemicals, Section 2: Effects on Biotic Systems*, OCDE Publishing, 2004.

40. P. Ramirez, J.-F. Vermette and S. Lefèvre, presented in part at the 17th European Meeting on Supercritical Fluids (EMSF 2019) - 7th European Meeting on High Pressure Technology, Ciudad Real, Spain, 2019-04-08, 2019.

41. M. I. Meo, S. Haydar, O. Nadeem, G. Hussain and H. Rashid, Characterization of hospital wastewater, risk waste generation and management practices in lahore, *Proc. Pak. Acad. Sci,*, 2014, **51**, 317-319.

42. P. Kajitvichyanukul and N. Suntronvipart, Evaluation of biodegradability and oxidation degree of hospital wastewater using photo-Fenton process as the pretreatment method, *J. Hazard. Mater.*, 2006, **138**, 384-391.

43. P. Fasahati, H. C. Woo and J. J. Liu, Industrial-scale bioethanol production from brown algae: Effects of pretreatment processes on plant economics, *Applied Energy*, 2015, **139**, 175-187.

44. M. Gómez-Chaparro, J. García Sanz-Calcedo and L. Armenta-Márquez, Study on the use and consumption of water in Spanish private hospitals as related to healthcare activity, *Urban Water J.*, 2018, **15**, 601-608.

45. J. N. Miller, Basic Statistical Methods for Analytical Chemistry Part 2. Calibration and Regression Methods - A Review, *Analyst*, 1991, **116**, 3-14.

46. M. Carrier, M. Besson, C. Guillard and E. Gonze, Removal of herbicide diuron and thermal degradation products under Catalytic Wet Air Oxidation conditions, *Appl. Catal. B-Environ.*, 2009, **91**, 275-283.

47. D. Kanakaraju, B. D. Glass and M. Oelgemöller, Advanced oxidation process-mediated removal of pharmaceuticals from water: a review, *J. Environ. Manage.*, 2018, **219**, 189-207.

48. S. K. Alharbi, W. E. Price, J. Kang, T. Fujioka and L. D. Nghiem, Ozonation of carbamazepine, diclofenac, sulfamethoxazole and trimethoprim and formation of major oxidation products, *Desalin. Water Treat.*, 2016, **57**, 29340-29351.

49. C. Baeza and D. R. Knappe, Transformation kinetics of biochemically active compounds in low-pressure UV photolysis and UV/H_2O_2 advanced oxidation processes, *Water Res.*, 2011, **45**, 4531-4543.

50. V. Naddeo, C. S. Uyguner-Demirel, M. Prado, A. Cesaro, V. Belgiorno and F. Ballesteros, Enhanced ozonation of selected pharmaceutical compounds by sonolysis, *Environ. Technol.*, 2015, **36**, 1876-1883.

51. C. Boillot, C. Bazin, F. Tissot-Guerraz, J. Droguet, M. Perraud, J. Cetre, D. Trepo and Y. Perrodin, Daily physicochemical, microbiological and ecotoxicological fluctuations of a hospital effluent according to technical and care activities, *Sci. Total Environ.*, 2008, **403**, 113-129.

52. M. J. Gómez, M. Petrović, A. R. Fernández-Alba and D. Barceló, Determination of pharmaceuticals of various therapeutic classes by solid-phase extraction and liquid chromatography–tandem mass spectrometry analysis in hospital effluent wastewaters, *J. Chromatogr. A*, 2006, **1114**, 224-233.

53. B. De Witte, H. Van Langenhove, K. Demeestere and J. Dewulf, Advanced oxidation of pharmaceuticals: chemical analysis and biological assessment of degradation products, *Crit. Rev. Environ. Sci. Tecnol.*, 2011, **41**, 215-242.

54. F. A. Almomani, M. Shawaqfah, R. R. Bhosale and A. Kumar, Removal of emerging pharmaceuticals from wastewater by ozone-based advanced oxidation processes, *Environ. Prog. Sustain.*, 2016, **35**, 982-995.

55. N. Klamerth, L. Rizzo, S. Malato, M. I. Maldonado, A. Agüera and A. R. Fernández-Alba, Degradation of fifteen emerging contaminants at μg L− 1 initial concentrations by mild solar photo-Fenton in MWTP effluents, *Water Res.*, 2010, **44**, 545-554.

56. A. Dirany, S. E. Aaron, N. Oturan, I. Sirés, M. A. Oturan and J. Aaron, Study of the toxicity of sulfamethoxazole and its degradation products in water by a bioluminescence method during application of the electro-Fenton treatment, *Anal. Bioanal. Chem.*, 2011, **400**, 353-360.

57. T. X. H. Le, T. Van Nguyen, Z. A. Yacouba, L. Zoungrana, F. Avril, D. L. Nguyen, E. Petit, J. Mendret, V. Bonniol and M. Bechelany, Correlation between degradation pathway and toxicity of acetaminophen and its by-products by using the electro-Fenton process in aqueous media, *Chemosphere*, 2017, **172**, 1-9.

58. A. Calleja, J. Baldasano and A. Mulet, Toxicity analysis of leachates from hazardous wastes via Microtox and Daphnia magna, *Toxic. Assess.*, 1986, **1**, 73-83.

59. M. W. Toussaint, T. R. Shedd, W. H. van der Schalie and G. R. Leather, A comparison of standard acute toxicity tests with rapid-screening toxicity tests, *Environ. Toxicol. Chem.*, 1995, **14**, 907-915.

60. F. Luck, Wet air oxidation: past, present and future, *Catalysis today*, 1999, **53**, 81-91.

61. A. Urtiaga, G. Pérez, R. Ibáñez and I. Ortiz, Removal of pharmaceuticals from a WWTP secondary effluent by ultrafiltration/reverse osmosis followed by electrochemical oxidation of the RO concentrate, *Desalination*, 2013, **331**, 26-34.

Comprehensive Evaluation of Non-Catalytic Wet Air Oxidation as a Pretreatment to Remove Pharmaceuticals from Hospital Effluents

*Valérie Boucher [a], Margot Beaudon [a], Pedro Ramirez [b], Pascal Lemoine [b], Kalyssa Volk [c], Viviane Yargeau [c], Pedro A. Segura [a, *]*

[a] Department of Chemistry, Université de Sherbrooke, Sherbrooke, QC, Canada

[b] Centre de transfert technologique en écologie industrielle (CTTÉI), Sorel-Tracy, QC, Canada

[c] Department of Chemical Engineering, McGill University, Montréal, QC, Canada

Electronic Supplementary Information

Section S1. Experimental methods

Table S1. Multiple reaction monitoring transitions and optimized parameters for quantitative analyses by LC-QqQMS (Waters Micromass Quattro Premier XE Mass Spectrometer).

Compound	RT[a] (min)	Precursor ion (*m/z*)	CV[b] (V)	Quantification Product ion (*m/z*)	CE[c] (V)	Confirmation Product ion (*m/z*)	CE[c] (V)
Acetaminophen	2.76	151.7	30	93.2	20	110.2	15
Baclofen	4.03	214.1	20	115.1	35	150.9	20
Carbamazepine	10.13	236.9	30	178.9	40	193.9	15
Cetirizine	11.30	389.1	30	165.9	40	200.9	20
Diclofenac	13.91	295.9	20	214.9	20	249.9	15
Gabapentin	3.66	171.9	25	137.3	15	154.4	15
Pregabalin	3.47	159.9	20	142.3	10	97.4	15
Quetiapine	8.74	383.9	40	253.3	25	221.3	35
Sulfamethoxazole	5.49	254.0	25	155.8	15	91.9	25
Trimethoprim	4.81	291.1	45	122.9	30	230.0	25

[a] Retention time; [b] Cone voltage; [c] Collision energy

Table S2. Multiple reaction monitoring transitions and optimized parameters for quantitative analyses by LC-QqQMS (Xevo TQ-S micro mass spectrometer).

Compound	RT[a] (min)	Precursor ion (*m/z*)	CV[b] (V)	Quantification Product ion (*m/z*)	CE[c] (V)	Confirmation Product ion (*m/z*)	CE[c] (V)
Acetaminophen	2.72	152.0	35	82.0	22	92.8	22
Baclofen	4.02	214.0	10	115.7	32	151.0	17
Carbamazepine	9.98	237.1	30	193.6	16	179.0	34
Cetirizine	11.16	389.1	5	165.9	43	201.0	19
Diclofenac	13.69	296.0	5	250.0	12	214.9	19
Gabapentin	3.62	172.1	20	137.0	15	95.0	22
Pregabalin	3.45	160.0	10	142.0	10	97.1	14
Quetiapine	8.63	384.1	10	253.0	22	158.1	22
Sulfamethoxazole	5.40	254.0	10	92.0	28	107.9	24
Trimethoprim	4.75	291.1	10	123.0	23	230.0	22

[a] Retention time; [b] Cone voltage; [c] Collision energy

Section S1.1. LC-QqQMS method performance

Since three types of samples with different sample preparation or mass spectrometers were analyzed (deionized water, untreated hospital wastewater, treated hospital water), method performance figures of merit such as limits of quantification, linearity, precision, and trueness were measured in each case. They are found in Tables S3, S4 and S5.

Table S3. Method performance for the analysis of spiked deionized water. This method was used for the optimization of WAO using spiked concentrations of target compounds at 1500 µg L^{-1}.

Compound	Linearity	LOQ [a] (µg L^{-1})	Precision [b] (%)	Trueness [b] (%)
Acetaminophen	0.9925	7.8	2.4	24.2
Baclofen	0.9972	16.6	6.9	10.7
Carbamazepine	0.9977	8.7	1.4	9.6
Cetirizine	0.9999	1.2	1.0	7.3
Diclofenac	0.9976	0.8	5.6	10.6
Gabapentin	0.9936	5.4	11.3	9.3
Pregabalin	0.9998	2.4	3.6	17.4
Quetiapine	0.9973	28.3	4.2	2.2
Sulfamethoxazole	0.9999	3.2	5.4	8.9
Trimethoprim	0.9945	12.2	3.9	7.9

[a] Determined using the standard deviation of the concentration of 10 replicates (5µg L^{-1}, except quetiapine and trimethoprim for which 10µg L^{-1} was used) multiplied by 10. [b] Determined using a quality control sample spiked at 40 µg L^{-1} (n=5).

Table S4. Method performance for the analysis of untreated hospital wastewater. This method was used for the quantification of pharmaceuticals shown in Figure 2 of the manuscript.

	Untreated hospital wastewater			
Compound	**Linearity**	**LOQ [a] (ng L^{-1})**	**Precision [b] (%)**	**Trueness [b] (%)**
Acetaminophen	N.A.	N.A.	N.A.	N.A.
Baclofen	0.9950	5.4	1.8	7.8
Carbamazepine	0.9985	1.7	0.8	6.1
Cetirizine	0.9891	0.12	2.3	14
Diclofenac	0.9996	0.22	2.8	12
Gabapentin	0.9847	6.4	1.3	8.8
Pregabalin	0.9688	26	1.5	15
Quetiapine	0.9988	4.6	2.0	12
Sulfamethoxazole	0.9840	0.18	1.6	2.7
Trimethoprim	0.9958	0.74	3.1	4.9

[b] Determined according to a S/N=10. [b] Determined using a quality control sample spiked at 150 ng L^{-1} (n=5). N.A.: Not available. Acetaminophen could not be quantified in the untreated hospital wastewater samples.

Table S5. Method performance for the analysis of WAO treated hospital wastewater. This method was employed to obtain the results shown in Table 4.

	WAO treated hospital wastewater			
Compound	**Linearity**	**LOQ [a] (ng L^{-1})**	**Precision [b] (%)**	**Trueness [b] (%)**
Acetaminophen	0.9978	83	2.2	-1.1
Baclofen	0.9972	58	9.6	24
Carbamazepine	0.9973	4.3	14	12
Cetirizine	0.9970	16	45	7.1
Diclofenac	0.9976	9.0	17	13
Gabapentin	0.9972	147	2.2	9.7
Pregabalin	0.9970	26	13	18
Quetiapine	0.9928	10.0	11	12
Sulfamethoxazole	0.9978	5.2	12	3.2
Trimethoprim	0.9963	10	8.0	14

[a] Determined using 10× the standard deviation of 10 blank samples divided by the slope of the calibration curve, except for acetaminophen, carbamazepine, quetiapine and sulfamethoxazole (10× standard error of the calibration curve divided by the slope) [b] Determined using a quality control sample spiked at 80 ng L^{-1}, except for gabapentin (2000 ng L^{-1}).

Section S1.2. Preparation of QC samples

For tests using batch reactor model Cellule 2646 1000, a volume of 0.5 mL of the test sample introduced in the reactor was pipetted in an amber vial and then diluted with 1.5 mL of deionized water was used as quality control (QC) sample. This dilution is the same as the sample will undergo in the reactor. During WAO tests, the QC sample is left at room temperature under the same conditions as the samples. At the end of the test, the QC sample is refrigerated at the same time as the test samples. Concentration values determined by LC-QqQMS should be the same for QC samples and tests samples collected immediately after dilution in the reactor. If there was a difference of more than 20% between these two values, the WAO test was considered invalid.

Section S1.3 *Daphnia magna* acute toxicity bioassay protocol and quality control

The culture medium used is standard freshwater prepared with the following salts in deionized water: $NaHCO_3$ (64.75 mg L^{-1}), $CaCl_2.2H_2O$ (294 mg L^{-1}), $MgSO_4.7H_2O$ (123.25 mg L^{-1}) and KCl (5.75 mg L^{-1}). The ephippia are rinsed and then transferred to a petri dish with 50 mL of the standard freshwater solution previously bubbled with air for 15 min. The hatching lasts 72 hours, at 20-22 ° C under lighting of 2000 ± 70 Lux. Five dilutions (C1 to C5) of the test sample with standard freshwater are evaluated during a test. Two hours before the test, daphnids were fed with spirulina powder in order to avoid high mortality (>10% of daphnids). The test plate consists of 30 wells: 6 rows (control, C1, C2, C3, C4 and C5) and 5 columns (one for transferring daphnids and four replicate exposure tests). Exactly five daphnids are then placed in each well of the test plate with 10 mL of standard freshwater (control) or the corresponding effluent dilutions. A piece of sealing film (Parafilm M) is placed on the test plate. After 24 and 48 hours of incubation (20 ±°C, in darkness), the number of immobilized daphnids is counted. Daphnids not moving after gentle agitation are considered immobilized. These results allow the calculate the median lethal concentration (LC_{50}).

The quality control sample was a solution of potassium dichromate ($K_2Cr_2O_7$), a toxic reference substance. The following series of dilutions were used 3.2, 1.8, 1.0, 0.56 and 0.32 mg L^{-1}. The median lethal concentration (LC_{50}) obtained with QC samples at 24 h must be located within the limits mentioned in the technical sheet of each Daphtoxkit (between 0.6 mg L^{-1} and 2.1 mg L^{-1}). Also, the mortality rate in control daphnids must not exceed 10%. If so, the test is considered

invalid because it means that part of the immobilization can be explained by something other than exposure to contaminants. LC_{50} values were obtaining after fitting the data on number of immobilized daphnids as a function of volume percentage of test sample using a dose-response model and the Levenberg Marquardt iteration algorithm in OriginPro 2021 developped by OriginLab (Northampton, MA). Quality of the fit was evaluated by the adjusted coefficient of determination (R'^2). In all cases R'^2 was > 0.9 except one set of data (exposure to untreated hospital wastewater). For one sample (hospital wastewater treated by WAO for 15 min) the fitting failed and no LC_{50} could be calculated.

Section S1.4 *Aliivibrio fischeri* acute toxicity bioassay protocol and quality control

Microtox bioassays were completed using standard kits purchased from EBPI and the Microtox M500 system. The testing kit included lyophilized *Aliivibrio fischeri*, reagent diluent, osmotic adjustment solution (OAS), and sample diluent. For each test, one vial of *Aliivibrio fischeri* was rehydrated with 1 mL of reagent diluent at 4 °C for 30 minutes. Before the assay, the reagent (*A. fischeri)* was incubated in the Microtox M500 at 15 °C for 30 minutes. To prepare the sample for the test, the pH was measured to ensure the test sample was between 6-8.5. All samples fell within this range, so no adjustment was required. Next, the salinity of the sample was adjusted by adding 1/10 of the sample volume of OAS. Then, the sample was diluted serially with sample diluent at a dilution factor of 1.5. Eight dilutions of the test sample were used for the analysis. After the reagent had properly incubated at 15 °C, 10 µL of reagent stock was pipetted into cuvettes with 500 µL of sample diluent also at 15°C. After stabilization for 15 minutes, initial light intensity readings of each cuvette (I_0) were taken. Next, 500 µL of each dilution of the test sample was transferred into the corresponding reagent cuvette. After five minutes, light intensity readings were taken again (I_5). EC_{20} values were then calculated by the Microtox Omni Software. If the tested sample was not toxic enough to cause a measurable light inhibition, the sample was retested for confirmation of the results.

Two blanks were analyzed in each run. The blank consisted of 500 µL of sample diluent. When calculating the EC_{20}, all light readings were compared to the blanks. The blanks account for the natural death of the *A. fischeri*. If the blanks had an inadequate light reading at any point in the

testing procedure, the results were not considered, and the test was restarted. As suggested by the EBPI kit, a positive control of phenol at a concentration of 45 mg L^{-1} was also used in each run. After 5 minutes, around 80% of light inhibition was observed in the positive control.

Section S2. Results

Table S6. Organic pharmaceuticals consumed in the local hospital.

Pharmaceutical	Mass (kg)
Acetaminophen	1.05×10^{2}
Metformin	1.87×10
Docusate	6.28
Lidocaine	4.98
Sodium divalproex	4.55
Amoxicillin	2.63
Cefazoline	2.57
Acetylsalicylic acid	2.32
Pantoprazole	1.86
Gabapentin	1.84
Quetiapine	1.70
Naproxen	1.50
Pregabalin	1.48
Ciprofloxacin	1.30
Levetiracetam	1.22
Levodopa	1.20
Furosemide	1.04
Moxifloxacin	1.03
Venlafaxine	1.01
Phenytoin	9.00×10^{-1}
Dexlansoprazole	8.57×10^{-1}
Clopidogrel	6.75×10^{-1}
Amiodarone	5.20×10^{-1}
Clozapine	4.80×10^{-1}
Tetracaine	4.08×10^{-1}
Thiamine	3.60×10^{-1}
Oxazepam	3.57×10^{-1}
Sennosides	3.43×10^{-1}
Carbidopa	3.00×10^{-1}
Dimenhydrinate	2.59×10^{-1}
Citalopram	2.57×10^{-1}
Allopurinol	2.50×10^{-1}
Trazodone	2.25×10^{-1}
Isosorbide-5-mononitrate	2.10×10^{-1}
Atorvastatin	1.75×10^{-1}
Metoprolol	1.75×10^{-1}
Gliclazide	1.68×10^{-1}
Mirtazapine	1.08×10^{-1}
Methylprednisolone	1.04×10^{-1}
Amlodipine	9.73×10^{-2}
Domperidone	9.00×10^{-2}
Phenobarbital	9.00×10^{-2}
Salbutamol	7.44×10^{-2}

Morphine	7.35×10^{-2}
Donepezil	6.70×10^{-2}
Rosuvastatin	6.50×10^{-2}
Prednisone	6.00×10^{-2}
Hydromorphone	5.25×10^{-2}
Bisoprolol	4.83×10^{-2}
Baclofen	4.50×10^{-2}
Olanzapine	4.16×10^{-2}
Hydralazine	4.00×10^{-2}
Cetirizine	3.90×10^{-2}
Buspirone	3.70×10^{-2}
Metoclopramide	3.15×10^{-2}
Midodrine	2.90×10^{-2}
Procyclidine	2.65×10^{-2}
Perindopril	2.64×10^{-2}
Apixaban	2.52×10^{-2}
Lorazepam	2.20×10^{-2}
Betamethasone	1.95×10^{-2}
Dexamethasone	1.20×10^{-2}
Loperamide	1.04×10^{-2}
Risperidone	8.50×10^{-3}
Methadone	4.00×10^{-3}
Tamsulosin	3.28×10^{-3}
Clonazepam	2.95×10^{-3}
Levothyroxine	2.03×10^{-3}
Fentanyl	3.00×10^{-4}
Tiotropium	1.67×10^{-4}
TOTAL	**170.71**

Table S7. Estimated amounts of the 25 top pharmaceuticals rejected in the hospital effluent using a conservative daily water consumption of 420.8 L/bed (number of beds = 166).

Pharmaceutical	Estimated concentration in the effluent ($\mu g\ L^{-1}$)
Metformin	979.23
Acetaminophen	165.08
Cefazoline	134.24
Amoxicillin	107.49
Gabapentin	96.22
Pregabalin	75.62
Ciprofloxacin	52.14
Furosemide	48.99
Levetiracetam	42.11
Lidocaine	26.06
Moxifloxacin	23.65
Acetylsalicylic acid	12.13
Divalproex	7.14
Levodopa	6.28
Carbidopa	5.49
Quetiapine	4.44
Rosuvastatin	3.06
Venlafaxine	2.63
Phenytoin	2.35
Baclofen	2.00
Thiamine	1.88
Citalopram	1.61
Allopurinol	1.31
Bisoprolol	1.26
Cetirizine	1.22
TOTAL	1803.64

Table S8. Energy balance for a WAO unit of 86 L min^{-1}.

Power Consumption		
	Installed Power kW	**Power Consumption MWh/year**
Compressor	10	75
Pump	23	183
Cooling System	100	791
Total Power Consumption (MWh)		1049
Heat Consumption		
	Flow Nm^3/h	**Heat Consumption GJ/year**
Natural gas	33.8	5344
Total Heat Consumption (MWh)		1484
Power and Heat		
Energy balance (MWh)		2533
Proportion		
Electricity		41%
Heat		59%

Table S9. Cases for WAO unit sensitivity analysis.

Inlet Flow rate (L/min)	**Concentration factor**	**COD (mg O_2/L)**
5	17	23800
10	9	12600
25	3.5	4900
50	1.7	2380
75	1.2	1680
86	1	1400