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► To cite this version:

Fidji Sandre, Nina Huynh, Emilie Caupos, Lamyae El-Mrabet, Chandirane Partibane, et al.. Occurrence and fate of an emerging drug pollutant and its by-products during conventional and advanced wastewater treatment: Case study of furosemide. *Chemosphere*, In press, 322, 10.1016/j.chemosphere.2023.138212 . hal-04013601

HAL Id: hal-04013601

<https://hal.u-pec.fr/hal-04013601>

Submitted on 28 Mar 2023

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1 **Occurrence and fate of an emerging drug pollutant and its by-products during**
2 **conventional and advanced wastewater treatment: case study of furosemide**

3

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15

16 **Abstract :**

17 Conventional wastewater treatment systems are not designed to remove pharmaceutical compounds
18 from wastewater. These compounds can be degraded into many other transformation products which
19 are hardly, if at all, studied. In this context, we studied the occurrence and degradation of furosemide,
20 a very frequently detected diuretic, along with its known degradation products in several types of
21 wastewater. Influent and effluent from the Seine-Centre Wastewater Treatment Plant (WWTP) (Paris,
22 France) as well as outlet of residential care homes (Dordogne, France) were analyzed by Ultra-
23 Performance Liquid Chromatography-tandem Mass Spectrometry (UPLC-MS/MS) to quantify
24 furosemide and its known degradation products, saluamine and pyridinium of furosemide. Oxidation
25 experiments (chlorination, ozonation and UV photolysis with hydrogen peroxide) were then performed

26 on furosemide solutions and on water from residential care facilities to study the degradation of
27 furosemide by potential advanced processes, and also to identify unknown oxidation products by high-
28 resolution mass spectrometry. Furosemide was well degraded in Seine-Centre WWTP (>75%) but did
29 not increase the concentrations of its main degradation products. Saluamine and pyridinium of
30 furosemide were already present at similar concentrations to furosemide in the raw wastewater (~2.5-
31 3.5 $\mu\text{g}\cdot\text{L}^{-1}$), and their removal in the WWTPs were very high (>80%). Despite their removal, the three
32 compounds remained present in treated wastewater effluents at concentrations of hundreds of
33 nanograms per liter. Chlorination degraded furosemide without pyridinium production unlike the
34 other two processes. Chlorination and ozonation were also effective for the removal of furosemide
35 and pyridinium in residential care home water, but they resulted in the production of saluamine. To
36 our knowledge this is the first evidence of saluamine and pyridinium of furosemide in real water
37 samples in either the particulate or dissolved phase.

38

39 **Keywords:** Pharmaceutical; wastewater; residential care home; degradation products; oxidation

40

41 **Declaration of interest:** none

42

43 **1. Introduction**

44 In the context of a wide consumption of medicines in high income and emerging countries, increasing
45 demographical urban pressure and population aging, hundreds of active substances used for
46 therapeutic purposes and marketed worldwide end up in the wastewater system. Conventional
47 wastewater treatment plant (WWTP) processes based on filtration, sand and grease removal,
48 decantation and biological or physico-chemical treatments are not designed for the elimination of
49 pharmaceutical compounds, so their removal can vary drastically depending on the molecule (e.g., its
50 hydrophobicity) (Chiffre et al. 2016). The active substances of these drugs are discharged with WWTP
51 effluents at concentrations ranging from $\text{ng}\cdot\text{L}^{-1}$ to $\mu\text{g}\cdot\text{L}^{-1}$ and end up in the aquatic environment,

52 representing a risk for organisms (Cizmas et al. 2015, Obinwanne Okoye et al. 2022). To overcome this
53 problem, the implementation of tertiary or quaternary treatments after conventional treatments is
54 increasingly studied, and several countries (e.g., Switzerland, Germany) already regulate the removal
55 of organic micropollutants from wastewater. The optimization of biological treatments, for example
56 with the addition of fungus (*Trametes versicolor*) in bioreactors (Cruz-Morato et al. 2014; Badia-
57 Fabregat et al. 2015), can be effective on potentially biodegradable compounds. However, the most
58 frequent processes used to achieve a satisfactory removal of micropollutants include adsorption on
59 activated carbon (Guillossou et al. 2019), membrane processes and oxidation processes such as
60 ozonation (Guillossou et al. 2020).

61
62 Ozone has been used for a long time as both an oxidant and a disinfectant for drinking water
63 production, and is increasingly applied for the treatment of wastewater effluents (Lim et al. 2022). It
64 is a very powerful oxidant that can react directly with organic molecules, mainly by electrophilic
65 reaction, and also indirectly by the production of radicals initiated by hydroxyl or hydroperoxide ions
66 in the aqueous medium (Guo et al. 2012). Ozonation has been shown to be effective in the degradation
67 of hormones, antibiotics, antivirals and pesticides (Lim et al. 2022). Advanced oxidation processes
68 (AOPs) are also very efficient for the degradation of organic molecules (Miklos et al. 2018). These
69 processes are based on the production of highly reactive hydroxyl radicals from one or more primary
70 oxidants (e.g., chlorine, ozone, hydrogen peroxide, etc.) (Sarathy & Mohseni 2006) or by photocatalysis
71 (Prieto-Rodriguez et al. 2012). Advanced oxidation processes in which Ultraviolet (UV) radiation is
72 combined with ozone, chlorine, peroxodisulfate or hydrogen peroxide are efficient to reach extensive
73 degradation. The most common combination is with H₂O₂ because it is much less energy-consuming
74 and expensive than with O₃, and it is also less sensitive to matrix changes and dissolved organic matter
75 than sulfates. While advanced treatment processes for organic micropollutants are not widely used,
76 many WWTP use a disinfection step before discharging effluents into the environment (e.g., in bathing
77 areas). Another process commonly used for disinfection and inactivation of pathogenic

78 microorganisms is based on UV irradiation (Hijnen et al. 2006). Direct UV photolysis with UV-C (100-
79 280 nm) shows good efficiency on pesticides (Sanches et al. 2010) but some pharmaceutical
80 compounds like carbamazepine are more resistant to it (Pereira et al. 2007).

81
82 Although oxidation treatments can be quite efficient for the degradation of micropollutants, they often
83 form oxidation by-products. Transformation products (e.g., metabolites) of pharmaceuticals can also
84 be already present in the incoming water or be formed during conventional biological processes. The
85 formation of oxidation by-products depends on the mode of oxidation, the medium (especially the
86 presence of nitrogen, halogens, organic matter) and the type of radical produced in the case of
87 advanced oxidation (Miklos et al. 2018). These degradation by-products present a hazard for health
88 (Stalter et al. 2016) and for the environment (Wang et al. 2018). Apart from the regulated disinfection
89 by-products (e.g., trihalomethanes and haloacetic acids), hundreds of chlorination by-products have
90 been identified (Zhang et al. 2012) from the reaction of chlorine with organic matter and their potential
91 toxicity can be a threat to human health (Stefán et al. 2019, Mazhar et al. 2020). Many products are
92 also generated during UV-H₂O₂ oxidations depending on the dose of oxidant, the UV fluence and the
93 pH of the medium. Oxidation by-products are often more toxic than the parent compounds on algae,
94 daphnia, and medaka fish (Wang et al. 2018), it is thus of critical importance to assess the toxicity of
95 degradation products to fully establish the potential impacts of organic micropollutants on the
96 environment.

97
98 To address the questions related to the presence of pharmaceuticals in the environment, we selected
99 furosemide from a list of high-risk emerging pollutants (Besse and Garric 2008) and subjected this drug
100 to a predictive study aiming to anticipate the fate of organic contaminants (Laurence et al, 2011, 2014;
101 Olvera Vargas et al 2016). Classified by the World Health Organization as an essential medicine,
102 furosemide is a loop diuretic prescribed all over the world for hypertension and heart, liver, and kidney
103 failure (Abbot and Kovacic 2008). Mostly eliminated unmodified by humans and moderately degraded

104 in conventional treatment plants (between 8 and 54% in Castiglioni et al. 2006, >65% in Matamoros et
105 al. 2009, 74% in Kasprzyk-Hordern et al. 2009, or between 30-80% according to the WWTP considered
106 in Jelic et al. 2011), furosemide is also widely found in the environment from several tens to few
107 thousand of ng.L⁻¹ in rivers (Banjac et al. 2015, Baken et al. 2018, Munro et al. 2019, White et al. 2019,
108 Cantwell et al. 2018). Applied to furosemide, our predictive study confirmed that saluamine and
109 furfural are two transformation products (TPs) of furosemide (Laurencé et al. 2014). More importantly,
110 it also identified the pyridinium of furosemide as a TP and a human metabolite of this drug (Laurencé
111 et al. 2019). Whereas furfural presents moderate acute toxicity in freshwater invertebrates (LC50 = 13
112 mg.L⁻¹ for 72h exposure in Reed & Kwok 2014), saluamine shows acute toxicity in rats (Al-Omar et al.
113 2009). We also previously demonstrated that pyridinium of furosemide exhibits neurodegenerative
114 properties in mice (Laurencé et al. 2019). Therefore, the fate of furosemide and its TPs in wastewater
115 and in the environment needs to be assessed to fully characterize the potential impacts of this
116 pharmaceutical on the aquatic ecosystems. Furosemide is also an interesting and highly relevant model
117 to study the fate of pharmaceuticals along with their TPs. Especially, the production of saluamine and
118 pyridinium of furosemide as well as their potential degradation during conventional and advanced
119 wastewater treatment remains unknown to date. The purpose of this work was thus i) to assess the
120 occurrence and removal of furosemide and its known TPs in a large WWTP and in wastewater from an
121 elderly care facility, ii) to study their removal by several advanced oxidation processes (ozonation,
122 UV/H₂O₂) and iii) to identify the subsequent formation of potential new TPs following these
123 treatments.

124

125

126 **2. Material & methods**

127 **2.1. Reagents**

128 The furosemide-d5 standard was purchased from Cluzeau Info Labo. Internal standards (atenolol-d7
129 and sulfamethoxazole-d4) and saluamine (SAL) were purchased from Sigma-Aldrich. For the extraction

130 and analysis, MS grade methanol was purchased from Fisher. Ultrapure water was produced by a Milli-
131 Q® IQ 7000 ultrapure water system. Furosemide (FUR) was purchased from Sigma. Pyridinium of
132 furosemide (PYR) was synthesized at ICMPE as previously described (Laurencé et al. 2011), and its
133 structure has been confirmed by NMR with over 96% purity. Hydrogen peroxide 50% was purchased
134 from CarlRoth.

135

136 **2.2. Sampling sites**

137 To assess the WWP efficiency on furosemide degradation, raw water (RW) and treated effluent water
138 (TW) were collected on 2021-12-07 and 2021-12-08 from the Seine-Centre WWTP (Colombes, France),
139 operated by the Paris public sanitation service (SIAAP) and treating wastewater of about 1,000,000
140 people equivalent with a flow of 240,000 m³/day. The Seine-Centre WWTP is mostly based on
141 biofiltration stages ensuring the treatment of organic carbon as well as nitrification and denitrification
142 processes. For the oxidation tests on raw sewerage water samples, wastewater from residential care
143 homes (RCH) was chosen because of its presumably high concentration of furosemide, thus allowing a
144 better identification of the possible degradation products. Three wastewater outlets of health care
145 institutions were collected in Dordogne, France. The first sample (RCH1) was collected on 2021-05-26
146 in a RCH of 10,000 m² located in Bergerac, in an urban area. It has a capacity of 90 beds plus 15 beds
147 for Alzheimer's patients, 10 places in daycare centers and 5 emergency beds. The sample was taken
148 from a lift station which only collects water from the facility. The second sample (RCH2) was collected
149 on 2021-06-09 from a reeducation center located in a national forest at Antonne-et-Trigonant with
150 120 places and 40 beds for senior residents. The third sample (RCH3) was collected on 2021-06-08
151 from a RCH at Lolme with 90 beds and 5 daycare places. Several physico-chemical parameters were
152 recorded: pH, Dissolved Organic Carbon (DOC), Chemical Oxygen Demand (COD) and Biological Oxygen
153 Demand at 5 days (DBO5), Suspended Matter (SM), Total Kjeldahl Nitrogen (TKN), ammoniacal
154 nitrogen and organic nitrogen (table 1). The RCH outlet water samples were filtered on GF/D filters
155 (2.7 µm pore size) and then on GF/F filters (0.7 µm pore size). pH and DOC were measured after

156 filtration (table 1). Particulate phase samples (i.e., particles collected on filters) were stored at -20 °C
157 and freeze-dried until treatment for analysis. For RCH samples, it is interesting to note the large gap
158 between the Kjeldahl nitrogen and ammonia nitrogen values, which implies a high proportion of
159 organic nitrogen, reflecting the short residence time of the effluent and confirming the relatively fresh
160 effluent sampling

161

162 **Table 1.** Physico-chemical parameters of samples from WWTP raw wastewater (RW1 = 2021-12-07,
163 RW2 = 2021-12-08), WWTP treated wastewater (TW1 = 2021-12-07, TW2 = 2021-12-08) and
164 wastewater outlets of residential care homes (RCH). NA = Not available (not measured). (BLACK AND
165 WHITE TABLE)

166

<Table 1>

167

168

169 **2.3. Oxidation assays**

170 Furosemide degradation kinetics experiments were performed in ultrapure water spiked with 1 mg.L⁻¹
171 of furosemide. UV/H₂O₂ and ozonation were applied at high doses or exposure as described below,
172 and chlorination was also conducted at high dose (35 mgCl₂.L⁻¹) to maximize the formation of
173 degradation products (see Text S1). Oxidation processes were also applied on 200 mL filtered
174 wastewater samples from RCH facilities.

175

176 **Photodegradation under UV light with H₂O₂.** The sample was placed in a beaker, under a UV lamp at
177 254 nm (UV-C ; 0.34 mW/cm²) with stirring. To establish degradation kinetics of furosemide in
178 ultrapure water, 1 mg.L⁻¹ of H₂O₂ was added and aliquots of 1 mL were taken at 2, 5, 10, 15, 20, 30, 45,
179 60, 90, 120, 210 and 600 minutes. For the oxidation of wastewater from RCH, the H₂O₂ dose was
180 determined according to the DOC value by using 0.375 mg of H₂O₂ per mg of DOC, and the total
181 reaction time under UV irradiation was 5 hours.

182

183 **Ozonation.** Ozone was produced by a generator with an external source (O₂ gas cylinder). The bottle
184 containing the sample to be oxidized was immersed in an ice bath throughout the experiment. For the
185 ozonation of furosemide solutions in ultrapure water, a concentrated ozone solution was first
186 produced (33 mg/L O₃) and diluted in the furosemide samples at the required ozone concentrations,
187 determined according to the DOC concentration of the sample (Equation 1).

$$188 \quad [O_3](mgO_3.L^{-1}) = 2 \times DOC (mgC.L^{-1}) \quad (\text{Eq. 1})$$

189

190 Aliquots of 1 mL were collected at 1, 2, 4, 5, 7, 10, 15, 20, 30, 45 and 60 minutes. For the oxidation of
191 RCH wastewater, ozone was bubbled directly into the samples for 1.5 hours with an O₂ flow to the
192 ozonator of 2 L.h⁻¹. The residual O₃ was measured by colorimetry with indigo carmine using a double
193 beam spectrometer (UV6300 PC, VWR) at 600 nm.

194

195 **2.4. Analytical procedures for quantification**

196 After filtration, the residential care home samples are split into several aliquots of which 5 are spiked.
197 Furosemide and its TPs present in dissolved phases of wastewater samples were extracted through an
198 automated extraction system (Thermo AutoTrace 280 SPE Instrument) on OASIS HLB cartridges (200
199 mg, 6 cc). After conditioning with methanol and ultrapure water, samples (200 mL) were loaded onto
200 cartridges and eluted by 10 mL of methanol. The particulate phases of RCH1 and RCH2 samples were
201 also analyzed. The filters (GF/D and GF/F) were frozen and freeze-dried to remove water and
202 determine their dry mass. Furosemide and its TPs were extracted by assisted microwave extraction
203 (Antoon Paar, Multiwave 3000). Two cycles of extractions of 30 minutes in a mixture of 60% methanol-
204 40% dichloromethane (v/v) were performed (100 °C, 800 W). The extracts were filtered on folded
205 filters washed with dichloromethane, evaporated to 1 mL under rotary evaporator and diluted in 100
206 mL ultrapure water to carry out a purification step on OASIS HLB cartridges. Cartridges were eluted
207 with 10 mL of methanol, internal standards (Atenolol-d7 and Sulfamethoxazole-d4) were added to the

208 purified extracts and the final volume was adjusted to 1 mL by evaporation. Extract concentrations
209 were evaluated using internal calibration. Internal standards were chosen based on their similar
210 retention time to the one of the targeted molecule (Table S2). An evaluation of matrix effects revealed
211 their low variability for all molecules across 16 urine samples. Spiked samples were also extracted,
212 leading to the evaluation of extraction yields of furosemide, saluamine and pyridinium. These
213 extraction yields were used for the correction of concentrations in the samples. The detection and
214 quantification limit of the instrument for each compound is presented in Table S3. Analyses were
215 performed using Ultra Performance Liquid Chromatography coupled with a triple quadrupole detector
216 (Acquity-TQD, Waters). Separation was carried out on an ACQUITY UPLC BEH C18 column (1.7 μm , 2.1
217 x 100 mm) with a 15 min gradient elution from 90:10 ultra-pure water (A) and methanol (B) both
218 acidified with 0.1% formic acid, to 0:100 (A:B) maintained for 5 min, before reequilibration of the
219 column (0.4 mL.min⁻¹). For the detection, furosemide was ionized in negative electrospray mode, and
220 saluamine and pyridinium of furosemide were ionized in positive mode. MS/MS acquisition was used
221 (Table S2).

222
223 The phase distribution (K_d value) was calculated according to equation (2) (Park et al. 2017), where K_d
224 is the solid-water distribution coefficient in L.kg⁻¹, C_s is the concentration of furosemide, saluamine or
225 pyridinium of furosemide adsorbed onto MES ng.L⁻¹ and C_w is the concentration on furosemide,
226 saluamine or pyridinium of furosemide in the liquid phase in ng.L⁻¹, and SS is that of suspended matter
227 in the mixture in mg.L⁻¹.

$$229 \quad K_d = \frac{C_s}{SS \times C_w} \times 10^6 \quad (\text{Eq. 2})$$

230

231 **2.5. Analytical procedures for the identification of TPs**

232 Degradation kinetics experiments were analysed by ultra-performance liquid-chromatography
233 coupled to ion-mobility time-of-flight mass spectrometry (UPLC-IMS-QTOF, Vion, Waters) to enable

234 the tentative identification of degradation products. The separation was carried out on an ACQUITY
235 UPLC BEH C18 column (1.7 μm , 2.1 x 100 mm) with a 25 min gradient from 98:2 ultra-pure water (A)
236 and acetonitrile (B) both acidified with 0.1% formic acid, to 2:98 (A:B) maintained for 5 min, before
237 reequilibration of the column. Ionization was performed by an electrospray source in both positive and
238 negative mode, in low energy (6 V) and high energy ramp (20 to 56 V). Data was acquired and analyzed
239 with the UNIFI software (Waters). Briefly, after 4D peak detection, the chromatograms at successive
240 kinetics points were compared to spot potential TPs. Molecular formula attribution was performed
241 with a restricted list of atoms (C, H, N, O, P, S and Cl) and several online libraries, as a part of
242 Chempider in UNIFI, were interrogated (Sigma-Aldrich, Drugbank, NIST, MassBank and LGC Standard)
243 to tentatively identify the detected products. In order to ensure mass precision lockspray infusion was
244 used during all the injections.

245

246

247 **3. Results & discussion**

248 **3.1. Occurrence and removal in wastewater treatment plants**

249 First, the concentrations of furosemide were evaluated in the Seine-Centre WWTP, along with the
250 possible presence of its known degradation products saluamine and pyridinium of furosemide. This
251 WWTP was chosen because it is located directly downstream of the city of Paris, thus receiving most
252 of Parisian wastewaters.

253

254 The two collected raw water samples (2021-12-07 and 2021-12-08 samples) exhibited substantial
255 concentrations of furosemide of 3351 and 2819 ng.L^{-1} respectively (table 2). These concentrations
256 were consistent with those found in recent literature for WWTPs raw water in other European
257 countries. Concentrations between 1 to 5 $\mu\text{g.L}^{-1}$ were found: 1491 ng.L^{-1} in Sweden (Baresel et al.
258 2019), 2625 ng.L^{-1} in Poland (Kot-Wasik et al. 2016), 2601 ng.L^{-1} in Greece (Papageorgiou et al. 2019),

259 1901 ng.L⁻¹ and 3410 ng.L⁻¹ in Spain (Collado et al. 2014; Celic et al. 2019), 4577 ng.L⁻¹ in Portugal
260 (Santos et al. 2013), 1652 ng.L⁻¹ in Italy (Feo et al. 2020), 2916 ng.L⁻¹ and in Switzerland (Lee et al. 2014).
261

262 Our samples concentrations at 24 hour interval were of the same order of magnitude, indicating little
263 variation over this period. This result is in contrast to Gomez-Canela et al. (2019), who observed
264 significant variations in furosemide concentrations over 5 consecutive days, but on nursing home
265 effluents. However, for furosemide, other studies usually reported seasonal rather than weekly
266 variations with lower concentrations in summer (Kot-Wasik et al. 2016; Delli Compagni et al. 2020).

267
268 The known degradation products of furosemide, saluamine, furfural and pyridinium of furosemide,
269 have been searched for in wastewater. Furfural could not be analyzed with our method, the compound
270 being possibly too small and/or too polar to be extracted and analyzed with the same method as the
271 other three. Although described as a furosemide transformation product since long ago (Andreasen et
272 al. 1942), reports on saluamine toxicity and occurrence in the environment are scarce. Nonetheless,
273 we found saluamine and pyridinium of furosemide in WWTP raw water both at concentrations of a
274 few thousands of ng.L⁻¹ (table 2).

275
276 **Table 2.** Concentrations (ng.L⁻¹) of Furosemide, Pyridinium of Furosemide and Saluamine in WWTP
277 water samples (RW = raw wastewater, TW = treated wastewater) (BLACK AND WHITE TABLE)

278 **<Table 2>**

279
280 Interestingly, the distribution between the three compounds in raw water was about one third for
281 each, which means that the degradation products are formed upstream of the WWTP, probably during
282 the journey through the water system as commonly observed. Indeed, other drug TPs have already
283 been found in WWTP influents such as N4-Acetylsulfamethoxazole, 2-hydroxycarbamazepine, O-
284 desmethylvenlafaxine, 4-hydroxydiclofenac which are TPs of sulfamethoxazole, carbamazepine,

285 venlafaxine and diclofenac, respectively (Aymerich et al. 2016). Furosemide could have been
286 hydrolyzed or biodegraded in the wastewater transport system. The hydrolysis of furosemide has been
287 known since the 70's and leads to the formation of saluamine in an acidic environment (Bundgaard et
288 al. 1988; Andreasen et al. 1982) and some studies showed that saluamine and pyridinium of
289 furosemide can be produced by biotransformation of furosemide by several microorganisms (Hezari &
290 Davis 1993; Laurencé et al. 2014; Olvera-vargas et al. 2016). These three compounds are still present
291 in the two WWTP effluents samples at several hundred nanograms per liter (table 2). Saluamine can
292 be formed in water sediments (Li et al. 2014) and by photolysis (Bundgaard et al. 1988) but to our
293 knowledge, this is the first evidence of saluamine and pyridinium of furosemide presence in
294 wastewater.

295

296

<Figure 1>

297 **Figure 1.** Removal percentage of furosemide, saluamine and pyridinium of furosemide in Seine-Centre
298 WWTP. Solid bars represent concentrations in raw samples and hatched bars represent concentrations
299 in samples after treatment in WWTP. The percentages shown on the hatched bars indicate the percent
300 removal for each compound. Error bars represent standard error. (BLACK AND WHITE FIGURE)

301

302 All three compounds exhibited some removal in the WWTP. Yields of removal for each compound were
303 very similar between the two sampling dates (figure 1). For furosemide, a reduction of over 70% was
304 observed for both samples, which ranked in the higher range of furosemide removal by comparison
305 with data from the literature. Matamoros et al. (2009) and Kasprzyk-Hordern et al. (2009) found similar
306 furosemide removal rates (65% and 74%, respectively), but other studies found variable removals, with
307 the lowest around 25% (Park et al. 2016), or 40 to 50% removal for WWTP with conventional
308 mechanical-biological treatment (Kot-Wasik et al. 2016, Gros et al. 2010). In some cases, the sampling
309 period could explain the differences in removal; Matamoros et al. (2009) and Kasprzyk-Hordern et al.
310 (2009) samples were collected in spring and summer while Kot-Wasik et al. (2016) collected theirs in

311 winter. Castiglioni et al. (2006) showed that the elimination rate of furosemide was much lower in
312 winter than in summer (8% versus 54%). These differences could be related to the lower temperatures
313 in winter, which possibly attenuated the biological activity. However, in our case, the samples were
314 collected in winter. Thus, the differences in efficiency of the treatment plants for furosemide removal
315 could be explained by the different processes used in the plants. For example, the plant studied in
316 Matamoros et al. (2009) included several types of wetland constructs that were shown to be relatively
317 efficient for the elimination of furosemide in recent literature (Ahmed et al. 2017; Machado et al.
318 2017). In the case of Seine-Centre, the purification process, which includes biofiltration, nitrification
319 and denitrification processes, also promoted an efficient elimination of furosemide.

320

321 **Table 3.** Concentrations (in ng.L⁻¹) of furosemide in WWTP effluents. (BLACK AND WHITE TABLE)

322

<Table 3>

323 *Tracol & Duchemin 2007¹; Celic et al. 2019²; Santos et al. 2013³; Castiglioni et al. 2018⁴; Giebułtowicz et al. 2016⁵; Huber*
324 *et al. 2016⁶; Frieberg 2018⁷; Diaz-Sosa et al. 2020⁸; Papageorgiou et al. 2016⁹; Kleywegt et al. 2016¹⁰; Estrada-Arriaga et*
325 *al. 2016¹¹; Afsa et al. 2020¹²; Hanamoto et al. 2018¹³; Al-Odaini et al. 2013¹⁴.*

326

327 In spite of a good elimination rate of furosemide and its TPs saluamine and pyridinium of furosemide
328 (70 to 90% removal), several hundreds of nanograms per liter still remained in the wastewater effluent.
329 Many authors reported significant concentrations of furosemide at the outlet of wastewater treatment
330 plants (table 3). Concentrations exceeding 10 µg.L⁻¹ were even found in a few studies (22300 ng.L⁻¹ in
331 De vieno et al. (2017), 26000 ng.L⁻¹ in Vymazal et al. (2017), and 11000 ng.L⁻¹ in Rozman et al. (2017)).

332

333 WWTP effluents concentrations not only depend on the influent concentrations, but also on the
334 treatment processes used within each WWTP. In some cases, furosemide concentrations can be higher
335 at the WWTP outlet than at the inlet (Kleywegt et al. 2016). Due to the fact that an important fraction
336 of furosemide is excreted as a glucuro-conjugated form (Yang et al. 2006), and thus not taken into
337 account during the analysis, this difference could be assigned to the deconjugation occurring during

338 the WWTP treatment, leading to an increased concentration of the native, unchanged form of
339 furosemide at the outlet. It cannot be excluded that in our raw samples, furosemide concentrations
340 could be underestimated for similar reasons, and consequently, the removal percentage as well.
341 Overall, the WWTP appeared to be relatively effective in removing furosemide as well as its TPs, thus
342 showing that there was no additional production of the targeted TPs during the biological process.

343

344

345 **3.2. Occurrence in residential care home wastewater**

346 The concentration of furosemide and its TPs was then evaluated in RCH wastewater samples (Table 4).
347 We anticipated this type of sample to be highly-charged in furosemide, as this medication is frequently
348 prescribed at high doses to elderly people affected by chronic and age-related diseases such as
349 hypertension and heart failure. Effluents from three different RCH were analyzed. In all three samples,
350 significant amounts of furosemide were found, and to a lesser extent, of pyridinium of furosemide and
351 saluamine, but their concentrations and proportions relative to each other were variable.

352

353 **Table 4.** Concentration of furosemide, saluamine and pyridinium of furosemide in residential care
354 homes wastewater in dissolved and particulate phases. (BLACK AND WHITE TABLE).

355

<Table 4>

356

357 Furosemide concentration variation across the three sites could be directly related to their hosting
358 capacity. The highest furosemide concentration was found in RCH2 which also had the highest hosting
359 capacity and on the contrary, the lowest concentration was observed in RCH3 which also has the
360 lowest number of beds. On the other hand, Gomez-Canela et al. (2019) showed that there were quite
361 large furosemide concentration variations (of a few thousand nanograms per liter) within the same
362 institution over several samples, thus making it more relevant in this case to discuss the orders of
363 magnitude. The concentrations of furosemide in the RCH1 and RCH2 samples were quite close, but the

364 concentration of saluamine was 2-fold higher in RCH2. The higher proportion of saluamine in RCH2
365 could be explained by a greater biological activity which could lead to a more important biodegradation
366 of furosemide (Laurencé et al. 2014; Olvera-Vargas et al. 2016). The proportion of pyridinium of
367 furosemide was also much lower in RCH2, implying a preferential transformation of furosemide to
368 saluamine in this case. This difference could be explained by the neutral pH (7.10 at 20°C) indeed the
369 formation of saluamine is promoted in acidic conditions (Bundgaard et al. 1988; Andreasen et al. 1982).

370

371 Few studies have investigated the presence of furosemide in non-treated effluents of RCH. Gomez-
372 Canela et al. (2019) reported concentrations up to 3200 ng.L⁻¹ and 3400 ng.L⁻¹ in two different senior
373 residence effluents in Spain with a capacity of 103 and 96 beds, respectively, and Nagarnaik et al.
374 (2010) found 1031 ng.L⁻¹ in nursing care facility effluents which were considerably lower than the
375 concentrations in this study for an equivalent hosting capacity. Slightly higher concentrations (median
376 6120 ng.L⁻¹ and maximum 25100 ng.L⁻¹) were found by Kleywegt et al. (2016) in a long care center for
377 senior residents and other clients in Canada but with a much larger capacity (289 beds).

378

379 Furosemide and its major degradation products were also analyzed in the solid fraction of RCH1 and
380 RCH2 samples (Table 4). Although the three compounds were difficult to analyze because of an
381 important matrix effect, significant concentrations (several hundreds of nanograms per gram) were
382 found.

383

384 Saluamine has only been detected once in natural sediments doped with furosemide (Li et al. 2014)
385 but our present work uncovers for the first time the presence of pyridinium of furosemide in the solid
386 fraction. In sediments, furosemide concentrations of 7, 98, and 350 ng.g⁻¹ were reported (Ferreira Da
387 Silva et al. (2011), Ferrari et al. (2011), and Björklund et al. (2016) respectively). The concentrations
388 obtained in our study are closer to those obtained in WWTP sludge, where the concentrations reached
389 up to 686 ng.g⁻¹ (Huber et al. 2016) and 3602 ng.g⁻¹ (Salgado et al. 2011). These values indicate that a

390 significant fraction of furosemide is adsorbed onto the particulate phase. The partition coefficients
391 between the liquid and solid phase (K_d) are good indicators of the compounds affinity with the solid
392 phase. The K_d values of the suspended matter of the samples RCH1 and RCH2 were 7.7 and 5.4 $L.kg^{-1}$
393 respectively. Jelic et al. (2012) found a K_d of 43 $L.kg^{-1}$ for furosemide in the solid phase of WWTP
394 effluent which is 5 to 8 fold higher than the values found in this study. The K_d value is very dependent
395 on the matrix considered. For example, in sediments, Björklund et al. (2016) found a K_d of 2517 $L.kg^{-1}$
396 which shows a very good affinity of furosemide for sediments whereas Jelic et al. (2012) found a lower
397 K_d in thickened sludge (127 $L.kg^{-1}$) and digested sludge (110 $L.kg^{-1}$). In a Membrane BioReactor (MBR)
398 or Anaerobic-Anoxic-Aerobic system (A2O) -treated sludge, Park et al. (2017) obtained a K_d of 2.1,
399 which is quite low in comparison. Narumya et al. (2013) showed a decrease of the K_d for furosemide
400 before and after sludge digestion. In sample RCH1, the K_d value of pyridinium of furosemide (12.5 $L.kg^{-1}$)
401 was quite close to the one of furosemide, but was much lower in RCH2 (0.36 $L.kg^{-1}$), which shows a
402 much better affinity of furosemide for the solid phase in sample 1. K_d values for saluamine were more
403 important (103.7 and 18.3 $L.kg^{-1}$), meaning that a significant fraction of saluamine was adsorbed on
404 the solid phase. Thus, total saluamine load in wastewater could be largely underestimated when only
405 performing the conventional analysis of the dissolved phase.

406

407

408 **3.3. Advanced oxidation in pure water and in residential care houses wastewater**

409 **3.3.1. Oxidation of furosemide in ultrapure water**

410 The partial resistance of hundreds of compounds to conventional wastewater treatments highlights
411 the need to go further in the degradation processes. We chose two AOPs which have the potential to
412 upgrade WWTPs worldwide and are already used in some countries like Japan or Switzerland (Prasse
413 et al, 2015). Chlorination oxidation experiments were also performed (Figures S3, S4 and Table S1).
414 Both oxidation processes have been used for a long time for disinfection and the oxidants produced
415 are likely to react with furosemide. The photodegradation of furosemide has been known for several

416 decades. UV irradiation leads to the substitution of chlorine by a hydroxyl group, to the hydrolysis of
417 the furfuryl group, that results in the production of furfural and saluamine, or the oxidation of the
418 sulfamoyl group (Bundgaard et al. 1988; Moore & Burt 1981). Furosemide is also degraded in sunlight
419 or artificial laboratory light which makes it a good candidate for UV degradation (Starling et al. 2019).
420 The use of ozonation has increased in recent years for the treatment of wastewaters due to its
421 effectiveness in removing organic compounds. As an electrophilic agent, the presence of electron-rich
422 moieties such as aromatic compounds determines the reactivity with ozone (Lim et al. 2022).
423 According to Zoumpouli et al. (2021), furosemide is expected to present an important reactivity with
424 ozone due to the presence of the furan ring and the aniline group. However, the potential formation
425 of furosemide TPs, especially pyridinium of furosemide, remains unknown for AOPs. AOPs are known
426 to generate a variety of TPs that are potentially hazardous to ecosystems, and whose identification is
427 a challenge due to the lack of analytical standards. Furosemide degradation was thus first investigated
428 in ultrapure water spiked with furosemide. Pyridinium of furosemide was quantified after the
429 oxidation, and aliquots were also taken to monitor the formation of unknown TPs by high-resolution
430 mass spectrometry.

431
432 As anticipated, the two AOPs were effective in degrading furosemide under our experimental
433 conditions. Ozonation was the most efficient (see supplementary information Figures S1, S2).

434
435 **Table 5.** Pyridinium of furosemide concentration and furosemide percentage of conversion during
436 oxidation experiments. (BLACK AND WHITE TABLE)

437 **<Table 5>**

438
439 The pyridinium of furosemide was produced during both oxidation experiments (table 5). During the
440 UV/H₂O₂ oxidation, the aliquot taken at 210 minutes already presented a few micrograms per liter of
441 pyridinium with 1.5% conversion rate of furosemide. This rate reached 5.8% after 300 minutes.

442 However, during this 5h-time lapse, less than 10% of furosemide was degraded, which means that
443 pyridinium formation is slow, probably because it involves reaction intermediates (Olvera-vargas et al.
444 2016; Zoumpouli et al. 2021). Pyridinium of furosemide was also produced by ozonation within a few
445 minutes. Its production started immediately after ozone addition, and its concentration increased
446 gradually until 4 minutes, with a furosemide conversion rate of 3.2% which remained unchanged after
447 10 minutes, in conjunction with a total consumption of ozone and furosemide concentration reaching
448 a plateau. As in the UV/H₂O₂ experiment, pyridinium of furosemide did not seem to be degraded by
449 the ozone treatment. Pyridinium of furosemide was also detected after chlorination (35 mgCl₂.L⁻¹) of
450 furosemide (3 mg.L⁻¹), with a maximum conversion rate of 1.4% after only 2 min of reaction time, but
451 contrary to the other oxidation processes, its concentration quickly decreased after 5 min, probably
452 because of the formation of chlorinated derivatives (Table S1). This result might be of importance for
453 the quality of drinking water produced from resources impacted by furosemide, even though the fast
454 degradation of pyridinium of furosemide seems to indicate a low risk of exposure.

455

456 **3.3.2. Oxidation of residential care houses wastewater**

457 In order to get insights on the AOPs efficiencies with furosemide heavily-loaded real samples and on
458 the formation of TPs in the presence of wastewater matrix components, we next subjected the
459 effluents from the three RCH samples to the two AOPs (figure 2). The overall abatement was quite
460 variable from one sample to another and for the different compounds, depending on the water
461 parameters and the oxidation process used. Ozonation was very effective at removing the three
462 pollutants, with an important reduction (below quantification limit) of furosemide and pyridinium of
463 furosemide for the three tested samples (figure 2). As for chlorination (supplementary data, figure S4,
464 SI), abatement rates of almost 100% were observed for furosemide and pyridinium. These results were
465 thus consistent with the experiments conducted with ultrapure water. Although the lifetime of ozone
466 in WWTP effluent is shorter because of background absorptions (Lim et al. 2022), ozone was injected
467 continuously in the samples and therefore furosemide reached higher removals than in the ultra-pure

468 water experiment (figure S2, SI). This could also explain why pyridinium of furosemide was not
469 observed in the ozonated samples, a higher ozone dose probably leading to its decomposition.

470

471 <Figure 2>

472 **Figure 2.** Effectiveness of a) UV/H₂O₂ and b) ozonation on residential care home (RCH) discharge water.

473 The bars represent removal efficiency in percentage calculated from initial concentration for each
474 compound (dark grey = furosemide, medium grey = saluamine, light grey = Pyridinium of furosemide).

475 Error bars represent standard error. For Ozonation, the samples were exposed for 1.5h with 2L.h⁻¹ O₃.

476 For UV/H₂O₂, the samples were exposed for 5H to (0.375xCOD value)mg.L⁻¹ H₂O₂. (BLACK AND WHITE

477 FIGURE)

478

479 Our results are in accordance with those reported in the litterature. Munoz et al. (2009) showed a

480 100% removal of furosemide and Gomez et al. (2008) a removal of 99% for both O₃ and O₃ with H₂O₂

481 treatments. Ikonen et al. (2021) obtained a reduction of 99.7% of furosemide in wastewater effluents

482 and Lee et al. (2012) observed a reduction to below their detection limits with a dose of 2 mg O₃.L⁻¹.

483 Experiments combining ozonation with other treatments such as biological activated carbon

484 (Reungoat et al. 2012) or ultrasonication (Ibanez et al. 2013) did not significantly improve the removal

485 efficiency and showed that the ozone treatment is responsible for most of the elimination of

486 furosemide.

487

488 Contrary to furosemide and pyridinium, saluamine was less removed and its removal rate was variable

489 depending on the sample. Saluamine was well degraded in the RCH3 sample, but higher concentrations

490 of saluamine were observed from RCH1 and RCH2 samples after ozonation. This production of

491 saluamine could be explained by the conversion of both furosemide and pyridinium to saluamine in

492 the conditions of these samples (e.g., different initial concentrations, competition reactions of ozone

493 with wastewater constituents such as nitrites or organic matter leading to a decrease in saluamine

494 decomposition). Contrary to experiments in ultrapure water, no additional formation of pyridinium
495 was observed, and all pyridinium already present in the RCH samples was degraded by ozone.

496
497 Furosemide removal by UV/H₂O₂ was between 70 and 80% for all the samples, which is very close to
498 the 82% removal found by Jie (2012) in hospital wastewater. However, the effectiveness of UV/H₂O₂
499 on furosemide elimination is still uncertain. Park et al. (2017) described the use of UV irradiation alone
500 as not very effective on pharmaceuticals and personal care products, and only achieved 23% of
501 removal of furosemide in WWTP post-treatment. However, as the treatment was performed during a
502 purification process in a WWTP, the suspended particles can interfere and reduce the effectiveness of
503 UV as compared to laboratory experiments performed with filtered samples. With UV/H₂O₂, Ikonen et
504 al. (2021) found no removal of furosemide while Singh et al. (2015) observed a complete degradation,
505 but with a lamp 8 times more powerful (Joule/cm²). The efficiency of furosemide degradation by
506 UV/H₂O₂ thus seems to be strongly dependent on the UV irradiation intensity. Similarly to ozonation
507 and chlorination, large differences of removal were observed between the three samples for the two
508 degradation products.

509

510 **3.4. Generation of furosemide new transformation by-products**

511 As these advanced oxidation processes have been reported to generate numerous by-products by
512 reaction with organic contaminants, many of them being often potentially more toxic than their parent
513 molecules (reviewed in Prasse et al. 2015), the formation of other transformation products of
514 furosemide was investigated after the oxidation experiments by high-resolution mass spectrometry
515 (HRMS). Noteworthy, two other by-products of furosemide were identified: one during chlorination
516 (Figure 2 e.) and one during UV/H₂O₂ treatment (Figure 3f.).

517

518

<Figure 3>

519 **Figure 3.** Molecular Structure of a. furosemide (m/z 329.74) and its transformation products. b.
520 Pyridinium of furosemide (m/z 328.73), c. Furfural (m/z 96.08), d. Saluamine (m/z 250.66).
521 Transformation products identified by high-resolution mass spectrometry analysis: e. Chlorination by
522 product m/z 276.99; f. UV/H₂O₂ by product m/z 311.03. (BLACK AND WHITE FIGURE).

523

524 To our knowledge, the product 3.e. was not clearly mentioned in the literature. However, Aalizadeh et
525 al. (2018) found a by-product of furosemide of similar mass (m/z 276.99) after ozonation but they did
526 not identify the structure. On the other hand, the compound 3.f. from UV/H₂O₂ oxidation has already
527 been observed as a photodegradation product of furosemide after exposure to fluorescent lamps, and
528 its structure was identified with ¹H-NMR (Katsura et al. 2015). Its structure resembles the one of
529 furosemide with m/z 311.03, except that the chlorine has been replaced by a hydroxyl group. In
530 Jakimska et al. (2014), this product has been found after photodegradation experiments carried out
531 on river water samples and was considered as one of the most persistent transformation products.
532 These authors then found it in WWTP influents and effluents. In our study, the 3.f product formation
533 kinetics was studied (see supplementary data, figure S4), showing that its degradation occurred after
534 one hour.

535

536 Jakimska et al. (2014) and Katsura et al. (2015) also identified saluamine and other degradation
537 products (m/z 352, m/z 555, m/z 231, m/z 295, m/z 215) which not only corresponded to losses or
538 substitution of Cl groups on furosemide or saluamine but also sometimes to recombination of
539 fragments as in the study of Della-Greca et al. (2004), which identified a dimer (m/z 623) after
540 photodegradation of furosemide. These by-products were not found in our oxidation experiments. The
541 Della-Greca et al. (2004) dimer is larger than the other molecules and very polar: it is possible that our
542 extraction method did not retain it. Moreover, these degradation products were observed after UV
543 irradiation alone, thus it is conceivable that by combining UV with H₂O₂ treatment, they were further
544 degraded as well, as described by Starling et al. (2017). Indeed, these authors found similar

545 degradation products of furosemide after UV and UV/H₂O₂ treatment, but they did not remain stable
546 after H₂O₂ addition. If these compounds were present in our experiments, they may be below the limit
547 of detection.

548
549 The m/z 276 and m/z 288 transformation products obtained after ozonation have also been mentioned
550 in the literature but their structure could not be elucidated (Aalizadeh et al. 2019). In Zoumpouli et al.
551 (2021), a molecule with a pyridinium structure (m/z 328) and a saluamine-like molecule (m/z 265) were
552 also obtained by ozonation of the furan ring.

553
554 Taken together, our data show that ozonation, UV/H₂O₂ and chlorination degrade furosemide,
555 generating several different by-products. High oxidant doses were chosen to maximize the formation
556 of transformation products in order to enhance their analytical detection and identification, so their
557 presence should still be investigated at realistic doses (e.g., at a specific ozone dose < 1 mgO₃/mgDOC)
558 and at the industrial scale (Guillossou et al, 2020). Besides saluamine production, the pyridinium of
559 furosemide was formed under all three conditions but was only degraded by chlorination.
560 Furthermore, chlorination also generated a product (m/z 276) never described before, but which was
561 degraded after a few hours. Another product (m/z 311), resulting from photodegradation and
562 previously reported (Katsura et al. 2015), was also identified.

563

564

565 **4. Conclusion**

566 This study provides new findings on the occurrence and fate of furosemide from its origin to
567 wastewater treatment plants. The known degradation products of furosemide, saluamine and
568 pyridinium of furosemide were searched and quantified for the first time in real samples (WWTP inlets
569 and outlets and RCH wastewaters). The Seine-Centre WWTP showed a good removal of furosemide
570 (>70%), saluamine (>80%) and pyridinium (>90%). However, concentrations of several hundred ng.L⁻¹

571 were found after treatment and are released into the aquatic environment. These concentrations
572 sometimes exceed $10 \mu\text{g}\cdot\text{L}^{-1}$ in the literature for furosemide and may pose a risk to ecosystems.

573

574 To limit the release of these pharmaceutical compounds in the environment, we investigated AOPs
575 and the possible production of TPs. UV/H₂O₂, chlorination and ozonation were first shown to be
576 effective in degrading furosemide in ultrapure water. In RCH wastewater, ozonation and chlorination
577 showed complete degradation of furosemide and pyridinium, but saluamine was still present in the
578 samples after treatment due to a possible production. UV/H₂O₂ showed variable removal rates
579 depending on the compounds. Although these treatments appeared quite effective, new TPs were
580 identified following the chlorination (m/z 276) and ozonation (m/z 311) processes. The elimination of
581 pollutants is used as a criterion for the evaluation of AOPs, but the presence of TPs should also be
582 considered. Before concluding on the effectiveness of these advanced treatments, the toxicity and
583 persistence of the end-products should be investigated. Thus, our study underlines the necessity and
584 the relevance to use approaches such as non-targeted analysis for the detection of emerging
585 pollutants, to unveil new TPs, combined with toxicity assessments in order to improve the
586 characterization and design of wastewater treatment processes. Keeping in mind that these data alone
587 do not provide information on their toxic risk and cocktail effects, our study highlights the need to
588 develop an integrative strategy coupling state-of-the art chemical analysis techniques with
589 ecotoxicological tests with defined end-points.

590

591 **CRedit author statement**

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599

600 **Acknowledgments**

601 Thanks to SIAAP for providing the WWTP inlet and outlet samples and to PRAMMICS platform (OSU-
602 EFLUVE UMS 3563) for the analytical equipment (UPLC-IMS-QTOF and AutoTrace SPE). The funding
603 was provided by the OPUR program and WaterOmics project (ANR-17-CE34-0009-01). Thanks to the
604 LDAR sampling service and specifically Benoît CHIRON and Jérôme PRADES for the residential care
605 homes samples. Thanks to Université Paris-Est Créteil and to the French ministry of higher education
606 research and innovation for F. Sandre PhD fellowship.

607

608

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