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1 **Pharmaceuticals in the marine environment: what are the present** 2 **challenges in their monitoring?**

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9 **Abstract:** During the last years, there has been a growing interest in the research focused on the
10 pharmaceutical residues in the environment. Their presence has been widely described in fresh surface
11 and ground waters, but less investigated in the marine environment, though it is the last receiver of the
12 continental contamination. Those compounds have been recognized as a possible threat to aquatic
13 ecosystems, due to their inherent biological activity and their “pseudo-persistence”. In Europe, the
14 Marine Strategy Framework Directive (2008) placed pharmaceuticals on the indicative list of elements
15 covering the qualitative and quantitative mix of the various pressures on the environmental status of
16 marine waters. Thus, pharmaceuticals monitoring data in marine waters are necessary to know the
17 water quality and allow enhancing future regulations and management decisions. However, some
18 marine environment specific features, such as the strong dilution occurring, the complex
19 hydrodynamic and local logistical constraints are making this monitoring a very difficult and
20 demanding task. A review of the current practices in monitoring strategies of pharmaceuticals in
21 marine matrices (water, sediment and biota) is provided through the analysis of the available recent
22 scientific literature. Key points are highlighted for the different strategy steps of marine waters
23 monitoring. For example, the knowledge of the site topology, hydrodynamic conditions and direct or
24 indirect contamination sources, is very useful when determining the sampling stations during the
25 sampling strategy consideration. Key knowledge gap priorities for future research are identified and
26 discussed, such as the need of suitable passive samplers to monitor pharmaceuticals levels, and to
27 conduct long-term ecotoxicological tests on sensitive marine species at environmental levels, in a view
28 to better assess the risk of these compounds for the marine ecosystems.

29 **Keywords:** pharmaceuticals, monitoring, marine environment

30 **Highlights:**

- 31 • Need for a more systematic inclusion of pharmaceuticals in monitoring strategies.
- 32 • Site-specific multicriteria analysis for sampling strategy is required.
- 33 • Prospects are passive sampling, non-target analysis and integrative monitoring.

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49 SM1: Watch lists of pharmaceuticals in water

50 SM2: Dataset on pharmaceutical occurrence in seawater (published papers over the 2014-2020 period) and statistical analysis (R software, version 3.6.3.)

51 SM3: Detailed maximal concentrations of pharmaceuticals in seawater, sediments/SPM and biota from the selected published papers (2014-2020)

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54

55

59 I. Introduction

60 Over 4,000 pharmaceuticals are used all over the world for medical and veterinary health care, as well
61 as growth promotion of livestock (Boxall Alistair et al., 2012). After use, pharmaceuticals end up in
62 the environment as metabolites or parent compounds, mainly via effluent rejection after treatment in
63 wastewater treatment plants (WWTPs) where they are often inefficiently removed. Identified
64 secondary pharmaceutical sources in the environment are manufacturing facilities, land application of
65 sewage sludge and agriculture, aquaculture, and veterinary practices (UNESCO and HELCOM, 2017).
66 Their occurrence has been widely described in fresh surface waters and in ground waters (Beek et al.,
67 2016) but their presence in the marine environment has been less investigated mainly because of the
68 complexity of the matrices to analyze and of pharmaceutical dilution in marine waters (Arpin-Pont et
69 al., 2016; Gaw et al., 2014). However, there is a growing interest these last years for this compartment
70 considered as the last receiver of continental contamination.

71 Pharmaceuticals are biologically active compounds designed to interact with specific physiological
72 pathways of target organisms. They may cause a risk to the health of marine non-target organisms and
73 act as additional stressors on marine ecosystems already impacted by climate change, overfishing and
74 eutrophication (Crain et al., 2009; Desbiolles et al., 2018; Mezzelani et al., 2018). As the antibiotic
75 class is one of the most frequently detected in marine waters and sediments (Arpin-Pont et al., 2016),

76 the overall contamination lead to the outbreak of antibiotic resistant bacteria at particular concern
77 (Marti et al., 2014).

78 Monitoring is generally defined as a long-term, standardized measurement and observation of the
79 aquatic environment to define status and trends of the contamination. The use of monitoring has
80 evolved to help determine trends in the quality of the aquatic environment and how that quality is
81 affected by the release of contaminants, other anthropic activities and by waste treatment operations
82 (UNESCO/WHO/UNEP, 1996). The availability of effective tools and standardized methodologies are
83 crucial for one-time or routine chemical contaminants monitoring, in a view to collect relevant
84 information at set locations and at regular intervals. The generation of such data is useful to future
85 decisions concerning the quality management of the studied marine areas and for further
86 environmental risk assessment initiatives.

87 Unfortunately, to this date, European and international legislation on chemical contamination of
88 marine resources concerns very few pharmaceuticals. In western Europe, the Convention for the
89 Protection of the Marine Environment of the North-East Atlantic (the ‘OSPAR Convention’ (OSPAR
90 Commission, 1992)) aims to monitor chemicals in marine waters of North-East Atlantic Ocean and
91 proposes guidelines with recommendations for seawater sampling and analysis of organic
92 contaminants in oceanic, coastal and estuarine waters (OSPAR Commission, 2013). Twenty
93 pharmaceuticals and five hormones are listed as ‘of possible concern’ and the antifungal clotrimazole
94 is listed as ‘of priority action’ (Supplementary Material 1). European Union regulation progresses to
95 the integration of pharmaceuticals in the Watch List of the Water Framework Directive (WFD)
96 2000/60/EC, updated in July 2018, covering freshwater and transitional waters (estuarine and coastal
97 areas up to one nautical mile from the shore). To this day, seven pharmaceutical compounds are
98 included in the Watch List: three hormones (estrone (E1), 17-beta-estradiol (E2) and 17-a-
99 ethinylestradiol (EE2)) and five antibiotics (amoxicillin, ciprofloxacin and the macrolides
100 azithromycin, clarithromycin and erythromycin), making them potential candidates for the Priority
101 Substance List. As well, monitoring programs for continuous evaluation of the marine waters
102 environmental status should be established according to the Marine Strategy Framework Directive
103 (MSFD) 2008/56/EC, including the evaluation of the impact of hazardous substances as
104 pharmaceuticals (European Parliament and Council, 2008).

105 This review aims to provide an overview of the current practices in pharmaceutical monitoring
106 strategies in the marine environment through the analysis of scientific literature, and to identify the
107 key knowledge gap priorities for future research. The different steps of the monitoring strategy
108 development are dissected to identify critical aspects to consider and the limits frequently encountered.

109 The research articles focusing of pharmaceutical occurrence in the marine environment included in
110 this review were published between the period 2012-2020 and selected according to several criteria
111 related to a previous article by (Arpin-Pont et al., 2016). As recommended by the European
112 Commission's "Guidance document on analytical quality control and validation procedures for
113 pesticide residues analysis in food and feed" ("SANCO/12571/2013" rev. 0 19/11/2013): (i) internal
114 standards are used; (ii) the given pharmaceutical concentrations are from gas chromatography or liquid
115 chromatography- tandem mass spectrometry (GC- or LC-MS/MS) analysis; (iii) the overall analytical
116 procedure from the sample treatment to the analysis must be developed and validated (linearity, limit
117 of quantification determination, matrix effect study, confirmation with two MRM) in marine waters,
118 sediments, or biota, but not necessarily following a whole standard validation; (iv) recoveries are in
119 the range of 70-120%; and (vi) precision of the instrumental method expressed as the relative standard
120 deviation (RSD) is under 20%.

121

122 **II. Monitoring of pharmaceuticals in the marine environment: a literature** 123 **analysis**

124 **II.1. Steps in strategy development**

125 **II.1.1. Definition of the objectives**

126 Generally, the main objective is to provide an overview regarding the occurrence of a panel of
127 pharmaceuticals in a defined area for a specific time. Surveillance, operational and investigative
128 monitoring are distinguished (European Commission and Directorate-General for the Environment,
129 2009). Surveillance monitoring is implemented mainly to assess long-term changes in natural or
130 anthropogenic conditions. Operational and investigative monitoring are problems or source-oriented
131 (Choi et al., 2020; Rimayi et al., 2018). Operational monitoring is focused on water bodies identified
132 at risk to not meet good environmental status and investigative monitoring is related to water bodies
133 that failed or did not meet environmental objectives.

134 Monitoring strategies can be aimed to generate a comprehensive dataset of the contamination (Biel-
135 Maeso et al., 2018; Kötke et al., 2019; Zhao et al., 2017) or to be a preliminary study intended as a
136 first-step exploratory survey establishing baseline levels which will facilitate comparisons through
137 long-term monitoring (Long et al., 2013). The objective is sometimes to fill data gaps or to complete
138 the results from previous research (Ali et al., 2018; Borecka et al., 2015). The identification of the
139 compounds and the observed concentration ranges are defined for one (Ali et al., 2017; Alygizakis et
140 al., 2016) or several compartments in a view to assess the distribution (or partition) of the compounds
141 between the different matrices, for example dissolved and suspended particulate matter (Cantwell et

142 al., 2017), water and sediment (Chen et al., 2015b; Moreno-González et al., 2015), water and
143 organisms (McEneff et al., 2014). The elucidation of contaminant spatial status or temporal trends can
144 also be looked for (Cantwell et al., 2016; Chen et al., 2015b; Moreno-González et al., 2015).

145 Along these occurrence issues, monitoring is sometimes intended to identify pollution sources
146 (Moreno-González et al., 2015; Zhang et al., 2013), and mainly point sources (Nödler et al., 2016).
147 The influence of a defined pollution source (e.g. WWTP effluent, river discharge) and the attenuation
148 process of the contamination after release in the marine waters can be assessed by comparing the
149 concentrations between the WWTP effluent or the riverine inputs and receiving waters (Choi et al.,
150 2020; Lara-Martín et al., 2014; Zhang et al., 2012). As an example of investigative monitoring, a one-
151 time contamination through unregulated discharge was monitored at the Umgeni River (South Africa)
152 estuary after an improper disposal of medical wastes (Rimayi et al., 2018).

153

154 Besides these main objectives, the impact of factors such as salinity, tides, hydrodynamics or
155 physicochemical properties of the compounds on their environmental behavior (spatial patterns) and
156 their occurrence (concentration levels) may be investigated in the same time (Bayen et al., 2013;
157 Cantwell et al., 2018; Zhao et al., 2015). Combination of river discharge flow rates and measured
158 concentrations allows an estimation of pharmaceutical fluxes entering into coastal areas in the
159 dissolved or particular phase (Cantwell et al., 2016; Szymczycha et al., 2020; Zhao et al., 2017).
160 Monitoring of pharmaceuticals also permits to collect data in order to evaluate the ecological risk at
161 environmental concentrations (Afsa et al., 2019; Azaroff et al., 2020; Biel-Maeso et al., 2018; Chen et
162 al., 2015b; Szymczycha et al., 2020), or the potential exposure (Chen et al., 2015b) and/or risks for
163 humans through seafood consumption (Silva et al., 2017).

164

165 **II.1.2. Selection of Substances**

166 Considering the great number of pharmaceuticals sold and used all over the world, a large scale
167 screening of pharmaceutical contamination would be preferable to have a comprehensive overview of
168 the studied marine area status. However, the differences in physical and chemical properties of target
169 compounds and the complexity of environmental matrices make their simultaneous analysis
170 challenging. It requires thus a compromise in the choice of the compounds between a large scale
171 screening of the substances present in the media and the technical feasibility. The selection of target
172 molecules is generally based on several criteria detailed below: (i) pre-existing lists of compounds
173 defined by international and/or national regulations or guidelines, (ii) information on local

174 prescriptions and/or consumption habits, (iii) previous occurrence data in the environment, and (iv)
175 physicochemical properties and environmental fate of these molecules.

176 As few pharmaceuticals are regulated, the selection of contaminants may be pre-defined by existing
177 lists of compounds defined as of possible concern for aquatic environments, published by national
178 environmental agencies or international institutions, for example as the OSPAR Commission, the
179 European Commission or the United States' Environmental Protection Agency (US EPA). The
180 identification of priority substances might permit to fill knowledge gaps concerning their occurrence
181 and, furthermore, their impacts on living organisms. One may refer to the established lists by the
182 Watch List of the WFD, by the OSPAR Commission (lists of substances of possible concern) and the
183 NORMAN Network (210 pharmaceuticals in the listed emerging substances¹). These lists are built
184 upon prioritization methodologies that permit to select the substances in relation with the lack of data
185 concerning their occurrence, analytical performance, and potential hazard upon living organisms. For
186 their monitoring in California's aquatic ecosystems, (Maruya et al., 2014a) included, as a priority,
187 unregulated contaminants that have been recommended by scientific experts to be monitored in
188 recycled water applications from the US EPA's Candidate Contaminant List 3² including the antibiotic
189 erythromycin. In the same way (Long et al., 2013) investigated the presence of pharmaceuticals in
190 sediments of the Puget Sound (US): 73 out of 115 were originally selected by the US EPA (US EPA,
191 2007) as being compounds of emerging concern, especially from WWTP water and biosolid
192 discharges. Of the 13 pharmaceuticals detected in the sediments, seven were selected by the US EPA
193 (diphenhydramine, azithromycin, oxytetracycline, 4-epitetracycline, anhydrotetracycline, ibuprofen,
194 miconazole).

195

196 Local surveys on prescription habits or selling data can bring more information on substances which
197 could be detected in the studied zone and permit to efficiently anticipate the monitoring campaign
198 design. Data are mainly obtained at national scale (Matongo et al., 2015; McEneff et al., 2014; Paíga
199 et al., 2015). For example (Cantwell et al., 2017) selected 15 pharmaceuticals highly prescribed in the
200 US and investigated their occurrence in estuarine waters of the Narragansett Bay in Rhode Island. Of
201 the 15 active pharmaceutical ingredients measured, 14 were consistently present in the dissolved
202 phase, and 8 were bound to suspended particulate matter collected by sediment traps over the studied
203 period.

204

¹ <https://www.norman-network.net/?q=node/81#sub23>

² <https://www.epa.gov/ccl/contaminant-candidate-list-3-ccl-3>

205 Another inclusion criterion can be their previously reported occurrence directly in receiving marine
206 environment. For example, in the California Pilot Study (2009-2010) of the USA Mussel Watch
207 Program, (Maruya et al., 2014a) based the target analyte selection on their known or suspected
208 occurrence in sediments and/or tissues from previous surveys in California or other regions, and in the
209 aqueous phase of receiving waters based on traditional or alternative (i.e. passive sampling) methods.
210 Diclofenac, azithromycin, metoprolol, carazolol, hydrochlorothiazide, tamsulosin, venlafaxine,
211 citalopram, carbamazepine and diazepam were proposed as prioritization substances for the
212 monitoring of coastal areas from several sites across Europe, due both to detection frequencies and
213 concentrations measured from their large sampling campaigns (Álvarez-Muñoz et al., 2015b).

214 To date over the 29 selected published papers between 2014 and 2020, 149 pharmaceuticals including
215 nine transformation products; and caffeine and its metabolites (paraxanthine, 1-methylxanthine, 3-
216 methylxanthine) and theophylline were quantified by grab sampling in estuaries, coastal and offshore
217 waters (Figure 1 and Supplementary Material 2) from Europe (France, Germany, Great Britain,
218 Greece, Ireland Italy, Poland, Portugal, Spain), Asia (China, Malaysia, Singapore, South Korea,
219 Taiwan), the Middle Est (Israel, Saudi Arabia, Turkey), Africa (South Africa , Tunisia), Oceania
220 (Australia), North America (the USA), the Antarctic and the Arctic.

221 This recent dataset enables to draw up a first preliminary global contamination profile of marine
222 waters according to therapeutic classes and marine water locations. All the therapeutic classes (AINS,
223 analgesics, antibiotics, central nervous system (CNS) drugs, cardiovascular system (CVS) drugs, lipid-
224 lowering and the miscellaneous pharmaceutical molecules class named ‘others’) are occurring at once
225 in estuaries, coastal and offshore waters. A significative difference between both estuary and coastal
226 concentrations and offshore mean concentrations (Wilcoxon rank sum test, p -value<0.05,
227 Supplementary Material 2) might be explained by pharmaceutical dilution in the water column at
228 offshore locations, with mean maximal concentrations of $492.14 \pm 1,641.92$ ng/L, 96.36 ± 155.48 ng/L
229 and 12.7 ± 7.10 ng/L in coastal, estuarian and offshore locations respectively. Significant differences
230 between some therapeutic class maximal concentration means are observed (Supplementary Material
231 3) but are not indicating a predominance of a particular class of pharmaceuticals in seawater.

232 However, one may highlight monitored substances with reported highest maximal concentrations
233 (Supplementary Material 4). Referring both to the number of reported occurrence (>10), median
234 concentrations higher than 100 ng/L and maximal concentrations (>500 ng/L), these were measured
235 for AINS, analgesics, antibiotics, CVS drugs, lipid-lowering (gemfibrozil), CNS drug (carbamazepine)
236 and several miscellaneous pharmaceuticals (antiretroviral, beta blockers; and caffeine), including
237 metabolites (2-hydroxy-ibuprofen, carboxyibuprofen, Cl-diclofenac, 1- and 2-methylxanthine and
238 paraxanthine. In particular, diclofenac, ibuprofen (up to 10,220 ng/L (Biel-Maeso et al., 2018)),

239 acetaminophen (up to 2,983 ng/L (Nödler et al., 2014)), carbamazepine (up to 1,410 ng/L (McEneff et
240 al., 2014)) and caffeine (up to 7,708 ng/L (Ali et al., 2017)) should be regularly included into target
241 list in monitoring programs. Additionally and despite low reported occurrence data (<10) one should
242 pay attention to the following molecules: salicylic acid, oxytetracycline, tetracycline theobromine,
243 iomeprol, iopamidol and metmorfin, along with transformation products of ibuprofen and diclofenac,
244 to elucidate if the reported concentrations reflect punctual peak pollution or if these are emerging
245 substances with high occurrence and concentrations in marine waters.

246 The argument of a high frequency of detection in wastewater effluents and freshwater is sometimes
247 advanced (Cantwell et al., 2016; McEneff et al., 2014; Paíga et al., 2015; Vidal- Dorsch et al., 2012).
248 (Ali et al., 2017) investigated the occurrence of 18 pharmaceuticals in the coastal waters of the Red
249 Sea, which were previously detected in sewage effluent samples collected from Saudi Arabia. Thirteen
250 pharmaceuticals were detected in most of the water samples collected in the Red Sea waters. As well,
251 molecules may be sometimes chosen for their poor removal efficiency in conventional WWTPs
252 (<20%) (Desbiolles et al., 2018).

253

254 The properties of the compound may be considered when selecting the molecules of interest when
255 helpful to predict their presence in the receiving compartment. To study the occurrence of compounds
256 of emerging concern in municipal effluents and in marine receiving waters in the Southern California
257 bight, Vidal- Dorsch et al. (2012) selected them based on their predicted environmental behavior such
258 as their water solubility. For example, the highly soluble molecule atenolol was frequently detected, in
259 90% of the samples. Similarly Desbiolles et al. (2018) and Brumovský et al. (2017) selected molecules
260 with a low octanol-water partition coefficient (K_{ow}) ($\log K_{ow} < 3$) predicting their predominant
261 distribution in the dissolved phase. Also, the potentiality of the molecule to be degraded through
262 environmental biodegradation or photodegradation (Felis et al., 2019) leading to the formation of
263 degradation products should be taken into account into the target molecule list. The predicted
264 ecological risk of compounds can be considered as well. Paíga et al. (2015) selected compounds from
265 two therapeutic classes (NSAIDs and analgesics) taking into account data that pointed out
266 pharmaceuticals like ibuprofen, diclofenac and acetaminophen, as being detected in Portuguese
267 environment at levels able to pose an ecotoxicological risk for aquatic organisms (Santos et al., 2013).
268 Some pharmaceutical classes are monitored because they represent public health issues, such
269 antibiotics as their presence in environmental waters is responsible for the development of antibiotic
270 resistant bacteria (Brumovský et al., 2017). Pharmaceuticals of interest can also be selected depending
271 on the availability of analytical methods (Vidal- Dorsch et al., 2012) with additional criteria such as
272 their robustness, their capability of processing a large set of samples and to be multi-residue (Álvarez-

273 Muñoz et al., 2015a), or their capacity of detecting the chemical of interest in at least one of the
274 investigated environmental matrices waters, sediments or biological tissues (Maruya et al., 2014c).

275

276 Multi-criterion decision analysis that is combining several criteria (e.g. volumes of production,
277 ecotoxicological relevance) permits to implement prioritization scheme for the selection of monitored
278 pharmaceuticals (Cantwell et al., 2018; Kötke et al., 2019; Li et al., 2020; Maruya et al., 2014c). In
279 particular the State of California developed a risk-based adaptive monitoring strategy in a view to
280 assess the potential effects of compounds of emerging concern on ecological health in California's
281 freshwater, estuarine and oceanic ecosystems (Maruya et al., 2014c). For this purpose, they defined an
282 initial list of relevant compounds for screening considering contaminant sources and their fate in
283 receiving environments, and by comparing environmental concentrations with biological thresholds of
284 adverse effects. However, they underlined that the availability of high-quality occurrence and effects
285 data for these compounds is typically limited. This assertion is especially true for pharmaceuticals in
286 the marine environment where such prioritization is limited by the rare data on their fate after release,
287 or their toxicity on marine organisms (Arpin-Pont et al., 2016).

288 Considering the great number of parent compounds used in therapeutics and released in the aquatic
289 environment, many transformation products (metabolites and degradation products) mostly of
290 unknown toxicity and persistence are expected to be present in surface waters. Data on transformation
291 products are even fewer than parent compounds as the traditional analytical approaches of applying
292 target screening (MS (SIM) or MS/MS (MRM)) for parent molecules results inevitably in the non-
293 detection of such compounds. However, some of them can be present in similar concentrations to or
294 exceeding the parent compound (Gaw et al., 2014). For example, carbamazepine-10,11-epoxide was
295 found in higher concentration than carbamazepine in seawater of the Oslofjord (Norway) (Langford
296 and Thomas, 2011); and the N-acetyl-sulfamethoxazole found in slightly higher concentration (28.6
297 ng/L) than sulfamethoxazole (25.2 ng/L) in the Liaodong Bay in China (Jia et al., 2011). Whereas few
298 studies are dealing with environmental degradation products (Afsa et al., 2019; Baena-Nogueras et al.,
299 2016; Biel-Maeso et al., 2018; Brumovský et al., 2017; Fenet et al., 2014; Gros et al., 2012; Lolić et
300 al., 2015; Paíga et al., 2015) metabolites are mainly researched in biota (Álvarez-Muñoz et al., 2015b;
301 Martínez Bueno et al., 2014a; Moreno-González et al., 2016; Silva et al., 2017) or in the dissolved
302 phase (Martínez Bueno et al., 2014b; Szymczycha et al., 2020). Paíga et al. (2015) developed a
303 method for pharmaceuticals including glucuronide acetaminophen, carboxyibuprofen and 2-
304 hydroxyibuprofen that was applied to seawater samples of Atlantic Ocean collected in the North of the
305 Portuguese coast during the 2013 summer season. Ibuprofen and its metabolite 2-hydroxyibuprofen

306 were detected in 100% of seawater samples with higher concentrations for the metabolite in some
307 sampling points.

308 Along with the target compounds in monitoring studies, some pharmaceuticals (e.g. carbamazepine,
309 valsartan) or other molecules from human activities (e.g. caffeine and its metabolite paraxanthine,
310 artificial sweeteners) can be analyzed because of their suitability to be anthropic tracers as they are
311 markers of domestic wastewater. The choice of the relevant tracer depends on the aim of the study, as
312 tracing pollution and its sources (Cantwell et al., 2018; Goh et al., 2017; Nödler et al., 2016), studying
313 of the dynamic of the contamination (Erostate et al., 2019; Szymczycha et al., 2020) or the
314 vulnerability of coastal systems (Paíga and Delerue-Matos, 2017). The above-mentioned
315 physicochemical properties of the molecules and particularly their persistence in the environment and
316 study location are also decision criteria (Vystavna et al., 2013). For example, in their study of the
317 contamination of the Hudson River estuary (US), (Cantwell et al., 2018) used the ratio
318 caffeine/sucralose to distinguish treated or untreated wastewater origins, because of the labile property
319 of caffeine that is easily degraded by WWTPs processes, contrary to the conservative behavior of
320 sucralose. Moreover, they evidenced the ability of sucralose to be a tracer for recalcitrant contaminants
321 whereas caffeine might reflect the fate of easily degradable contaminants. Thus, in marine water
322 monitoring these tracers should be monitored in addition to target substances (Choi et al., 2020;
323 Nödler et al., 2016).

324

325 **II.1.3. Sampling Strategy**

326 Guidelines for the monitoring of various contaminants (trace metals, organic contaminants, priority
327 substances, etc.) in the marine environment were produced early by international institutions, e.g. the
328 “Guidance on surface water chemical monitoring under the Water Framework Directive” (surface
329 waters include inland waters except groundwater; transitional waters and coastal waters) (European
330 Commission and Directorate-General for the Environment, 2009), the “JAMP Guidelines for
331 Monitoring of Contaminants” (seawater, sediments, biota) (OSPAR Commission, 2013), or the
332 “Sampling and Consideration of Variability (Temporal and Spatial) for Monitoring of Recreational
333 Waters” (US EPA, 2010). However, no specific guideline currently exists for monitoring
334 pharmaceuticals in the marine environment. Thus, we aimed to provide above a synthesis of
335 monitoring strategy considerations and their application in the selected published papers.

336

337 **II.1.3.1. Selection of the study site and sampling scheme definition**

338 Characterization of the studied marine receiving environment prior to the setup of a routine monitoring
339 sampling strategy is recommended (Figure 2). The definition of the sampling scheme depends on the
340 objective(s) of the monitoring, the location and the configuration of the marine studied area. The
341 combination of pre-existing contamination data, the use of numerical modeling and a time-limited
342 pilot study may permit a first screening of the contamination. Based on these first data a site-specific
343 monitoring sampling scheme can be setup with optimal spatial and temporal sampling step scales and
344 might be a compromise between a sufficient area coverage, limited costs and meaningful results.

345

346 **Choice of the Study Site**

347 Factors such as a high anthropogenic pressure or identified pollution sources may guide the type and
348 the location of the study site.

349 Among the different marine environments, estuaries are relevant locations to study pharmaceutical
350 contamination because they are important economic areas (harbors, agriculture, aquaculture, industrial
351 activities, urbanization, etc.) Thus, they represent privileged places for contaminant transportation
352 from upstream treated or untreated sewage effluents or from agricultural lands to marine waters
353 (Cantwell et al., 2017; Stewart et al., 2014). Besides, they are transitory environments characterized by
354 complex mixing between fresh contaminated waters and saltwater, and specific hydrological dynamics
355 due to tides and river inputs. Pharmaceutical contamination dynamics in water (Baena-Nogueras et al.,
356 2016; Bayen et al., 2013; Borecka et al., 2015; Cantwell et al., 2018, 2017, 2016; Nödler et al., 2014;
357 Zhao et al., 2017, 2015), sediments and suspended particular matter (SPM) (Lara-Martín et al., 2014;
358 Liang et al., 2013; Stewart et al., 2014), and biota (Álvarez-Muñoz et al., 2015b; Klosterhaus et al.,
359 2013; Meador et al., 2016) are documented in urbanized estuaries but their monitoring remains
360 difficult to implement due to their complexity. Other types of marine sites can be selected depending
361 on the aim of the study as coasts (bays, gulfs, beaches, etc.) (Afsa et al., 2019; Beretta et al., 2014;
362 McEneff et al., 2014), offshore sites (Alygizakis et al., 2016; Brumovský et al., 2017) , harbors
363 (Cantwell et al., 2018; Stewart et al., 2016), mangroves (Bayen et al., 2016) lagoons and aquaculture
364 areas (Chen et al., 2015a; Ismail et al., 2019).

365

366 The site location choice is mainly based on its potential to show zones that are highly contaminated by
367 pharmaceutical residues. The analysis of the land use surrounding each sampling station is
368 informative, as the presence of pharmaceuticals in receiving marine waters is often linked to the
369 proximity of highly urbanized or dense animal husbandry areas (Maruya et al., 2014b). The
370 distribution of the contamination may largely depend on the hydrodynamics (Bayen et al., 2013).

371 Identification and characterization of direct or indirect contamination point sources such as WWTP
372 effluent discharges (Ali et al., 2017), contaminated rivers discharging to coastal waters (Cantwell et
373 al., 2016), sewage outfalls or aquaculture farms (Chen et al., 2015a) are useful to predict the most
374 contaminated areas and the contamination patterns. Recently Szymczycha et al. (2020) measured
375 diclofenac, caffeine, carbamazepine and sulfapyridine in submarine groundwater that thus could be a
376 supplementary source of coastal contamination of the bay of Puck (Poland, Baltic Sea). Sites directly
377 impacted by WWTP releases are frequently selected, as WWTP effluents are primary sources of
378 anthropogenic contaminants found in coastal waters, such as human pharmaceuticals. As an example
379 Afsa et al. (2019) measured the concentrations of 40 pharmaceuticals in the wastewater of the
380 university hospital of Mahdia (Tunisia), in the effluents of the local WWTP and at the coastal area
381 receiving the discharges. As expected, they observed a gradient of concentration from the hospital
382 effluent (concentration range around 200-4,700 ng/L) to the coastal zone (maximal concentration
383 around 200 ng/L). Zones with important stakes and sensitivities can be focused (Białk-Bielińska et al.,
384 2016; UNESCO and HELCOM, 2017), such as marine areas particularly vulnerable to human
385 activities. For example, coastal lagoons, mangrove forests or semi-enclosed bights, where the dilution
386 of the contamination is limited due to their confinement from the open sea and their shallowness are
387 more vulnerable than open seas (Erostate et al., 2019; Moreno-González et al., 2015; Nödler et al.,
388 2016).

389

390 **Spatial and Temporal Features of Sampling Scheme Definition**

391 Spatial and temporal features of the selected study site are crucial to apprehend contamination patterns
392 and to determine the number of sampling stations and the frequency of sampling events. Spatial
393 factors are linked with pollution sources, the marine site configuration (coast, bay, estuary, offshore,
394 etc.), its depth and width whereas temporal factors are linked with seasonality in pharmaceutical inputs
395 and meteorological conditions.

396 Hydrodynamic conditions are strongly controlling the occurrence and the dynamics of contaminants in
397 the marine environment (Bayen et al., 2013) thus their comprehension and estimation must be
398 included in the monitoring programs, for example through numerical modelling. The spatial
399 distribution of the contamination is influenced by factors such as tributary inputs, river flows or tides
400 (Zhao et al., 2015) that play an important role by controlling dilution and, consequently,
401 pharmaceutical concentrations (Biel-Maeso et al., 2018; Cantwell et al., 2018). As well, the complex
402 hydrodynamics of water combined with the location such as in estuaries (Cantwell et al., 2017; Liang
403 et al., 2013), the monsoon in tropical estuaries (Bayen et al., 2013), the contribution of submarine
404 groundwater (Szymczycha et al., 2020) and the presence of a thermocline can explain the observed

405 spatial patterns of pharmaceutical distribution. Due to temperature stratification periods,
406 pharmaceuticals can be trapped in the deeper layers of the water column, as shown by (Fenet et al.,
407 2014) in winter for carbamazepine in Mediterranean coastal waters impacted by a submarine outfall
408 (Montpellier, France).

409

410 Thus a progressive or staged approach should provide a rational method for determining the number
411 and spacing of the sampling stations both to be cost-effective and to allow an acceptable
412 representativeness of the measurement (US EPA, 2010). To overview the spatial distribution and to
413 enable numerical modelling of the contamination (Björlenius et al., 2018; Fonseca et al., 2020), the
414 distribution of monitoring points should be sufficient to cover the studied area (Kötke et al., 2019).
415 These monitoring points should include reference sites although laborious to found. Indeed they have
416 to be sampled at a sufficient distance of the studied contamination sources in order to describe the
417 background conditions and to compare that contamination levels to those of most directly impacted
418 stations (Moreno-González et al., 2015; Turja et al., 2015).

419

420 *Sampling Station Location*

421 With a simple source of contamination and in a shallow site, few locations within and outside the sites
422 and few points per location may be enough to obtain an overall impression of the site contamination.
423 However, for sites with complex contaminant distribution and hydrodynamic, such as estuaries, deep
424 sites, or open sea (Brumovský et al., 2017) appreciably more monitoring locations and monitoring
425 points at each location are likely to be required. As well, for deep sites, the sampling at different
426 depths allows to investigate the vertical distribution of the contamination (Biel-Maeso et al., 2018;
427 Borecka et al., 2015; Goh et al., 2017). If the aim is to identify and study local sources of
428 contaminants, then the sampling grid should be denser in the vicinity of the suspected sources (Kim et
429 al., 2017). To study the influence of a punctual source of contamination such as WTP effluents and the
430 attenuation of the plume, a multi-site sampling is needed at regular distances from the source (Biel-
431 Maeso et al., 2018), for example in a delimited spatial area to assess direct and indirect impacts of the
432 pollution source and the background condition far from the source (Andral et al., 2013). Fang et al.
433 (2012) investigated the occurrence of diclofenac, ibuprofen, clofibric acid and ketoprofen in the
434 nearby coastal waters receiving WTP effluent discharges through an ocean outfall pipe in Taiwan's
435 surface waters, and found the highest concentrations at the estuarine mouth and close to the ocean
436 outfall area.

437 When monitoring large areas, to tackle logistical constraints, cost-effective approaches are desirable.
438 Unmanned sampling on ships and marine platforms could be a possible strategy. As proof-of-concept
439 Brumovský et al. (2016) collected aggregated samples in five different areas in the North Sea by
440 robotic devices installed on commercial vessels, three times along routes approximately 120 km to 200
441 km long within each of the selected areas. The suitability of such existing infrastructure for carrying
442 out both routine and exploratory monitoring of contaminants in marine waters has been demonstrated
443 in this study, with the detection of pharmaceuticals at trace levels. However, focused experiments on
444 the stability of the analytes in the samples during collection and on-board storage were considered as a
445 further step to improve the accuracy of quantitative analysis. The variability of salinity or SPM content
446 of seawater can also give an indication of the spatial variability of pollutants and act as
447 “normalization” factors (OSPAR Commission, 2013).

448

449 *Exploring temporal trends*

450 A one-time study permits to give a screenshot of the contamination, by sampling several matrices or
451 several depths at selected sites, to determine the partitioning of target compounds or the influence of
452 tides and the sampling depth in a defined area (Lara-Martín et al., 2014).

453 Concentrations at a fixed geographical position may vary over the tidal cycle, the river flow in
454 estuaries or seasons (e.g. dry or wet seasons, monsoon in tropical countries) and water body retention
455 time. For example, seasonal differences can be observed in seawater stratification. Cantwell et al.
456 (2017) observed seasonal trends in the riverine discharge with the peak concentrations of
457 pharmaceuticals in the Narragansett Bay during the river low-flow period during the summer. Low
458 temporal variation was observed in seawater concentrations in the Southern California Bight. Seasonal
459 differences may not play a strong role in near-bottom seawater, where temperatures and other
460 oceanographic conditions are relatively constant for most of the year (Vidal- Dorsch et al., 2012).

461 Further temporal variability may arise from variation in local inputs, as some classes of
462 pharmaceuticals are seasonally used although temporal disparities are difficult to assess (Pouzol et al.,
463 2020). For example (Martínez Bueno et al., 2014a) hypothesizes that venlafaxine consumption is
464 increased during the January to April months because of depression disorders treatment during this
465 period in the south of France. In order to identify temporal trends, a particular attention should be
466 given to sources of variability such as seasonal consumption habits. For example, touristic seasons
467 imply an increase in wastewater effluents thus potentially an increase in pharmaceutical amount inputs
468 in receiving waters (Moreno-González et al., 2015). These include sampling at pre-defined times of
469 the year and at the same phase of the tidal cycle (e.g. always at high tide), although for ship-based

470 discrete sampling it should be recognized that logistic constraints do not always allow such measures
471 to be taken (OSPAR Commission, 2013).

472

473 *Spatial and temporal trend elucidation*

474 When the aim is the spatial and temporal trend elucidation, several stations are sampled at several
475 times (Cantwell et al., 2018, 2017, 2016). Identifying such trends for pharmaceutical concentrations in
476 marine and coastal waters is crucial for determining periods during which sensitive ecosystems may be
477 at greater risk from exposure (Hedgespeth et al., 2012). In case of a periodic monitoring of a specific
478 area, sampling stations are generally the same as in the previous campaigns to allow a comparison of
479 the concentrations between monitoring periods in a view to assess the evolution of the contamination
480 (concentrations or nature of compounds detected) (Martínez Bueno et al., 2014b).

481 High resolution hydrodynamic models can be useful tools for providing estimations of
482 hydrodynamics in the studied marine region, to understand the fate (transport, dilution, attenuation)
483 and the spatio-temporal variations of the contaminants (James et al., 2020; Pairaud et al., 2011), and
484 to calculate the predicted environmental concentrations (Fenet et al., 2014). At a local scale they can
485 permit to predict contaminant dispersion in the studied area and help to choose sampling station
486 location and the sampling depth (Bayen et al., 2013; Björlenius et al., 2018; Tian et al., 2019). They
487 could permit to give a representation of tidal and seasonal forcing and investigating spatial-temporal
488 water changes in complex marine environments. Contaminant trajectories can be simulated thanks to
489 the combination of identified input discharges and local hydrodynamic modelling. For example Bayen
490 et al. (2013) predicted the residence time of selected pharmaceuticals in Singapore's coastal marine
491 environment using the hydrodynamic model "Singapore Regional Model", including river discharges.
492 The hydrodynamic flushing and high residence time for confined water bodies are factors reported
493 increasing concentrations in seawater and sediments. At the scale of the Tagus estuary (Portugal)
494 Fonseca et al. (2020) combined a hydrodynamic model (MOHID Water Modeling system,
495 (MARETEC, 2018)) to a Lagrangian particle tracking numerical model (Duarte et al., 2017) to
496 identify the most vulnerable areas of the estuary considering their exposure to pharmaceuticals. It
497 provided an integrated approach by including the multiple pharmaceutical entry points into the marine
498 environment (WWTP effluents, river discharges), estuarian specific hydrodynamics and the different
499 ecological environments.

500 Another approach is through the analysis of concentration spatial variations in the hydrological
501 system considered. Björlenius et al. (2018) selected carbamazepine to be included in a grey-box
502 model (mass-balance model PhATE combined to GREATER) to assess its fate in different locations

503 of the Baltic Sea. They estimated a flushing half-time of ten years and thus its occurrence in seawater
504 several years after the end of its consumption. Tian et al. (2019) used the mechanistic Salish Sea
505 hydrodynamic and biogeochemical model designed to consider that the ocean contaminant
506 concentrations are derived from their initial concentrations in point (WWTP, outfalls) and diffuse
507 (runoff) sources, after dilution and transport but do not comprise environmental degradation
508 processes. Spatial patterns identified at the estuary of Puget Sound (USA) with the model compared
509 with measured concentrations support that sucralose and lamotrigine can act as urban wastewater
510 tracers.

511 However, one may notice that specific challenges are raised by numerical modelling. They are related
512 to the need of model calibration and validation, along with the choices of the integration of
513 conservative or non-conservative behavior of the target contaminant, and the multiple forcing features
514 to include (as wind) to provide a coherent simulation of the fate of the molecules. Thus, their use and
515 outputs need to be exploited prudently.

516

517 **II.1.3.2. Matrix Selection**

518 The knowledge of the fate of pharmaceuticals after their release is useful when choosing study matrix
519 of the sample. Once discharged into aquatic environments, their distribution between the
520 environmental compartments (water, sediments/SPM and biota) is a function of their physicochemical
521 properties, their interactions with the different matrices and the site hydrodynamic conditions (Bayen
522 et al., 2013). The contaminants will undergo biotic and abiotic transformations (degradation); they can
523 be (ab/ad)sorbed to SPM and sediments, and in some case be accumulated in the tissues of organisms,
524 depending on their partition coefficients (K_{ow} ; K_{oc}). However, fate studies of pharmaceuticals in
525 marine systems, such as studies on sorption or degradation processes, are rare in the literature.
526 Existing data on the environmental fate of pharmaceuticals available for freshwater ecosystems are
527 generally not transposable to marine environments (Pazdro et al., 2016; Weigel et al., 2004) because of
528 their differences in physicochemical and biological properties. In particular ionizable pharmaceuticals
529 might undergo different fate under environmental pH, ionic strength and temperature, e.g. as
530 fluoxetine and the tricyclic antidepressant compounds' amitriptyline, doxepine and imipramine
531 (Togola and Budzinski, 2007), trimethoprim, naproxen and ketoprofen (Domínguez et al., 2011) or
532 selected antibiotics (Wang et al., 2010; Xie et al., 2017).

533

534

535 **Water**

536 Pharmaceuticals are mostly polar compounds and will be investigated principally in the water column,
537 even though they are quantified in other matrices (sediment, biota). Sampling of water column is not a
538 trivial action in order to provide an accurate measurement of the contamination. Indeed, concentrations
539 in water can evolve rapidly and are highly affected by hydrodynamic conditions (Bayen et al., 2014).
540 Moreover, unlike concentrations in sediments and biota, pharmaceutical concentrations in water
541 respond quickly to changes in inputs or other environmental conditions u.

542 In most reviewed articles, water was collected with pumps or grab (active) sampling (Arpin-Pont et
543 al., 2016) then filtered (1-0.45 μm) to report concentrations of pharmaceuticals present in the
544 dissolved phase. This strategy is particularly interesting as it allows a direct quantification of target
545 compounds and permits to detect peak contamination events. However, these samples show high
546 variability which can result in a low representativeness. To detect a peak event or to investigate
547 temporal variation during a long-term monitoring, a high-sampling frequency should be performed but
548 implies high costs (OSPAR Commission, 2013).

549

550 Although passive sampling (PS) techniques are more challenging than grab sampling particularly due
551 to sampler calibration requirements and hydrodynamic control issues, they have been recommended in
552 the European Commission Guidance Document on surface water chemical monitoring, then in the
553 WFD daughter 2013/39/UE, as complementary methods to improve the level of confidence in water
554 monitoring data in comparison with conventional spot sampling (Miège et al., 2015). PS is assumed to
555 have a positive influence on the future design and output of monitoring programs in the context of the
556 WFD and the MSFD. In contrast with spot-sampling strategy, PS provides time-integrated
557 concentrations of pollutants over the deployment period of the devices (Alvarez et al., 2008) by
558 accumulating and concentrating the targeted molecules thus allowing to improve their detection limits
559 (Miège et al., 2015; Vrana et al., 2016).

560 However, in addition to the need of suited deployment sites and the risk of a loss in the sea, some
561 barriers still remain that prevent regulatory acceptance and actual implementation of these tools for
562 routine monitoring of contaminants in aquatic systems, explaining why this technique is not widely
563 used at the moment. In order to endorse PS use in monitoring programs, several actions have been
564 conducted, including interlaboratory studies to evaluate performances of PS methods with a focus on
565 emerging substances *in situ* (NORMAN network, (Miège et al., 2015; Vrana et al., 2016)).

566 Various types and configurations of PS exist today for a wide range of compounds depending on their
567 physicochemical properties and particularly their $\log K_{ow}$. For polar compounds ($1 < \log K_{ow} < 4$)

568 including pharmaceuticals, the main PS employed are Polar Organic Chemical Integrative Samplers
569 (POCIS), Chemcatcher® and organic Diffusive Gradient in Thin film (o-DGT) devices. The choice of
570 the most appropriate receiving phase permit to retain molecules on a wide log K_{ow} range (e.g. HLB
571 sorbent), to target highly polar (e.g. SDB-RPS) or low-polar molecules (e.g. C_{18} disks in
572 Chemcatcher®) (Gong et al. 2018). Metal Organic Framework (MOF) derived porous carbon was
573 used as binding gel in o-DGT for the sampling of various antibiotics in seawater (Ren et al., 2018).
574 This configuration shows an interesting capacity to bind antibiotics in seawater, due to their specific
575 mesoporous structure and large surface area, without being influenced by pH and ionic strength during
576 this study.

577 For pharmaceuticals, the POCIS are the most used in marine waters (Table 1). It was acknowledged
578 that at present the mechanisms of uptake and release of hydrophilic substances from water into these
579 adsorption-based PS are not fully understood. Almost all reviewed articles used laboratory-based
580 sampling rates (R_s , liter per day) from experiments or literature. The R_s is dependent of the
581 physicochemical properties of the compounds and of sampling device exposure conditions, mainly by
582 flow velocity (Ibrahim et al., 2013), and temperature and salinity (Togola and Budzinski, 2007). The
583 main R_s values were determined in freshwater then not suitable for time weighted average (TWA)
584 concentration calculation in marine waters. Thus, there is a need of a specific calibration in the
585 seawater matrix. Currently, adsorption-based passive sampling for hydrophilic compounds allows only
586 semi-quantitative information to be obtained, because of the uncertainty in applying laboratory-based
587 sampling rates to *in situ* field conditions. Performance Reference Compounds (PRCs) can be spiked
588 into the passive samplers before exposure. Their dissipation into the environment enable to estimate
589 the sampling rate of the device through mass transfer kinetic information between the sampler and the
590 environment (Joyce and Burgess, 2018; Li et al., 2018). However, the exchange of compounds
591 between POCIS and the aqueous phase can often be considered as an anisotropic process.
592 Consequently, it is generally not possible to use the release of PRC to calibrate the uptake rate and
593 allow calculation of TWA water concentrations for a wide range of compounds (Vrana et al., 2016).
594 Nonetheless, PRCs should be used as surrogates to check that exposure conditions (temperature,
595 salinity, water flow) are within the limits for which the laboratory derived the calibration data (quality
596 controls). In the reported studies Gonzalez-Rey et al. (2015) used caffeine- ^{13}C and
597 deisopropylatrazine-d5 as PRCs to calibrate POCIS.

598 The DGT devices firstly developed for monitoring dissolved trace metals (Zhang and Davison, 1995)
599 were adapted to the sample of organic compounds (namely 'o-DGT') including pharmaceuticals. o-
600 DGT were made of a XAD-18 resin gel as a binding phase to sample sulfamethoxazole in water (Chen
601 et al., 2012). It has been assumed that the advantages of o-DGT over POCIS are (i) that the compound
602 uptake (with o-DGT with or without a PES outer membrane) is mainly controlled by the hydrogel

603 diffusive layer then is significantly less sensitive to the hydrodynamic conditions (Belles et al., 2017;
604 Challis et al., 2016; Zhang and Davison, 1995); (ii) Rs for o-DGT can be calculated from temperature-
605 specific diffusion coefficients (D) determined in the laboratory by relatively easy to implement cell-
606 diffusion calibration (Challis et al., 2016; Guibal et al., 2019); and (iii) it is possible to choose the
607 appropriate combination of diffusive gel (type, thickness), binding phase and outer membrane
608 considering the target molecules and the deployment conditions. (Guibal et al., 2019) provided a
609 complete overview on the adaptations and field applications of o-DGT. Most of the studies focused on
610 the device design, the influence of environmental factors (flow, temperature, biofouling, pH, ionic
611 strength, organic matter) and performance assessment (Belles et al., 2018). Over the period 2011-
612 2019, 50% of the published papers on o-DGT concerned pharmaceuticals and in particular
613 sulfamethoxazole and the sulfamide family. The most used sorbent phases were XAD-18 and Oasis
614 HLB. Some studies provided in-field results in natural waters mostly in freshwater and waste waters;
615 with efficient sampling in the pH range of 4-9 and in the ionic strength range of 0.001-0.100 M. To
616 date only four studies relate the application of o-DGT to monitor marine waters (Ren et al., 2018;
617 Stroski et al., 2020; Xie et al., 2018, 2017) (Table 1). Thus specific challenges for the sampling of
618 pharmaceuticals in seawater with o-DGT are (i) high dilution of these molecules and the relative small
619 surface sampling area of DGT (3.14 cm²) as compared to POCIS (41 cm²) (Challis et al., 2016); (ii)
620 hydrodynamics (currents, tides) (Belles et al., 2018; Buzier et al., 2019) and (iii) physicochemical
621 properties of seawater (pH around 8 and ionic strength around 0.7 M) that affect ionization of certain
622 compounds (antibiotics).

623

624 Despite the inherent interest of the *in situ* calibration of PS devices, it remains difficult to implement.
625 According to our knowledge only one study implemented *in situ* calibration of POCIS in the marine
626 environment for a selected range of pharmaceuticals (Shi et al., 2014). POCIS were deployed in three
627 sites highly impacted by human activities (sewage outfalls) in the Yangtze Estuary, China. They
628 compared the laboratory and *in situ* calibrations and evidenced that field Rs were higher than
629 laboratory Rs probably due to environmental conditions and especially water flow rate and significant
630 turbulence in the estuary. Although a demanding task, *in situ* calibration of PS devices is, however, a
631 relevant approach to significantly increase confidence in TWA estimation.

632 Interlaboratory studies showed that accurate analysis of some hydrophilic substances, including
633 pharmaceuticals, remains a challenge. The reported variability of TWA concentrations partly stems
634 from the calibration of the PS devices, for example leading to TWA estimation variation coefficient of
635 73-256% for pharmaceuticals with POCIS (Vrana et al., 2016). Even if PS tools for hydrophilic
636 substances still need developments and adaptations, guidelines describing how to conduct PS

637 calibrations and deployment are required. Such guidance should define a common set of metadata and
638 calibration conditions (water flow, temperature, type of exposure system, salinity) to be reported
639 together with the obtained sampler calibration parameters. All this information is required for the
640 assessment of the possible relationship between the observed variability in available calibration data
641 and the exposure conditions used in calibrations. According to (Miège et al., 2015), data obtained by
642 PS techniques are as representative as low frequency spot sampling (4-12 sampling times per year)
643 used in compliance monitoring for the WFD, considering that the uncertainty of PS concentrations is
644 lower than the variability of environmental concentrations.

645

646 Besides the Passive Sampling with Ionic Liquids technique (PASSIL) was proposed as a new
647 receiving phase in passive sampler device designed as a dosimeter for selected pharmaceuticals
648 (carbamazepine, diclofenac, 17- β -estradiol, sulfapyridine and sulfamethoxazole) (Caban et al., 2016),
649 and was tested at the marine pH and salinity (Męczykowska et al., 2018, 2017). Their interest lies in
650 their ability to sample molecules with a wide range of polarities due to their heterogeneous structure at
651 the nanometer scale. It is therefore possible to design specific ILs for the extraction of various
652 analytes. Thus they represent an additional promising tool for the passive sampling of pharmaceuticals
653 in water.

654

655 **Sediments and suspended matter**

656 Sediments constitute a reservoir and even a sink for the accumulation of pharmaceuticals in marine
657 ecosystems. They reflect the quality of the habitat of benthic organisms and give an overview of the
658 'time-integrated' environmental contamination completing water and biota monitoring (Chen et al.,
659 2015b; Na et al., 2013). Pharmaceutical deposition and adsorption on sediments are depending on the
660 flow velocity, pH, salinity, organic matter content and texture of sediments (Ismail et al., 2019;
661 Rimayi et al., 2018). The inner properties of the considered molecules also influence strongly their
662 distribution between sediments and aqueous phase. Sorption is expected for the compounds which pKa
663 corresponds to the seawater pH (7.4-8.35) (Guo et al., 2019). The adsorption coefficient (K_d) and high
664 hydrophobic partition coefficients (K_{ow}) are in favor of pharmaceutical bind to sediments (Lara-
665 Martín et al., 2014). The normalized K_d with the fraction of organic carbon (K_{oc}) may give
666 information about specific interaction of certain pharmaceuticals with sediments linked to their content
667 (Cantwell et al., 2016). Thus sediments can act as a secondary pollution source (Pazdro et al., 2016)
668 from which pharmaceuticals can be released by changes in environmental conditions such as salinity
669 and pH (Gaw et al., 2014) and resuspension of the bed sediment, by environmental disturbances

670 (storms, currents, bioturbation, etc.) or anthropic causes (dredging, trawling) (Ismail et al., 2019;
671 Snelgrove, 2013).

672 The advantages of sediment sampling belong to their capacity to concentrate and to be an integrative
673 matrix of the contamination (Gonzalez-Rey et al., 2015), to reflect long-time contamination and to
674 assess spatial variability. In response depending on the molecule persistence, the dating of the
675 contamination and/or the tracking of the pollution source is tricky. Sediments can be sampled along
676 with water to compare the spatial distribution of the contamination (differences between sites and
677 difference between the types of molecules) (Guo et al., 2019).

678 Depending on the location, sediments can be sampled with grab samplers (Shipek, Petersen, Van-Veen
679 Ekman) for surface sediments or with spades or scoops, and with a gravity corer or even ruby scuba
680 divers with hand corers for deeper samples. Sometimes very deep sampling requires a Hybrid
681 Remotely Operated Vehicle (HROV) as for the study of the Capbreton Canyon (France) (Azaroff et
682 al., 2020). The pharmaceutical concentrations in sediments are depending on their chemical
683 composition and texture and thus there is a need of normalization of the results (Cantwell et al., 2017).

684 However seasonal monitoring is not always possible, because of the sedimentation rates and the
685 mixing between the superficial layer in coastal area due to specific hydrodynamics and bioturbation
686 (Schutte et al., 2019). As sedimentation rates are not always determined, temporal variations of the
687 contamination are difficult to apprehend in routine monitoring.

688 The occurrence of pharmaceuticals on the suspended matter phase is the subject of few studies
689 (Cantwell et al., 2017, 2016; Lara-Martín et al., 2014) and aimed partly to determine partition
690 coefficients.

691

692 **Organisms**

693 A commonly used tool for describing the quality of the aquatic environment is biomonitoring, which
694 makes use of various aquatic biota, including invertebrates and fishes (Maruya et al., 2014b; Świacka
695 et al., 2019) or algae (Ali et al., 2018; Cunha et al., 2017). Bivalves, such as mussels, are often used as
696 bioindicators for aquatic pollution monitoring (Almeida et al., 2020) and are representative of the
697 sampling area because of their sedentary behavior. Being filter-feeders, mussels bioconcentrate
698 chemicals to concentrations much higher than those found in the surrounding waters and reflect a
699 much longer time frame than conventional sampling (Cunha et al., 2017; Świacka et al., 2019). Native
700 mussels can be collected (passive biomonitoring, namely ‘mussel watch’) (Maruya et al., 2014b,
701 2014a) or caged mussels can be deployed (active biomonitoring) (Bayen et al., 2016; McEneff et al.,

702 2014; Moreno-González et al., 2016). Fishes are less representative of a site, because they are highly
703 mobile and may have migratory behavior, thus complicating data interpretation, or requiring benthic
704 species (Maranho et al., 2015; Snelgrove, 2013). The question of the distribution of the
705 pharmaceuticals into the different tissues of fishes was raised by (Liu et al., 2018), whereas
706 bioaccumulation mechanisms in mussels depend on their physiologic status (Arpin-Pont et al., 2016)
707 and are not fully understood because it is not relying only on the K_{ow} distribution coefficient (Martínez
708 Bueno et al., 2014a). Also pharmaceuticals can be readily metabolized in living organisms (Atashgahi
709 et al., 2018) thus limiting bioaccumulation (US EPA, 1998) and increasing analysis complexity in
710 biota matrices.

711 Studies on marine organisms are limited, maybe caused by the lack of suitable analytical methods for
712 these challenging matrices, as these samples required extensive extraction and clean-up procedures for
713 proteins and lipids (Pazdro et al., 2016). Moreover pharmaceuticals are mainly metabolized by marine
714 organisms which induce the release of metabolites that need to be investigated (Bonfille et al.,
715 2017).

716

717 **II.1.4. Sample treatments and analytical methodology**

718 Białk-Bielińska et al. (2016) and Pazdro et al. (2016) provided complete synthesis concerning current
719 trends of pharmaceutical analysis in the marine environment. The main steps in the analytical
720 procedures are briefly detailed above.

721

722 **Sample Pretreatment**

723 The sample size and the number of replicates must be sufficient to support the desired detection limits
724 for the contaminants of interest, and to enable descriptions of spatial and temporal trends. For example
725 (Phuong et al., 2018) evidenced that ten sediment replicates are needed to achieve a good
726 representativeness of the sediment contamination. Steps of cleaning and purification permit to limit the
727 interaction between the target molecules and the components of the sample and reduce or suppress
728 matrix effects. The more often, water samples are filtered through glass-fiber filters (1-0.45 μm) to
729 eliminate SPM thus only the dissolved fraction is considered. Acidification is sometimes necessary to
730 reduce potential biodegradation of the target molecules and insure the sample stabilization. A pH
731 control and/or modification can be realized to improve the extraction of ionic target analytes and
732 eventually the addition of Na_2EDTA for antibiotic analysis to avoid their chelation to metallic ions.

733 Sediments and sample biota are freeze-dried and/or homogenized and/or grounded prior to the analyte
734 extraction steps.

735

736 **Sample Extraction**

737 Water samples undergo solid phase extraction (SPE) procedures. The choice of the sorbent depends on
738 the properties of the target compounds. Oasis HLB (Waters) and Strata-X (Phenomenex) sorbents
739 remain the more used for pharmaceuticals. (Vanryckeghem et al., 2019) reports the use of Bakerbond
740 hydrophilic divinylbenzene (DVB) Speedisk that enable the extraction of large volumes (500 mL) of
741 seawater to improve detection limits and reduce the time of extraction. Elution of pharmaceuticals is
742 mainly realized with the polar solvent methanol.

743 Extraction of pharmaceuticals from sediments and biota matrices requires liquid (solvent) extraction
744 then purification steps to take into account molecular interactions of target compounds with sediment
745 due to their nature (texture, pH, organic matter, etc.); and high amounts of lipids and proteins
746 contained in biota. Solvent extractions can be operated with ultrasonication or accelerated solvent
747 extraction (ASE). Then liquid extracts from sediments are purified through SPE methods (C₁₈ or
748 anion-exchange columns, in tandem with reversed-phase column as Oasis HLB). Clean-up procedures
749 of biota extracts consist of adsorption columns (polar sorbent with normal phase) or gel-permeation
750 chromatography.

751 The QuECHERS (Quick, Easy, Cheap, Effective Rugged and Safe) (Anastassiades et al., 2003)
752 method briefly consists in the succession of the following steps: organic sample homogenization;
753 extraction with solvent, specific salts and buffer to separate the aqueous and organic phases; then
754 purification with dispersive-SPE with appropriate sorbent mixtures. It has been recognized as
755 adaptable and suitable to extract pharmaceuticals from biota, for example venlafaxine and its
756 metabolites (Martínez Bueno et al., 2014a), carbamazepine and oxcarbazepine (Martínez Bueno et al.,
757 2013) in marine mussels, diclofenac in algae and mussels (Cunha et al., 2017).

758

759 **Separation and Detection**

760 Separation, detection and quantification of pharmaceuticals require trace analysis in complex
761 matrices. Chromatographic techniques, mostly liquid chromatography (LC) because of the polarity of
762 pharmaceuticals, coupled with MS or better with MS/MS with electrospray ionization (LC-ESI-
763 MS/MS) for sensitivity and selectivity are mostly used for this purpose (Pazdro et al., 2016). Ultra-

764 high-performance liquid chromatography (UHPLC) permitting to achieve a better resolution thus
765 higher selectivity and faster analysis than HPLC is developed. High-resolution mass spectrometry
766 (HRMS) as time-of-flight (TOF), Orbitrap or linear ion trap, and hybrid HRMS as QTOF or QTrap
767 (Loos et al., 2016) permit to increase sensitivity and selectivity and its use is reported in some studies
768 (Álvarez-Muñoz et al., 2015a; Bayen et al., 2013; Borecka et al., 2013; Martínez Bueno et al., 2014b;
769 Vanryckeghem et al., 2019).

770

771 Matrix effects due to high salinity and dissolved organic matter are a major challenge in
772 pharmaceutical analysis in the marine matrices. Internal standard and surrogates are efficient to correct
773 the matrix effects, but they are expensive and not enough references are available for each compound
774 especially for metabolites and degradation products. Development and application of multiresidue
775 analytical methods remain difficult because pharmaceuticals belong to a wide range of different
776 physicochemical properties. Then the simultaneous analysis of diverse and different molecules
777 requires concessions in the experimental conditions thus in the method performance for certain
778 compounds.

779 Non-target analysis is a relatively recent qualitative approach in analytical chemistry aiming at
780 identifying the occurrence of molecules in the environment but not previously target thus enhancing
781 the water contamination screening (Choi et al., 2020; Tian et al., 2019). Also, it enables a posteriori
782 data mining of the whole acquired information relative to each analyzed sample. It is permitted thanks
783 to the development of tandem HRMS techniques. The main difficulty is relative to the confidence in
784 the proper identification of the molecules through their structure. For this reason, identification
785 confidence levels for MS analysis were proposed based on the available or acquired data relative to
786 molecular structure and analytical parameters. Building of workflows permit to prioritize and identify
787 the molecules (Schymanski et al., 2014).

788 To date according to our knowledge four published studies developed suspect and non-target analysis
789 applied to marine environment samples (seawater, sediments and mussels). (Ccanccapa-Cartagena et
790 al., 2019) combined target, suspected and non-target screenings to assess the occurrence of several
791 classes of contaminants in sediments and seawater of the Mediterranean Sea; in particular eprosartan
792 was identified with non-target screening. Preliminary screening by suspect and non-target screening of
793 the shoreline and the offshore waters of the Kongsfjorden in the Arctic in 2016 permitted during a
794 second campaign in 2017 to target confirmed substances (Choi et al., 2020). A large screening of the
795 North-Est Atlantic Ocean was led by Lara-Martín et al. (2020) and permitted to identify over 500
796 sewage-derived contaminants including pharmaceuticals (parents and metabolites) that represented
797 over 25% of the detected substances. These studies emphasis the wide contamination of the ocean

798 shelf, and the complementarity approach of target and non-target screening that permit then to focus
799 on specific target methodologies in order to assess the potential risk for the marine ecosystem. Besides
800 Bonnefille et al. (2017) identified 13 metabolites of diclofenac in *M. galloprovincialis* tissues with non-
801 target analysis (exposed/non-exposed to diclofenac experimentations), quantified them and proposed
802 several metabolic pathways of these new compounds that remained undocumented until their study.

803

804 **Validation and Quality Assurance/Quality Control**

805 Up to now, there are no existing guidelines for the analysis of pharmaceuticals in environmental
806 matrices (Arpin-Pont et al., 2016). Thus there is a need of validation and quality assurance criteria for
807 this purpose (Białk-Bielińska et al., 2016; Maruya et al., 2014a), using of other not best suited
808 guidelines (pesticide residues in food SANCO/12571/2013 or veterinary pharmaceuticals in food
809 2002/657/EC). International standardized system as ISO/CEI 17025:2017 ('General requirements for
810 the competence of testing and calibration laboratories') might be implemented and specific criteria are
811 needed for validation (matrix effects, instrumental calibration, surrogate recoveries, chromatographic
812 separation quality and analyte identification) and quality assurance (analyte-specific reporting limits, ,
813 procedural blanks, internal standards, and when available agreement with certified/standard reference
814 materials).

815

816 **Databases**

817 The development, improvement and optimization of each steps from the sampling techniques to the
818 analysis of pharmaceuticals in the marine environment should lead to a harmonized methodology for
819 the future monitoring. Management of the generated data is thus a crucial point, taking for example the
820 databases of the Norman Network³ or the master database of the analytical data passing the QA/QC
821 evaluation from the Mussel Watch (Maruya et al., 2014a).

822

823 **III. Monitoring of pharmaceuticals in the marine environment: conclusion** 824 **and perspectives**

825

826 Since 2012; an increasing number of monitoring strategies included or focused on pharmaceutical
827 contamination of the marine environment despite the lack of international guidelines. Most often, data
828 available in the literature are generated by one-time surveys. These are intensive monitoring programs

³³ Norman Network Databases : <https://www.norman-network.net/?q=node/24>

829 set up during a punctual period of time, to measure and observe the quality of the aquatic environment
830 for a specific purpose. The broad occurrence and variability of the marine environment pharmaceutical
831 contamination highlighted by recent studies (Arpin-Pont et al., 2016) suggest that pharmaceutical
832 compounds should be more systematically included both in large (UNESCO and HELCOM, 2017)
833 and in routine marine environment monitoring programs.

834 Prioritization methodologies permitted to set up watch lists of targeted molecules by some
835 international institutions on which certain monitoring are based. At the local scale, the specificities of
836 the study area might be considered i.e. the local pharmaceutical sources. Drug local consumption
837 patterns might be identified (examples of high occurrence of antiretroviral and antimalarial in Africa
838 (K'oreje et al., 2020)), or data gathered from the pollution sources as WWTP effluents. The priority
839 substance lists might be built in the prospect to be regularly monitored to set up databases and to allow
840 analysis of temporal trends.

841 Sampling strategy should be site-specific and preceded by a pilot study to choose the most relevant
842 and cost-effective sampling locations and frequency. Marine sites configuration (offshore, bay, gulf,
843 beaches, etc.) plays a crucial role in hydrodynamics thus in pharmaceutical concentrations especially
844 when using PS techniques. Seawater is the systematically sampled matrix as pharmaceuticals are
845 rather polar, and sediments and biota are the subject of several studies as their sampling give
846 complementary information to better assess the overall contamination. Thanks to the development of
847 HRMS techniques, highly sensitive analyses can be conducted to quantify trace concentrations of
848 pharmaceuticals diluted in the seawater column. Non-target analysis represent a promising approach to
849 identify fate of known contaminants, new molecules of interest and to redefine the monitoring by
850 updating the target list of compounds (Tian et al., 2019).

851 In the light of this dataset, and to go along with future protective measures to limit the evidenced
852 overall contamination by these compounds (Arpin-Pont et al., 2016), several perspectives might
853 permit to go further in the ongoing assessment of the environmental status of the seawater, sediment
854 and biota.

855 ▪ Beyond the objectives of the monitoring strategy, monitoring of contaminants in water can
856 provide information on the fate of pharmaceuticals in the environment, e.g. transformation,
857 partitioning, and transport processes. Thus, such inclusion requires further investigations on
858 the fate, the behavior and the toxicity of the parent compounds and the transformation
859 products. The inclusion of metabolites and degradation products in monitoring strategies is
860 essential and can be implemented with the development and the complementarity of non-
861 target analysis (Pazdro et al., 2016); it would permit to assess their potential combined
862 ecotoxicological effects.

- 863 ▪ As cited above there is an urgent need of harmonization in the monitoring procedures of
864 pharmaceuticals in the marine environment and particularly the validation of the developed
865 analytical methods. The design and adaptations of PS devices less sensitive to environmental
866 conditions and particularly to marine conditions (hydrodynamics, pH, ionic strength) is a
867 promising perspective to complete grab sampling of seawater. *In situ* calibration of PS devices
868 are rare and although it is demanding it could permit to achieve a better accuracy in TWA
869 measurements by using *in situ* determinate RS.
- 870 ▪ For the priority substances identified, integrated monitoring of the environmental matrices
871 conducted in parallel with the measure of biomarkers of exposure and effects (ecological
872 endpoints) would enable to link contaminant occurrence and related ecological responses
873 (Hylland et al., 2017; Vethaak et al., 2017). The broadening of the data about ecological
874 impacts of pharmaceuticals present in the studied environment would permit to develop
875 environmental quality standards and/or guidelines for pharmaceuticals in seawater, sediments,
876 and biota. Extensive monitoring of pharmaceuticals in the environment and their impact on
877 living organisms is listed among the proposed short-term measures to minimize the exposure
878 of humans, animals and ecosystems to these compounds (Klatte et al., 2017). Last, a
879 compromise is necessary between recommended scientific approaches and economic and
880 logistic constraints.
- 881 ▪ The implementation of routine pharmaceutical monitoring strategies in the marine
882 environment implies urgent measures to reduce the sources of contamination. The main stake
883 lies in the reduction in human and veterinary drug consumption. This obviously opens wide,
884 complex, and delicate social and scientific debates, and is turning the fight against
885 environmental pollutions from the opposition of the ‘guilty pollutant industries’ vs the ‘brave
886 environmentalists’, to the ‘nasty environmentalists’ vs the ‘sick victims’. Beyond this, one
887 may question about the implementation of preventive measures and the reduction of disease
888 risk factors to lastingly improve general animal and human health. To conclude this work and
889 questions raised highlight the ecological imbalances and the wide impacts caused by
890 anthropization of water resources.

891

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