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► To cite this version:

Perrine Branchet, Lauren Arpin-Pont, Anne Piram, Pierre Boissery, Pascal Wong-Wah-Chung, et al.. Pharmaceuticals in the marine environment: What are the present challenges in their monitoring?. Science of the Total Environment, 2021, 766, pp.142644. 10.1016/j.scitotenv.2020.142644. hal-03142468

HAL Id: hal-03142468

<https://hal.science/hal-03142468v1>

Submitted on 21 Feb 2022

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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

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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

892 **Acknowledgments**

893 The authors thank the Rhône-Méditerranée-Corse French Water Agency for the GEstion des MILieux
894 (GEMIL) project funding and the postdoctoral grant.

895 **References**

- 896 Afsa, S., Hamden, K., Lara Martin, P.A., Mansour, H.B., 2019. Occurrence of 40 pharmaceutically
 897 active compounds in hospital and urban wastewaters and their contribution to Mahdia
 898 coastal seawater contamination. *Environ. Sci. Pollut. Res. Int.*
 899 <https://doi.org/10.1007/s11356-019-06866-5>
- 900 Ali, A.M., Rønning, H.T., Alarif, W., Kallenborn, R., Al-Lihaibi, S.S., 2017. Occurrence of
 901 pharmaceuticals and personal care products in effluent-dominated Saudi Arabian coastal
 902 waters of the Red Sea. *Chemosphere* 175, 505–513.
 903 <https://doi.org/10.1016/j.chemosphere.2017.02.095>
- 904 Ali, A.M., Rønning, H.T., Sydnnes, L.K., Alarif, W.M., Kallenborn, R., Al-Lihaibi, S.S., 2018. Detection of
 905 PPCPs in marine organisms from contaminated coastal waters of the Saudi Red Sea. *Sci. Total*
 906 *Environ.* 621, 654–662. <https://doi.org/10.1016/j.scitotenv.2017.11.298>
- 907 Almeida, Â., Silva, M.G., Soares, A.M.V.M., Freitas, R., 2020. Concentrations levels and effects of
 908 17alpha-Ethinylestradiol in freshwater and marine waters and bivalves: A review. *Environ.*
 909 *Res.* 185, 109316. <https://doi.org/10.1016/j.envres.2020.109316>
- 910 Alvarez, D.A., Cranor, W.L., Perkins, S.D., Clark, R.C., Smith, S.B., 2008. Chemical and Toxicologic
 911 Assessment of Organic Contaminants in Surface Water Using Passive Samplers. *J. Environ.*
 912 *Qual.* 37, 1024–1033. <https://doi.org/10.2134/jeq2006.0463>
- 913 Alvarez, D.A., Maruya, K.A., Dodder, N.G., Lao, W., Furlong, E.T., Smalling, K.L., 2014. Occurrence of
 914 contaminants of emerging concern along the California coast (2009–10) using passive
 915 sampling devices. *Mar. Pollut. Bull., U.S. Coastal Monitoring: NOAA’s Mussel Watch*
 916 *investigates Contaminants of Emerging Concern* 81, 347–354.
 917 <https://doi.org/10.1016/j.marpolbul.2013.04.022>
- 918 Álvarez-Muñoz, D., Huerta, B., Fernandez-Tejedor, M., Rodríguez-Mozaz, S., Barceló, D., 2015a.
 919 Multi-residue method for the analysis of pharmaceuticals and some of their metabolites in
 920 bivalves. *Talanta* 136, 174–182. <https://doi.org/10.1016/j.talanta.2014.12.035>
- 921 Álvarez-Muñoz, D., Rodríguez-Mozaz, S., Maulvault, A.L., Tediosi, A., Fernández-Tejedor, M., Heuvel,
 922 Van den F., Kotterman, M., Marques, A., Barceló, D., 2015b. Occurrence of pharmaceuticals
 923 and endocrine disrupting compounds in macroalgae, bivalves, and fish from coastal areas in
 924 Europe. *Environ. Res.* 143, 56–64.
- 925 Alygizakis, N.A., Gago-Ferrero, P., Borova, V.L., Pavlidou, A., Hatzianestis, I., Thomaidis, N.S., 2016.
 926 Occurrence and spatial distribution of 158 pharmaceuticals, drugs of abuse and related
 927 metabolites in offshore seawater. *Sci. Total Environ.* 541, 1097–1105.
 928 <https://doi.org/10.1016/j.scitotenv.2015.09.145>
- 929 Anastassiades, M., Lehotay, S.J., Štajnbaher, D., Schenck, F.J., 2003. Fast and Easy Multiresidue
 930 Method Employing Acetonitrile Extraction/Partitioning and “Dispersive Solid-Phase
 931 Extraction” for the Determination of Pesticide Residues in Produce. *J. AOAC Int.* 86, 412–431.
 932 <https://doi.org/10.1093/jaoac/86.2.412>
- 933 Andral, B., Cambert, H., Turquet, J., Ropert, M., Duval, M., Vermetot, C., Boissery, P., Talec, P., 2013.
 934 Guide méthodologique pour la surveillance des rejets urbains dans les eaux littorales
 935 réunionnaises.
- 936 Arpin-Pont, L., Bueno, M.J.M., Gomez, E., Fenet, H., 2016. Occurrence of PPCPs in the marine
 937 environment: a review. *Environ. Sci. Pollut. Res. Int.* 23, 4978–4991.
 938 <https://doi.org/10.1007/s11356-014-3617-x>
- 939 Atashgahi, S., Shetty, S.A., Smidt, H., de Vos, W.M., 2018. Flux, Impact, and Fate of Halogenated
 940 Xenobiotic Compounds in the Gut. *Front. Physiol.* 9.
 941 <https://doi.org/10.3389/fphys.2018.00888>
- 942 Azaroff, A., Miossec, C., Lancelleur, L., Guyoneaud, R., Monperrus, M., 2020. Priority and emerging
 943 micropollutants distribution from coastal to continental slope sediments: A case study of

944 Capbreton Submarine Canyon (North Atlantic Ocean). *Sci. Total Environ.* 703, 135057.
945 <https://doi.org/10.1016/j.scitotenv.2019.135057>

946 Baena-Nogueras, R.M., G. Pintado-Herrera, M., González-Mazo, E., A. Lara-Martín, P., 2016.
947 Determination of Pharmaceuticals in Coastal Systems Using Solid Phase Extraction (SPE)
948 Followed by Ultra Performance Liquid Chromatography – tandem Mass Spectrometry (UPLC-
949 MS/MS). *Curr. Anal. Chem.* 12, 183–201.
950 <https://doi.org/10.2174/1573411012666151009193254>

951 Bayen, S., Estrada, E.S., Juhel, G., Kit, L.W., Kelly, B.C., 2016. Pharmaceutically active compounds and
952 endocrine disrupting chemicals in water, sediments and mollusks in mangrove ecosystems
953 from Singapore. *Mar. Pollut. Bull.*, Turning the tide on mangrove loss 109, 716–722.
954 <https://doi.org/10.1016/j.marpolbul.2016.06.105>

955 Bayen, S., Segovia, E., Loh, L.L., Burger, D.F., Eikaas, H.S., Kelly, B.C., 2014. Application of Polar
956 Organic Chemical Integrative Sampler (POCIS) to monitor emerging contaminants in tropical
957 waters. *Sci. Total Environ.* 482–483, 15–22. <https://doi.org/10.1016/j.scitotenv.2014.02.082>

958 Bayen, S., Zhang, H., Desai, M.M., Ooi, S.K., Kelly, B.C., 2013. Occurrence and distribution of
959 pharmaceutically active and endocrine disrupting compounds in Singapore’s marine
960 environment: Influence of hydrodynamics and physical–chemical properties. *Environ. Pollut.*
961 182, 1–8. <https://doi.org/10.1016/j.envpol.2013.06.028>

962 Beek, T. aus der, Weber, F.-A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A., Küster, A., 2016.
963 Pharmaceuticals in the environment—Global occurrences and perspectives. *Environ. Toxicol.*
964 *Chem.* 35, 823–835. <https://doi.org/10.1002/etc.3339>

965 Belles, A., Alary, C., Aminot, Y., Readman, J.W., Franke, C., 2017. Calibration and response of an
966 agarose gel based passive sampler to record short pulses of aquatic organic pollutants.
967 *Talanta* 165, 1–9. <https://doi.org/10.1016/j.talanta.2016.12.010>

968 Belles, A., Alary, C., Laguerre, N., Franke, C., 2018. Analyzing the uncertainty of diffusive gel-based
969 passive samplers as tools for evaluating the averaged contamination of surface water by
970 organic pollutants. *Environ. Sci. Pollut. Res.* 25, 20231–20240.
971 <https://doi.org/10.1007/s11356-018-2246-1>

972 Beretta, M., Britto, V., Tavares, T.M., da Silva, S.M.T., Pletsch, A.L., 2014. Occurrence of
973 pharmaceutical and personal care products (PPCPs) in marine sediments in the Todos os
974 Santos Bay and the north coast of Salvador, Bahia, Brazil. *J. Soils Sediments* 14, 1278–1286.
975 <https://doi.org/10.1007/s11368-014-0884-6>

976 Białk-Bielińska, A., Kumirska, J., Borecka, M., Caban, M., Paszkiewicz, M., Pazdro, K., Stepnowski, P.,
977 2016. Selected analytical challenges in the determination of pharmaceuticals in
978 drinking/marine waters and soil/sediment samples. *J. Pharm. Biomed. Anal.* 121, 271–296.
979 <https://doi.org/10.1016/j.jpba.2016.01.016>

980 Biel-Maeso, M., Baena-Nogueras, R.M., Corada-Fernández, C., Lara-Martín, P.A., 2018. Occurrence,
981 distribution and environmental risk of pharmaceutically active compounds (PhACs) in coastal
982 and ocean waters from the Gulf of Cadiz (SW Spain). *Sci. Total Environ.* 612, 649–659.
983 <https://doi.org/10.1016/j.scitotenv.2017.08.279>

984 Björlenius, B., Ripszám, M., Haglund, P., Lindberg, R.H., Tysklind, M., Fick, J., 2018. Pharmaceutical
985 residues are widespread in Baltic Sea coastal and offshore waters – Screening for
986 pharmaceuticals and modelling of environmental concentrations of carbamazepine. *Sci. Total*
987 *Environ.* 633, 1496–1509. <https://doi.org/10.1016/j.scitotenv.2018.03.276>

988 Bonnefille, B., Arpin-Pont, L., Gomez, E., Fenet, H., Courant, F., 2017. Metabolic profiling
989 identification of metabolites formed in Mediterranean mussels (*Mytilus galloprovincialis*)
990 after diclofenac exposure. *Sci. Total Environ.* 583, 257–268.
991 <https://doi.org/10.1016/j.scitotenv.2017.01.063>

992 Borecka, M., Białk-Bielińska, A., Siedlewicz, G., Kornowska, K., Kumirska, J., Stepnowski, P., Pazdro, K.,
993 2013. A new approach for the estimation of expanded uncertainty of results of an analytical

994 method developed for determining antibiotics in seawater using solid-phase extraction disks
995 and liquid chromatography coupled with tandem mass spectrometry technique. *J.*
996 *Chromatogr. A* 1304, 138–146. <https://doi.org/10.1016/j.chroma.2013.07.018>
997 Borecka, M., Siedlewicz, G., Haliński, Ł.P., Sikora, K., Pazdro, K., Stepnowski, P., Białk-Bielińska, A.,
998 2015. Contamination of the southern Baltic Sea waters by the residues of selected
999 pharmaceuticals: Method development and field studies. *Mar. Pollut. Bull.* 94, 62–71.
1000 <https://doi.org/10.1016/j.marpolbul.2015.03.008>
1001 Boxall Alistair, B.A., Rudd Murray A., Brooks Bryan W., Caldwell Daniel J., Choi Kyungho, Hickmann
1002 Silke, Innes Elizabeth, Ostapyk Kim, Staveley Jane P., Verslycke Tim, Ankley Gerald T., Beazley
1003 Karen F., Belanger Scott E., Berninger Jason P., Carriquiriborde Pedro, Coors Anja, DeLeo Paul
1004 C., Dyer Scott D., Ericson Jon F., Gagné François, Giesy John P., Gouin Todd, Hallstrom Lars,
1005 Karlsson Maja V., Larsson D. G. Joakim, Lazorchak James M., Mastrocco Frank, McLaughlin
1006 Alison, McMaster Mark E., Meyerhoff Roger D., Moore Roberta, Parrott Joanne L., Snape
1007 Jason R., Murray-Smith Richard, Servos Mark R., Sibley Paul K., Straub Jürg Oliver, Szabo Nora
1008 D., Topp Edward, Tetreault Gerald R., Trudeau Vance L., Van Der Kraak Glen, 2012.
1009 *Pharmaceuticals and Personal Care Products in the Environment: What Are the Big*
1010 *Questions?* *Environ. Health Perspect.* 120, 1221–1229. <https://doi.org/10.1289/ehp.1104477>
1011 Brumovský, M., Bečanová, J., Kohoutek, J., Borghini, M., Nizzetto, L., 2017. Contaminants of emerging
1012 concern in the open sea waters of the Western Mediterranean. *Environ. Pollut. Barking Essex*
1013 1987 229, 976–983. <https://doi.org/10.1016/j.envpol.2017.07.082>
1014 Brumovský, M., Bečanová, J., Kohoutek, J., Thomas, H., Petersen, W., Sørensen, K., Sáňka, O.,
1015 Nizzetto, L., 2016. Exploring the occurrence and distribution of contaminants of emerging
1016 concern through unmanned sampling from ships of opportunity in the North Sea. *J. Mar.*
1017 *Syst., Progress in marine science supported by European joint coastal observation systems:*
1018 *The JERICO-RI research infrastructure* 162, 47–56.
1019 <https://doi.org/10.1016/j.jmarsys.2016.03.004>
1020 Buzier, R., Guibal, R., Lissalde, S., Guibaud, G., 2019. Limitation of flow effect on passive sampling
1021 accuracy using POCIS with the PRC approach or o-DGT: A pilot-scale evaluation for
1022 pharmaceutical compounds. *Chemosphere* 222, 628–636.
1023 <https://doi.org/10.1016/j.chemosphere.2019.01.181>
1024 Caban, M., Męczykowska, H., Stepnowski, P., 2016. Application of the PASSIL technique for the
1025 passive sampling of exemplary polar contaminants (pharmaceuticals and phenolic
1026 derivatives) from water. *Talanta* 155, 185–192.
1027 <https://doi.org/10.1016/j.talanta.2016.04.035>
1028 Cantwell, M.G., Katz, D.R., Sullivan, J.C., Ho, K., Burgess, R.M., 2017. Temporal and spatial behavior of
1029 pharmaceuticals in Narragansett Bay, Rhode Island, United States. *Environ. Toxicol. Chem.*
1030 36, 1846–1855. <https://doi.org/10.1002/etc.3710>
1031 Cantwell, M.G., Katz, D.R., Sullivan, J.C., Ho, K., Burgess, R.M., Cashman, M., 2016. Selected
1032 pharmaceuticals entering an estuary: Concentrations, temporal trends, partitioning, and
1033 fluxes. *Environ. Toxicol. Chem.* 35, 2665–2673. <https://doi.org/10.1002/etc.3452>
1034 Cantwell, M.G., Katz, D.R., Sullivan, J.C., Shapley, D., Lipscomb, J., Epstein, J., Juhl, A.R., Knudson, C.,
1035 O’Mullan, G.D., 2018. Spatial patterns of pharmaceuticals and wastewater tracers in the
1036 Hudson River Estuary. *Water Res.* 137, 335–343.
1037 <https://doi.org/10.1016/j.watres.2017.12.044>
1038 Ccancapa-Cartagena, A., Pico, Y., Ortiz, X., Reiner, E.J., 2019. Suspect, non-target and target
1039 screening of emerging pollutants using data independent acquisition: Assessment of a
1040 Mediterranean River basin. *Sci. Total Environ.* 687, 355–368.
1041 <https://doi.org/10.1016/j.scitotenv.2019.06.057>
1042 Challis, J.K., Hanson, M.L., Wong, C.S., 2016. Development and Calibration of an Organic-Diffusive
1043 Gradients in Thin Films Aquatic Passive Sampler for a Diverse Suite of Polar Organic

1044 Contaminants. *Anal. Chem.* 88, 10583–10591.
1045 <https://doi.org/10.1021/acs.analchem.6b02749>
1046 Chaves-Barquero, L.G., Luong, K.H., Mundy, C.J., Knapp, C.W., Hanson, M.L., Wong, C.S., 2016. The
1047 release of wastewater contaminants in the Arctic: A case study from Cambridge Bay,
1048 Nunavut, Canada. *Environ. Pollut.* 218, 542–550.
1049 <https://doi.org/10.1016/j.envpol.2016.07.036>
1050 Chen, C.-E., Zhang, H., Jones, K.C., 2012. A novel passive water sampler for in situ sampling of
1051 antibiotics. *J. Environ. Monit.* 14, 1523. <https://doi.org/10.1039/c2em30091e>
1052 Chen, H., Liu, S., Xu, X.-R., Liu, S.-S., Zhou, G.-J., Sun, K.-F., Zhao, J.-L., Ying, G.-G., 2015a. Antibiotics in
1053 typical marine aquaculture farms surrounding Hailing Island, South China: Occurrence,
1054 bioaccumulation and human dietary exposure. *Mar. Pollut. Bull.* 90, 181–187.
1055 <https://doi.org/10.1016/j.marpolbul.2014.10.053>
1056 Chen, H., Liu, S., Xu, X.-R., Zhou, G.-J., Liu, S.-S., Yue, W.-Z., Sun, K.-F., Ying, G.-G., 2015b. Antibiotics in
1057 the coastal environment of the Hailing Bay region, South China Sea: Spatial distribution,
1058 source analysis and ecological risks. *Mar. Pollut. Bull.* 95, 365–373.
1059 <https://doi.org/10.1016/j.marpolbul.2015.04.025>
1060 Choi, Y., Kim, K., Kim, D., Moon, H.-B., Jeon, J., 2020. Ny-Ålesund-oriented organic pollutants in
1061 sewage effluent and receiving seawater in the Arctic region of Kongsfjorden. *Environ. Pollut.*
1062 *Barking Essex* 1987 258, 113792. <https://doi.org/10.1016/j.envpol.2019.113792>
1063 Crain, C.M., Halpern, B.S., Beck, M.W., Kappel, C.V., 2009. Understanding and Managing Human
1064 Threats to the Coastal Marine Environment. *Ann. N. Y. Acad. Sci.* 1162, 39–62.
1065 Cunha, S.C., Pena, A., Fernandes, J.O., 2017. Mussels as bioindicators of diclofenac contamination in
1066 coastal environments. *Environ. Pollut.* 225, 354–360.
1067 <https://doi.org/10.1016/j.envpol.2017.02.061>
1068 Desbiolles, F., Malleret, L., Tiliacos, C., Wong-Wah-Chung, P., Laffont-Schwob, I., 2018. Occurrence
1069 and ecotoxicological assessment of pharmaceuticals: Is there a risk for the Mediterranean
1070 aquatic environment? *Sci. Total Environ.* 639, 1334–1348.
1071 <https://doi.org/10.1016/j.scitotenv.2018.04.351>
1072 Domínguez, J.R., González, T., Palo, P., Cuerda-Correa, E.M., 2011. Removal of common
1073 pharmaceuticals present in surface waters by Amberlite XAD-7 acrylic-ester-resin: Influence
1074 of pH and presence of other drugs. *Desalination* 269, 231–238.
1075 <https://doi.org/10.1016/j.desal.2010.10.065>
1076 Duarte, B., Vaz, N., Valentim, J., Dias, J., Silva, H., Marques, J., Sleimi, N., Caçador, I., 2017. Revisiting
1077 the Outwelling Hypothesis: Modelling Salt Marsh Detrital Metal Exports under Extreme
1078 Climatic Events. *Mar. Chem.* 191, 24. <https://doi.org/10.1016/j.marchem.2016.12.002>
1079 Erostate, M., Huneau, F., Garel, E., Vystavna, Y., Santoni, S., Pasqualini, V., 2019. Coupling isotope
1080 hydrology, geochemical tracers and emerging compounds to evaluate mixing processes and
1081 groundwater dependence of a highly anthropized coastal hydrosystem. *J. Hydrol.* 578,
1082 123979. <https://doi.org/10.1016/j.jhydrol.2019.123979>
1083 European Commission, Directorate-General for the Environment, 2009. Guidance on surface water
1084 chemical monitoring under the water framework directive.
1085 European Parliament and Council, 2008. Directive 2008/56/EC of the European Parliament and of the
1086 Council of 17 June 2008 establishing a framework for community action in the field of marine
1087 environmental policy (Marine Strategy Framework Directive) (Text with EEA relevance), 164.
1088 Fang, T.-H., Nan, F.-H., Chin, T.-S., Feng, H.-M., 2012. The occurrence and distribution of
1089 pharmaceutical compounds in the effluents of a major sewage treatment plant in Northern
1090 Taiwan and the receiving coastal waters. *Mar. Pollut. Bull.* 64, 1435–1444.
1091 <https://doi.org/10.1016/j.marpolbul.2012.04.008>

- 1092 Felis, E., Kalka, J., Sochacki, A., Kowalska, K., Bajkacz, S., Harnisz, M., Korzeniewska, E., 2019.
 1093 Antimicrobial pharmaceuticals in the aquatic environment - occurrence and environmental
 1094 implications. *Eur. J. Pharmacol.* 172813. <https://doi.org/10.1016/j.ejphar.2019.172813>
- 1095 Fenet, H., Arpin-Pont, L., Vanhoutte-Brunier, A., Munaron, D., Fiandrino, A., Martínez Bueno, M.-J.,
 1096 Boillot, C., Casellas, C., Mathieu, O., Gomez, E., 2014. Reducing PEC uncertainty in coastal
 1097 zones: A case study on carbamazepine, oxcarbazepine and their metabolites. *Environ. Int.* 68,
 1098 177–184. <https://doi.org/10.1016/j.envint.2014.03.025>
- 1099 Fonseca, V.F., Reis-Santos, P., Duarte, B., Cabral, H.N., Caçador, M.I., Vaz, N., Dias, J.M., Pais, M.P.,
 1100 2020. Roving pharmacies: Modelling the dispersion of pharmaceutical contamination in
 1101 estuaries. *Ecol. Indic.* 115, 106437. <https://doi.org/10.1016/j.ecolind.2020.106437>
- 1102 Gaw, S., Thomas, K.V., Hutchinson, T.H., 2014. Sources, impacts and trends of pharmaceuticals in the
 1103 marine and coastal environment. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 369.
 1104 <https://doi.org/10.1098/rstb.2013.0572>
- 1105 Goh, S.G., Bayen, S., Burger, D., Kelly, B.C., Han, P., Babovic, V., Gin, K.Y.-H., 2017. Occurrence and
 1106 distribution of bacteria indicators, chemical tracers and pathogenic vibrios in Singapore
 1107 coastal waters. *Mar. Pollut. Bull.* 114, 627–634.
 1108 <https://doi.org/10.1016/j.marpolbul.2016.09.036>
- 1109 Gonzalez-Rey, M., Tapie, N., Le Menach, K., Dévier, M.-H., Budzinski, H., Bebianno, M.J., 2015.
 1110 Occurrence of pharmaceutical compounds and pesticides in aquatic systems. *Mar. Pollut.*
 1111 *Bull.* 96, 384–400. <https://doi.org/10.1016/j.marpolbul.2015.04.029>
- 1112 Gros, M., Rodríguez-Mozaz, S., Barceló, D., 2012. Fast and comprehensive multi-residue analysis of a
 1113 broad range of human and veterinary pharmaceuticals and some of their metabolites in
 1114 surface and treated waters by ultra-high-performance liquid chromatography coupled to
 1115 quadrupole-linear ion trap tandem mass spectrometry. *J. Chromatogr. A* 1248, 104–121.
 1116 <https://doi.org/10.1016/j.chroma.2012.05.084>
- 1117 Guibal, R., Buzier, R., Lissalde, S., Guibaud, G., 2019. Adaptation of diffusive gradients in thin films
 1118 technique to sample organic pollutants in the environment: An overview of o-DGT passive
 1119 samplers. *Sci. Total Environ.* 693, 133537. <https://doi.org/10.1016/j.scitotenv.2019.07.343>
- 1120 Guo, X., Feng, C., Gu, E., Tian, C., Shen, Z., 2019. Spatial distribution, source apportionment and risk
 1121 assessment of antibiotics in the surface water and sediments of the Yangtze Estuary. *Sci.*
 1122 *Total Environ.* 671, 548–557. <https://doi.org/10.1016/j.scitotenv.2019.03.393>
- 1123 Hedgespeth, M.L., Sapozhnikova, Y., Pennington, P., Clum, A., Fairey, A., Wirth, E., 2012.
 1124 Pharmaceuticals and personal care products (PPCPs) in treated wastewater discharges into
 1125 Charleston Harbor, South Carolina. *Sci. Total Environ.* 437, 1–9.
 1126 <https://doi.org/10.1016/j.scitotenv.2012.07.076>
- 1127 Hylland, K., Robinson, C.D., Burgeot, T., Martínez-Gómez, C., Lang, T., Svavarsson, J., Thain, J.E.,
 1128 Vethaak, A.D., Gubbins, M.J., 2017. Integrated chemical and biological assessment of
 1129 contaminant impacts in selected European coastal and offshore marine areas. *Mar. Environ.*
 1130 *Res.*, The ICON Project (the trans-European research project on field studies related to a
 1131 large-scale sampling and monitoring 124, 130–138.
 1132 <https://doi.org/10.1016/j.marenvres.2016.05.014>
- 1133 Ibrahim, I., Togola, A., Gonzalez, C., 2013. In-situ calibration of POCIS for the sampling of polar
 1134 pesticides and metabolites in surface water. *Talanta* 116, 495–500.
 1135 <https://doi.org/10.1016/j.talanta.2013.07.028>
- 1136 Ismail, N.A.H., Wee, S.Y., Haron, D.E.M., Kamarulzaman, N.H., Aris, A.Z., 2019. Occurrence of
 1137 endocrine disrupting compounds in mariculture sediment of Pulau Kukup, Johor, Malaysia.
 1138 *Mar. Pollut. Bull.* 110735. <https://doi.org/10.1016/j.marpolbul.2019.110735>
- 1139 James, C.A., Lanksbury, J., Khangaonkar, T., West, J., 2020. Evaluating exposures of bay mussels
 1140 (*Mytilus trossulus*) to contaminants of emerging concern through environmental sampling

1141 and hydrodynamic modeling. *Sci. Total Environ.* 709, 136098.
1142 <https://doi.org/10.1016/j.scitotenv.2019.136098>

1143 Jia, A., Hu, J., Wu, X., Peng, H., Wu, S., Dong, Z., 2011. Occurrence and source apportionment of
1144 sulfonamides and their metabolites in Liaodong Bay and the adjacent Liao River basin, North
1145 China. *Environ. Toxicol. Chem.* 30, 1252–1260. <https://doi.org/10.1002/etc.508>

1146 Joyce, A.S., Burgess, R.M., 2018. Using performance reference compounds to compare mass transfer
1147 calibration methodologies in passive samplers deployed in the water column. *Environ.*
1148 *Toxicol. Chem.* 37, 2089–2097. <https://doi.org/10.1002/etc.4167>

1149 Kim, H.-Y., Lee, I.-S., Oh, J.-E., 2017. Human and veterinary pharmaceuticals in the marine
1150 environment including fish farms in Korea. *Sci. Total Environ.* 579, 940–949.
1151 <https://doi.org/10.1016/j.scitotenv.2016.10.039>

1152 Klatte, S., Schaefer, H.-C., Hempel, M., 2017. Pharmaceuticals in the environment – A short review on
1153 options to minimize the exposure of humans, animals and ecosystems. *Sustain. Chem.*
1154 *Pharm.* 5, 61–66. <https://doi.org/10.1016/j.scp.2016.07.001>

1155 Klosterhaus, S.L., Grace, R., Hamilton, M.C., Yee, D., 2013. Method validation and reconnaissance of
1156 pharmaceuticals, personal care products, and alkylphenols in surface waters, sediments, and
1157 mussels in an urban estuary. *Environ. Int.* 54, 92–99.
1158 <https://doi.org/10.1016/j.envint.2013.01.009>

1159 K’oreje, K.O., Okoth, M., Van Langenhove, H., Demeestere, K., 2020. Occurrence and treatment of
1160 contaminants of emerging concern in the African aquatic environment: Literature review and
1161 a look ahead. *J. Environ. Manage.* 254, 109752.
1162 <https://doi.org/10.1016/j.jenvman.2019.109752>

1163 Kötke, D., Gandrass, J., Xie, Z., Ebinghaus, R., 2019. Prioritised pharmaceuticals in German estuaries
1164 and coastal waters: Occurrence and environmental risk assessment. *Environ. Pollut.* 255,
1165 113161. <https://doi.org/10.1016/j.envpol.2019.113161>

1166 Langford, K., Thomas, K.V., 2011. Input of selected human pharmaceutical metabolites into the
1167 Norwegian aquatic environment. *J. Environ. Monit.* 13, 416–421.
1168 <https://doi.org/10.1039/C0EM00342E>

1169 Lara-Martín, P.A., Chiaia-Hernández, A.C., Biel-Maeso, M., Baena-Nogueras, R.M., Hollender, J., 2020.
1170 Tracing urban wastewater contaminants into the Atlantic Ocean by non-target screening.
1171 *Environ. Sci. Technol.* <https://doi.org/10.1021/acs.est.9b06114>

1172 Lara-Martín, P.A., González-Mazo, E., Petrovic, M., Barceló, D., Brownawell, B.J., 2014. Occurrence,
1173 distribution and partitioning of nonionic surfactants and pharmaceuticals in the urbanized
1174 Long Island Sound Estuary (NY). *Mar. Pollut. Bull.*, 7th International Conference on Marine
1175 Pollution and Ecotoxicology 85, 710–719. <https://doi.org/10.1016/j.marpolbul.2014.01.022>

1176 Li, F., Chen, L., Bao, Y., Zheng, Y., Huang, B., Mu, Q., Feng, C., Wen, D., 2020. Identification of the
1177 priority antibiotics based on their detection frequency, concentration, and ecological risk in
1178 urbanized coastal water. *Sci. Total Environ.* 141275.
1179 <https://doi.org/10.1016/j.scitotenv.2020.141275>

1180 Li, Y., Yao, C., Zha, D., Yang, W., Lu, G., 2018. Selection of performance reference compound (PRC) for
1181 passive sampling of pharmaceutical residues in an effluent dominated river. *Chemosphere*
1182 211, 884–892. <https://doi.org/10.1016/j.chemosphere.2018.07.179>

1183 Liang, X., Chen, B., Nie, X., Shi, Z., Huang, X., Li, X., 2013. The distribution and partitioning of common
1184 antibiotics in water and sediment of the Pearl River Estuary, South China. *Chemosphere* 92,
1185 1410–1416. <https://doi.org/10.1016/j.chemosphere.2013.03.044>

1186 Liu, S., Bekele, T.-G., Zhao, H., Cai, X., Chen, J., 2018. Bioaccumulation and tissue distribution of
1187 antibiotics in wild marine fish from Laizhou Bay, North China. *Sci. Total Environ.* 631–632,
1188 1398–1405. <https://doi.org/10.1016/j.scitotenv.2018.03.139>

1189 Lolić, A., Paíga, P., Santos, L.H.M.L.M., Ramos, S., Correia, M., Delerue-Matos, C., 2015. Assessment
1190 of non-steroidal anti-inflammatory and analgesic pharmaceuticals in seawaters of North of

1191 Portugal: Occurrence and environmental risk. *Sci. Total Environ.* 508, 240–250.
1192 <https://doi.org/10.1016/j.scitotenv.2014.11.097>

1193 Long, E.R., Dutch, M., Weakland, S., Chandramouli, B., Benskin, J.P., 2013. Quantification of
1194 pharmaceuticals, personal care products, and perfluoroalkyl substances in the marine
1195 sediments of Puget Sound, Washington, USA. *Environ. Toxicol. Chem.* 32, 1701–1710.
1196 <https://doi.org/10.1002/etc.2281>

1197 Loos, G., Van Schepdael, A., Cabooter, D., 2016. Quantitative mass spectrometry methods for
1198 pharmaceutical analysis. *Philos. Transact. A Math. Phys. Eng. Sci.* 374.
1199 <https://doi.org/10.1098/rsta.2015.0366>

1200 Maranho, L.A., DelValls, T.A., Martín-Díaz, M.L., 2015. Assessing potential risks of wastewater
1201 discharges to benthic biota: An integrated approach to biomarker responses in clams
1202 (*Ruditapes philippinarum*) exposed under controlled conditions. *Mar. Pollut. Bull.* 92, 11–24.
1203 <https://doi.org/10.1016/j.marpolbul.2015.01.009>

1204 MARETEC, 2018. MOHID Water Modelling System [WWW Document]. URL <http://www.mohid.com/>
1205 (accessed 6.2.20).

1206 Marti, E., Variatza, E., Balcazar, J.L., 2014. The role of aquatic ecosystems as reservoirs of antibiotic
1207 resistance. *Trends Microbiol.* 22, 36–41. <https://doi.org/10.1016/j.tim.2013.11.001>

1208 Martínez Bueno, M.J., Boillot, C., Fenet, H., Chiron, S., Casellas, C., Gómez, E., 2013. Fast and easy
1209 extraction combined with high resolution-mass spectrometry for residue analysis of two
1210 anticonvulsants and their transformation products in marine mussels. *J. Chromatogr. A* 1305,
1211 27–34. <https://doi.org/10.1016/j.chroma.2013.06.071>

1212 Martínez Bueno, M.J., Boillot, C., Munaron, D., Fenet, H., Casellas, C., Gómez, E., 2014a. Occurrence
1213 of venlafaxine residues and its metabolites in marine mussels at trace levels: development of
1214 analytical method and a monitoring program. *Anal. Bioanal. Chem.* 406, 601–610.
1215 <https://doi.org/10.1007/s00216-013-7477-x>

1216 Martínez Bueno, M.J., Herrera, S., Munaron, D., Boillot, C., Fenet, H., Chiron, S., Gómez, E., 2014b.
1217 POCIS passive samplers as a monitoring tool for pharmaceutical residues and their
1218 transformation products in marine environment. *Environ. Sci. Pollut. Res.* 23, 5019–5029.
1219 <https://doi.org/10.1007/s11356-014-3796-5>

1220 Maruya, K.A., Dodder, N.G., Schaffner, R.A., Weisberg, S.B., Gregorio, D., Klosterhaus, S., Alvarez,
1221 D.A., Furlong, E.T., Kimbrough, K.L., Lauenstein, G.G., Christensen, J.D., 2014a. Refocusing
1222 Mussel Watch on contaminants of emerging concern (CECs): The California pilot study (2009–
1223 10). *Mar. Pollut. Bull., U.S. Coastal Monitoring: NOAA’s Mussel Watch investigates*
1224 *Contaminants of Emerging Concern* 81, 334–339.
1225 <https://doi.org/10.1016/j.marpolbul.2013.04.027>

1226 Maruya, K.A., Dodder, N.G., Weisberg, S.B., Gregorio, D., Bishop, J.S., Klosterhaus, S., Alvarez, D.A.,
1227 Furlong, E.T., Bricker, S., Kimbrough, K.L., Lauenstein, G.G., 2014b. The Mussel Watch
1228 California pilot study on contaminants of emerging concern (CECs): Synthesis and next steps.
1229 *Mar. Pollut. Bull., U.S. Coastal Monitoring: NOAA’s Mussel Watch investigates* *Contaminants*
1230 *of Emerging Concern* 81, 355–363. <https://doi.org/10.1016/j.marpolbul.2013.04.023>

1231 Maruya, K.A., Schlenk, D., Anderson, P.D., Denslow, N.D., Drewes, J.E., Olivieri, A.W., Scott, G.I.,
1232 Snyder, S.A., 2014c. An Adaptive, Comprehensive Monitoring Strategy for Chemicals of
1233 Emerging Concern (CECs) in California’s Aquatic Ecosystems. *Integr. Environ. Assess. Manag.*
1234 10, 69–77. <https://doi.org/10.1002/ieam.1483>

1235 Matongo, S., Birungi, G., Moodley, B., Ndungu, P., 2015. Occurrence of selected pharmaceuticals in
1236 water and sediment of Umgeni River, KwaZulu-Natal, South Africa. *Environ. Sci. Pollut. Res.*
1237 22, 10298–10308. <https://doi.org/10.1007/s11356-015-4217-0>

1238 McEneff, G., Barron, L., Kelleher, B., Paull, B., Quinn, B., 2014. A year-long study of the spatial
1239 occurrence and relative distribution of pharmaceutical residues in sewage effluent, receiving

1240 marine waters and marine bivalves. *Sci. Total Environ.* 476–477, 317–326.
1241 <https://doi.org/10.1016/j.scitotenv.2013.12.123>

1242 Meador, J.P., Yeh, A., Young, G., Gallagher, E.P., 2016. Contaminants of emerging concern in a large
1243 temperate estuary. *Environ. Pollut.* 213, 254–267.
1244 <https://doi.org/10.1016/j.envpol.2016.01.088>

1245 Męczykowska, H., Kobylis, P., Stepnowski, P., Caban, M., 2017. Ionic liquids for the passive sampling
1246 of sulfonamides from water—applicability and selectivity study. *Anal. Bioanal. Chem.* 409,
1247 3951–3958. <https://doi.org/10.1007/s00216-017-0342-6>

1248 Męczykowska, H., Stepnowski, P., Caban, M., 2018. Effect of salinity and pH on the calibration of the
1249 extraction of pharmaceuticals from water by PASSIL. *Talanta* 179, 271–278.
1250 <https://doi.org/10.1016/j.talanta.2017.11.012>

1251 Mezzelani, M., Gorbí, S., Regoli, F., 2018. Pharmaceuticals in the aquatic environments: Evidence of
1252 emerged threat and future challenges for marine organisms. *Mar. Environ. Res.* 140, 41–60.
1253 <https://doi.org/10.1016/j.marenvres.2018.05.001>

1254 Miège, C., Mazzella, N., Allan, I., Dulio, V., Smedes, F., Tixier, C., Vermeirssen, E., Brant, J., O’Toole, S.,
1255 Budzinski, H., Ghestem, J.-P., Staub, P.-F., Lardy-Fontan, S., Gonzalez, J.-L., Coquery, M.,
1256 Vrana, B., 2015. Position paper on passive sampling techniques for the monitoring of
1257 contaminants in the aquatic environment – Achievements to date and perspectives. *Trends*
1258 *Environ. Anal. Chem.* 8, 20–26. <https://doi.org/10.1016/j.teac.2015.07.001>

1259 Moreno-González, R., Rodríguez-Mozaz, S., Gros, M., Barceló, D., León, V.M., 2015. Seasonal
1260 distribution of pharmaceuticals in marine water and sediment from a mediterranean coastal
1261 lagoon (SE Spain). *Environ. Res.* 138, 326–344. <https://doi.org/10.1016/j.envres.2015.02.016>

1262 Moreno-González, R., Rodríguez-Mozaz, S., Huerta, B., Barceló, D., León, V.M., 2016. Do
1263 pharmaceuticals bioaccumulate in marine molluscs and fish from a coastal lagoon? *Environ.*
1264 *Res.* 146, 282–298. <https://doi.org/10.1016/j.envres.2016.01.001>

1265 Munaron, D., Tapie, N., Budzinski, H., Andral, B., Gonzalez, J.-L., 2012. Pharmaceuticals, alkylphenols
1266 and pesticides in Mediterranean coastal waters: Results from a pilot survey using passive
1267 samplers. *Estuar. Coast. Shelf Sci.* 114, 82–92. <https://doi.org/10.1016/j.ecss.2011.09.009>

1268 Na, G., Fang, X., Cai, Y., Ge, L., Zong, H., Yuan, X., Yao, Z., Zhang, Z., 2013. Occurrence, distribution,
1269 and bioaccumulation of antibiotics in coastal environment of Dalian, China. *Mar. Pollut. Bull.*
1270 69, 233–237. <https://doi.org/10.1016/j.marpolbul.2012.12.028>

1271 Nödler, K., Tsakiri, M., Aloupi, M., Gatidou, G., Stasinakis, A.S., Licha, T., 2016. Evaluation of polar
1272 organic micropollutants as indicators for wastewater-related coastal water quality
1273 impairment. *Environ. Pollut.* 211, 282–290. <https://doi.org/10.1016/j.envpol.2016.01.014>

1274 Nödler, K., Voutsas, D., Licha, T., 2014. Polar organic micropollutants in the coastal environment of
1275 different marine systems. *Mar. Pollut. Bull.* 85, 50–59.
1276 <https://doi.org/10.1016/j.marpolbul.2014.06.024>

1277 OSPAR Commission, 2013. JAMP Guidelines for monitoring of contaminants in seawater.

1278 OSPAR Commission, 1992. Convention for the protection of the marine environment of the North-Est
1279 Atlantic.

1280 Paíga, P., Delerue-Matos, C., 2017. Anthropogenic contamination of Portuguese coastal waters
1281 during the bathing season: Assessment using caffeine as a chemical marker. *Mar. Pollut. Bull.*
1282 120, 355–363. <https://doi.org/10.1016/j.marpolbul.2017.05.030>

1283 Paíga, P., Lolić, A., Hellebuyck, F., Santos, L.H.M.L.M., Correia, M., Delerue-Matos, C., 2015.
1284 Development of a SPE–UHPLC–MS/MS methodology for the determination of non-steroidal
1285 anti-inflammatory and analgesic pharmaceuticals in seawater. *J. Pharm. Biomed. Anal., SI:*
1286 *Analytical approaches* 106, 61–70. <https://doi.org/10.1016/j.jpba.2014.06.017>

1287 Pairaud, I.L., Gatti, J., Bensoussan, N., Verney, R., Garreau, P., 2011. Hydrology and circulation in a
1288 coastal area off Marseille: Validation of a nested 3D model with observations. *J. Mar. Syst.*,

1289 41st International Liege Colloquium on Ocean Dynamics"Science based management of the
1290 coastal waters 88, 20–33. <https://doi.org/10.1016/j.jmarsys.2011.02.010>

1291 Pazdro, K., Borecka, M., Siedlewicz, G., Bia.k-Bieli.ska, A., Stepnowski, P., 2016. Analysis of the
1292 Residues of Pharmaceuticals in Marine Environment: State-of-the-art, Analytical Problems
1293 and Challenges. *Curr. Anal. Chem.* 12, 202–226.
1294 <https://doi.org/10.2174/1573411012666151009193536>

1295 Phuong, N.N., Poirier, L., Lagarde, F., Kamari, A., Zalouk-Vergnoux, A., 2018. Microplastic abundance
1296 and characteristics in French Atlantic coastal sediments using a new extraction method.
1297 *Environ. Pollut.* 243, 228–237. <https://doi.org/10.1016/j.envpol.2018.08.032>

1298 Pouzol, T., Lévi, Y., Bertrand-Krajewski, J.-L., 2020. Modelling daily and hourly loads of
1299 pharmaceuticals in urban wastewater. *Int. J. Hyg. Environ. Health* 229, 113552.
1300 <https://doi.org/10.1016/j.ijheh.2020.113552>

1301 Ren, S., Tao, J., Tan, F., Cui, Y., Li, X., Chen, J., He, X., Wang, Y., 2018. Diffusive gradients in thin films
1302 based on MOF-derived porous carbon binding gel for in-situ measurement of antibiotics in
1303 waters. *Sci. Total Environ.* 645, 482–490. <https://doi.org/10.1016/j.scitotenv.2018.07.013>

1304 Rimayi, C., Odusanya, D., Weiss, J.M., de Boer, J., Chimuka, L., 2018. Contaminants of emerging
1305 concern in the Hartbeespoort Dam catchment and the uMngeni River estuary 2016 pollution
1306 incident, South Africa. *Sci. Total Environ.* 627, 1008–1017.
1307 <https://doi.org/10.1016/j.scitotenv.2018.01.263>

1308 Santos, L.H.M.L.M., Gros, M., Rodriguez-Mozaz, S., Delerue-Matos, C., Pena, A., Barceló, D.,
1309 Montenegro, M.C.B.S.M., 2013. Contribution of hospital effluents to the load of
1310 pharmaceuticals in urban wastewaters: Identification of ecologically relevant
1311 pharmaceuticals. *Sci. Total Environ.* 461–462, 302–316.
1312 <https://doi.org/10.1016/j.scitotenv.2013.04.077>

1313 Schutte, C.A., Ahmerkamp, S., Wu, C.S., Seidel, M., de Beer, D., Cook, P.L.M., Joye, S.B., 2019. Chapter
1314 12 - Biogeochemical Dynamics of Coastal Tidal Flats, in: Perillo, G.M.E., Wolanski, E., Cahoon,
1315 D.R., Hopkinson, C.S. (Eds.), *Coastal Wetlands*. Elsevier, pp. 407–440.
1316 <https://doi.org/10.1016/B978-0-444-63893-9.00012-5>

1317 Schymanski, E.L., Jeon, J., Gulde, R., Fenner, K., Ruff, M., Singer, H.P., Hollender, J., 2014. Identifying
1318 Small Molecules via High Resolution Mass Spectrometry: Communicating Confidence.
1319 *Environ. Sci. Technol.* 48, 2097–2098. <https://doi.org/10.1021/es5002105>

1320 Shi, X., Zhou, J.L., Zhao, H., Hou, L., Yang, Y., 2014. Application of passive sampling in assessing the
1321 occurrence and risk of antibiotics and endocrine disrupting chemicals in the Yangtze Estuary,
1322 China. *Chemosphere* 111, 344–351. <https://doi.org/10.1016/j.chemosphere.2014.03.139>

1323 Silva, L.J.G., Pereira, A.M.P.T., Rodrigues, H., Meisel, L.M., Lino, C.M., Pena, A., 2017. SSRIs
1324 antidepressants in marine mussels from Atlantic coastal areas and human risk assessment.
1325 *Sci. Total Environ.* 603–604, 118–125. <https://doi.org/10.1016/j.scitotenv.2017.06.076>

1326 Snelgrove, P.V.R., 2013. Marine Sediments, in: Levin, S.A. (Ed.), *Encyclopedia of Biodiversity* (Second
1327 Edition). Academic Press, Waltham, pp. 105–115. <https://doi.org/10.1016/B978-0-12-384719-5.00008-3>

1329 Stewart, M., Cameron, M., McMurtry, M., Sander, S., Benedict, B., Graham, L., Hosie, M., Green, T.,
1330 2016. Development of passive sampling devices for bioavailable contaminants of current and
1331 emerging concern: Waitemata Harbour case study. *N. Z. J. Mar. Freshw. Res.* 50, 526–548.
1332 <https://doi.org/10.1080/00288330.2016.1181662>

1333 Stewart, M., Olsen, G., Hickey, C.W., Ferreira, B., Jelić, A., Petrović, M., Barcelo, D., 2014. A survey of
1334 emerging contaminants in the estuarine receiving environment around Auckland, New
1335 Zealand. *Sci. Total Environ.* 468–469, 202–210.
1336 <https://doi.org/10.1016/j.scitotenv.2013.08.039>

1337 Stroski, K.M., Luong, K.H., Challis, J.K., Chaves-Barquero, L.G., Hanson, M.L., Wong, C.S., 2020.
1338 Wastewater sources of per- and polyfluorinated alkyl substances (PFAS) and pharmaceuticals

1339 in four Canadian Arctic communities. *Sci. Total Environ.* 708, 134494.
1340 <https://doi.org/10.1016/j.scitotenv.2019.134494>

1341 Świacka, K., Maculewicz, J., Smolarz, K., Szaniawska, A., Caban, M., 2019. Mytilidae as model
1342 organisms in the marine ecotoxicology of pharmaceuticals - A review. *Environ. Pollut.* 254,
1343 113082. <https://doi.org/10.1016/j.envpol.2019.113082>

1344 Szymczycha, B., Borecka, M., Białk-Bielińska, A., Siedlewicz, G., Pazdro, K., 2020. Submarine
1345 groundwater discharge as a source of pharmaceutical and caffeine residues in coastal
1346 ecosystem: Bay of Puck, southern Baltic Sea case study. *Sci. Total Environ.* 713, 136522.
1347 <https://doi.org/10.1016/j.scitotenv.2020.136522>

1348 Tian, Z., Peter, K.T., Gipe, A.D., Zhao, H., Hou, F., Wark, D.A., Khangaonkar, T., Kolodziej, E.P., James,
1349 C.A., 2019. Suspect and non-target screening for contaminants of emerging concern in an
1350 urban estuary. *Environ. Sci. Technol.* <https://doi.org/10.1021/acs.est.9b06126>

1351 Togola, A., Budzinski, H., 2007. Development of Polar Organic Integrative Samplers for Analysis of
1352 Pharmaceuticals in Aquatic Systems. *Anal. Chem.* 79, 6734–6741.
1353 <https://doi.org/10.1021/ac070559i>

1354 Turja, R., Lehtonen, K.K., Meierjohann, A., Brozinski, J.-M., Vahtera, E., Soirinsuo, A., Sokolov, A.,
1355 Snoeijls, P., Budzinski, H., Devier, M.-H., Peluhet, L., Pääkkönen, J.-P., Viitasalo, M., Kronberg,
1356 L., 2015. The mussel caging approach in assessing biological effects of wastewater treatment
1357 plant discharges in the Gulf of Finland (Baltic Sea). *Mar. Pollut. Bull.* 97, 135–149.
1358 <https://doi.org/10.1016/j.marpolbul.2015.06.024>

1359 UNESCO, HELCOM, 2017. Pharmaceuticals in the aquatic environment of the Baltic Sea region – A
1360 status report. (UNESCO Publishing No. No. 1), UNESCO Emerging Pollutants in Water Series.
1361 UNESCO, Paris.

1362 UNESCO/WHO/UNEP, 1996. Water quality assessments : a guide to the use of biota, sediments and
1363 water in environmental monitoring. London : E & FN Spon.

1364 US EPA, 2010. Sampling and consideration of variability (temporal and spatial) for monitoring of
1365 recreational waters (No. EPA-823-R-10-005). U.S. Environmental Protection Agency Office of
1366 Water.

1367 US EPA, 2007. Method 1694: Pharmaceuticals and personal care product in water, soil, sediment and
1368 biosolids by HPLC/MS/S. (No. EPA-821-R-08-002). Office of Water, Office of Science and
1369 Technology, Engineering and Analysis Division, Washington DC, USA.

1370 US EPA, 1998. National Sediment Bioaccumulation Conference proceedings. U.S. Environmental
1371 Protection Agency, Office of Water, Washington, DC.

1372 Vanryckeghem, F., Huysman, S., Van Langenhove, H., Vanhaecke, L., Demeestere, K., 2019. Multi-
1373 residue quantification and screening of emerging organic micropollutants in the Belgian Part
1374 of the North Sea by use of Speedisk extraction and Q-Orbitrap HRMS. *Mar. Pollut. Bull.* 142,
1375 350–360. <https://doi.org/10.1016/j.marpolbul.2019.03.049>

1376 Vethaak, A.D., Davies, I.M., Thain, J.E., Gubbins, M.J., Martínez-Gómez, C., Robinson, C.D., Moffat,
1377 C.F., Burgeot, T., Maes, T., Wosniok, W., Giltrap, M., Lang, T., Hylland, K., 2017. Integrated
1378 indicator framework and methodology for monitoring and assessment of hazardous
1379 substances and their effects in the marine environment. *Mar. Environ. Res.*, The ICON Project
1380 (the trans-European research project on field studies related to a large-scale sampling and
1381 monitoring 124, 11–20. <https://doi.org/10.1016/j.marenvres.2015.09.010>

1382 Vidal-Dorsch, D.E., Bay, S.M., Maruya, K., Snyder, S.A., Trenholm, R.A., Vanderford, B.J., 2012.
1383 Contaminants of emerging concern in municipal wastewater effluents and marine receiving
1384 water. *Environ. Toxicol. Chem.* 31, 2674–2682. <https://doi.org/10.1002/etc.2004>

1385 Vrana, B., Smedes, F., Prokeš, R., Loos, R., Mazzella, N., Miege, C., Budzinski, H., Vermeirssen, E.,
1386 Ocelka, T., Gravell, A., Kaserzon, S., 2016. An interlaboratory study on passive sampling of
1387 emerging water pollutants. *TrAC Trends Anal. Chem.* 76, 153–165.
1388 <https://doi.org/10.1016/j.trac.2015.10.013>

1389 Vystavna, Y., Le Coustumer, P., Huneau, F., 2013. Monitoring of trace metals and pharmaceuticals as
1390 anthropogenic and socio-economic indicators of urban and industrial impact on surface
1391 waters. *Environ. Monit. Assess.* 185, 3581–3601. <https://doi.org/10.1007/s10661-012-2811-x>
1392 Wang, J., Hu, J., Zhang, S., 2010. Studies on the sorption of tetracycline onto clays and marine
1393 sediment from seawater. *J. Colloid Interface Sci.* 349, 578–582.
1394 <https://doi.org/10.1016/j.jcis.2010.04.081>
1395 Weigel, S., Berger, U., Jensen, E., Kallenborn, R., Thoresen, H., Hühnerfuss, H., 2004. Determination
1396 of selected pharmaceuticals and caffeine in sewage and seawater from Tromsø/Norway with
1397 emphasis on ibuprofen and its metabolites. *Chemosphere* 56, 583–592.
1398 <https://doi.org/10.1016/j.chemosphere.2004.04.015>
1399 Xie, H., Chen, J., Chen, Q., Chen, C.-E.L., Du, J., Tan, F., Zhou, C., 2017. Development and evaluation of
1400 diffusive gradients in thin films technique for measuring antibiotics in seawater. *Sci. Total*
1401 *Environ.* 618, 1605–1612. <https://doi.org/10.1016/j.scitotenv.2017.09.330>
1402 Xie, H., Chen, Q., Chen, J., Chen, C.-E.L., Du, J., 2018. Investigation and application of diffusive
1403 gradients in thin-films technique for measuring endocrine disrupting chemicals in seawaters.
1404 *Chemosphere* 200, 351–357. <https://doi.org/10.1016/j.chemosphere.2018.02.096>
1405 Zhang, Hao., Davison, William., 1995. Performance Characteristics of Diffusion Gradients in Thin Films
1406 for the in Situ Measurement of Trace Metals in Aqueous Solution. *Anal. Chem.* 67, 3391–
1407 3400. <https://doi.org/10.1021/ac00115a005>
1408 Zhang, R., Tang, J., Li, J., Cheng, Z., Chaemfa, C., Liu, D., Zheng, Q., Song, M., Luo, C., Zhang, G., 2013.
1409 Occurrence and risks of antibiotics in the coastal aquatic environment of the Yellow Sea,
1410 North China. *Sci. Total Environ.* 450–451, 197–204.
1411 <https://doi.org/10.1016/j.scitotenv.2013.02.024>
1412 Zhang, R., Zhang, G., Zheng, Q., Tang, J., Chen, Y., Xu, W., Zou, Y., Chen, X., 2012. Occurrence and
1413 risks of antibiotics in the Laizhou Bay, China: Impacts of river discharge. *Ecotoxicol. Environ.*
1414 *Saf.* 80, 208–215. <https://doi.org/10.1016/j.ecoenv.2012.03.002>
1415 Zhao, H., Cao, Z., Liu, X., Zhan, Y., Zhang, J., Xiao, X., Yang, Y., Zhou, J., Xu, J., 2017. Seasonal variation,
1416 flux estimation, and source analysis of dissolved emerging organic contaminants in the
1417 Yangtze Estuary, China. *Mar. Pollut. Bull.* 125, 208–215.
1418 <https://doi.org/10.1016/j.marpolbul.2017.08.034>
1419 Zhao, H., Zhou, J.L., Zhang, J., 2015. Tidal impact on the dynamic behavior of dissolved
1420 pharmaceuticals in the Yangtze Estuary, China. *Sci. Total Environ.* 536, 946–954.
1421 <https://doi.org/10.1016/j.scitotenv.2015.06.055>
1422