Pharmaceuticals and their metabolites in the marine environment: Sources, analytical methods and occurrence

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ABSTRACT

The occurrence of pharmaceuticals in the environmental waters is a global concern. There is little research conducted on the monitoring of pharmaceuticals in the marine environment. In this article, the occurrence of pharmaceuticals and their metabolites in the coastal waters as well as associated risks related to their uptake by marine organisms are critically reviewed. The literature showed antibiotics as the most plentiful pharmaceuticals in the marine environment. Other therapeutic classes of pharmaceuticals appeared prominently in the marine environment are non-steroidal anti-inflammatory drugs and β-blockers, while gemfibrozil and carbamazepine were singled-out as the most studied lipid regulator and antiepileptic, respectively. Some pharmaceuticals have been found present in the marine organisms that are regarded as important food sources for humans. We reviewed the negative effects associated with the presence of pharmaceuticals in the marine environment. This article is concluded by deliberating on the possible future studies in this research niche area.

Keywords:

Pharmaceuticals; metabolites; occurrence; analytical methods; marine environment

Abbreviations

ESI - electrospray ionization; GC - gas chromatography; HLB - hydrophilic lipophilic balanced; IPs - identification points; IT - ion trap; LC - liquid chromatography; MDL – method detection limit; MIPs - molecularly imprinted polymers; MS - mass spectroscopy; MS/MS – tandem mass spectrometry; LOQs - limits of quantitation; MRM - multiple reaction monitoring; Nd – no detection; NSAIDs - non-steroidal anti-inflammatory drugs; PEDs - polyethylene devices; POCIS - polar organic chemical integrative samplers; QqQ – triple quadrupole; RSD – relative standard deviation; SPE - solid-phase extraction; SPME - solid-phase microextraction; SRM - selective reaction monitoring; WWTP – wastewater treatment plants

1 Introduction

Pharmaceutical uptake by humans and animals for the treatment of different ailments and promotion of health is increasing worldwide. Both humans and animals excrete pharmaceuticals through urine or faeces in their native forms or after metabolic reactions [1–3]. Metabolic reactions convert the main drugs into metabolites prior to the excretion. The excreted pharmaceuticals and their metabolites are mostly transferred as part of sewage into the sewage treatment facilities. Due to high water solubility and presence of polar functional groups in chemical structures, pharmaceuticals and their metabolites are discharged into surface water as part of wastewater treatment plant (WWTP) effluent [4].

The first report on the occurrence of pharmaceuticals in river water was published in 1970 [5]. Since then, there has been a rigorous research devoted to the monitoring of pharmaceuticals in the aquatic environment. The major focus of the environmental monitoring studies has been directed to the monitoring of pharmaceuticals (main drugs) in WWTPs and river water. The occurrence of pharmaceuticals as the organic contaminants in seawater was only discovered in the early 2000's [6]. Therefore, scientific research on the occurrence of pharmaceuticals in the oceans which are known as the important sink of contaminants is ongoing [7]. Hence, there is now wide availability of research articles reporting the occurrence of pharmaceuticals in the coastal environment with more emphasis on the contamination of seawaters. This resulted in the publication of review articles that are critically evaluating the available scientific data [8–15]. The focus of the published review articles has been directed to specific pharmaceuticals such as the occurrence of diclofenac in the marine environment [10] and the contamination of selected seawater regions such as the Mediterranean Sea [16] and Arctic environments [17]. In Australia, pharmaceuticals were reviewed as part of emerging contaminants in the marine environments of the Great Barrier Reef and Torres Strait [15]. The two general review articles on the occurrence of pharmaceuticals in the marine environment were published in 2016 [9,11], and the latest one in 2019 [8]. One of 2016 review articles focussed mainly on the occurrence of pharmaceuticals and personal care products in the marine environment [9] while the other reviewed the exposure and biological effects of pharmaceuticals on animal species [11]. The scope of the recent

general review included the occurrence of pharmaceuticals in seawater, sediments and marine organisms, while identifying research gaps and providing future opportunities [8]. Białk-Bielińska et al. (2016) presented the improvements and challenges encountered in the analysis of pollutants in water samples which included the marine waters [18]. Other published review articles assessed the health risks for marine organisms associated with the occurrence of pharmaceuticals in seawater and / or ecotoxicological aspects [19,20]. In one case, the review article focussed on the effects of pharmaceuticals and personal care products on marine organisms providing an investigation from the single-species studies to an ecosystem-based approach [21].

The aim of the present study was to critically review the occurrence of pharmaceuticals in the marine environment with the major focus devoted to the sources, analytical methods and recent trends of all the drugs found in seawaters. While one most recent review only focussed on anti-inflammatory drugs reported in the period 2010 to 2020 with main focus on effects in marine bivalves [13], the other review had 17alpha-Ethinylestradiol as the subject of investigation [14]. The classes of pharmaceuticals detected in seawaters thus far are given in this study, and the concentrations of all individual drugs found in marine waters are presented and discussed. The scope of the current study was extended to the occurrence of metabolites of pharmaceuticals in the marine environment. Furthermore, we have summarized the health risks associated with the presence of pharmaceuticals and their metabolites in seawaters and analysed the research gaps with intensions of outlining the future research studies.

2 Sources of pharmaceuticals in the marine environment

Estuaries are the major source of pharmaceuticals in the ocean. Pharmaceuticals are mostly discharged from the WWTPs into the rivers and transported into the estuaries. Other sources of pharmaceuticals in freshwater which include the contribution of agricultural fields where animal waste is used as fertilizer, leachates from the landfill sites are well described in literature [22]. The detection of pharmaceuticals in estuaries has been reported across the different continents of the world [23–31]. In this case, the levels of detected pharmaceuticals in the estuaries vary from one estuary to the other, and they are influenced by many factors. Such factors include variations in weather conditions and communities residing on river banks as well as sewage water leakages into the estuaries via the storm

water systems [24]. Limited access into modern ablution facilities is another factor that contributes significantly to the pollution of rivers mostly in the developing countries. In this case, human wastes are released into the ground where they are likely to be swept into the nearby rivers by water run-off during the rainy days. Therefore, the concentrations of pharmaceuticals in the estuaries are widely distributed in the range of low ng L^{-1} to low µg L^{-1} [23].

Numerous studies have reported the incomplete removal of pharmaceuticals during the sewage treatment processes [2,32–34]. Some WWTPs discharge their influent directly into the sea via the marine outfalls [32,35]. This leads to the detection of pharmaceuticals in ocean waters that are in proximity to the effluent / sewage discharge points [36,37]. In southern California (USA), the highest concentrations found for naproxen, gemfibrozil and atenolol in effluents prior to their disposal in the marine outfalls exceeded 1 µg L^{-1} [36]. Therefore, marine outfalls are considered as the main input source of pharmaceuticals in seawater [38]. Urination while swimming or bathing in the beaches is also natural for humans. This has a potential to release pharmaceuticals from humans directly into the ocean.

3 Analytical methods

3.1 Sampling methods

Grab sampling is the most common approach for collection of environmental samples. However, the concentrations of pharmaceuticals entering the marine environment are largely diluted to trace amounts by the seawater. Due to such dilutions, Ngubane et al. (2019) could only detect one pharmaceutical, naproxen, out of 3 investigated drugs with a mean concentration of 160 ng L^{-1} in a sampling site located in a distance of approximately 6 km from the estuary [39]. To improve the detection frequency for pharmaceuticals in the open oceans, passive sampling devices have been introduced as they are able to pre-concentrate contaminants from the aqueous medium in the receiving phase over the extended periods of time while deployed in the environmental waters [40]. Passive sampling devices are also useful for the determination of mean concentrations of water pollutants over a certain time frame in an integrated space [41]. Full description of these devices which play crucial role in sampling and pre-concentration of analytes from water is available in literature [42–47]. Three

passive sampling devices, polar organic chemical integrative samplers (POCIS), polyethylene devices (PEDs), and solid-phase microextraction (SPME) samplers have been investigated for sampling a variety of chemicals in the coastal waters of San Francisco Bay and the Southern California Bight [48]. In other studies, POCIS is a more common approach [40,41]. The receiving phase in POCIS devices in often the Oasis hydrophilic lipophilic balanced (HLB) sorbent [41,48] which is capable of extracting highly polar and less-polar chemicals from water. Therefore, the analytical procedures that include the use of POCIS devices usually lack selectivity and allows for the analysis of wide variety of chemicals.

In environmental studies where the primary focus is on identification and quantitation of pharmaceuticals in seawaters, the collection and treatment of large volumes (10-50 L) of water has been performed [6,28,49]. In these cases, the prolonged sample percolation time on solid-phase extraction (SPE) was overcome by using high loading flow rates of up to 500 mL min^{-1} [6,28]. To accommodate high breakthrough volumes of seawater samples, high sorbent mass reaching 4 g was utilized [49]. This approach was intended to increase the analyte pre-concentration factors with the view of improving the detection limits of the analytical methods. As a result, the application of gas chromatography equipped with mass spectrometry detector led to low detection limits ranging from 0.1 to 0.7 ng L^{-1} [6].

3.2 Analyte isolation and pre-concentration

Ocean water is largely contaminated from the land-based activities, and contaminants reaching this water body are immensely diluted. Therefore, during the monitoring of pharmaceuticals in the oceans, it is imperative to isolate and pre-concentrate analytes prior to their identification and quantitation on suitable analytical instruments. SPE remains the most useful sample preparation technique for the monitoring of water pollutants due to its ability to extract analytes by sorption on solid material from large volumes of aqueous samples and subsequently performing elution with a small amount of organic solvent thereby resulting in pre-concentration of target compounds. Oasis HLB is the widely used SPE sorbent as it has the ability to extract a wide range of pharmaceuticals. As a result, Oasis HLB sorbent has been used in the SPE of pharmaceuticals belonging to different therapeutic classes from seawater samples [50–54]. Among other reported SPE sorbents, molecularly imprinted polymers (MIPs) provide a different dimension as they are able to extract a single molecule or group of

analytes selectively utilizing their unique features such as functional groups, molecular shape and size [55]. In this way, sample matrix effects are eliminated and the analysis can be performed with affordable analytical equipment such as liquid chromatography with photodiode array detector. This approach was applied by Liang and Wang, achieving a detection limit of 5 ng L^{-1} for chloramphenicol in seawater [56].

The use of disks to perform SPE by utilizing H_2O-Philic divinylbenzene [57,58] as a sorbent has also been reported in literature. In a different perspective, the bag SPE sampler developed elsewhere [59] was used for isolating pharmaceuticals in seawater samples [60]. In this approach, 100 mg polystyrene-divinylbenzene enclosed in a woven polyester fabric was directly immersed in the water sample for a pre-determined time followed by desorption of extracted compounds using the organic solvents [60]. This approach works like a passive sampler and can be very useful for extraction of analytes from large sample volumes. This is followed by the chromatographic analysis.

In view of large dilution of environmental pollutants in the oceans, large sample volumes which are translated to greater pre-concentration factors thus leading to higher sensitivity of analytical methods need to be treated for analysis. However, in SPE this approach results in lengthy analytical sample preparation approach which could only be improved by utilizing high sample loading flow rates into the sorbent. Careful optimizing is recommended in this regard as high sample loading flow rates in SPE are likely to be accompanied by poor uptake of analytes by the sorbent. Also the influence of high salinity in the oceanic waters on SPE is not yet well understood.

3.3 Analytical techniques

Nowadays, focus is on multi-residue analytical techniques that allow for fast simultaneous analysis of basic, neutral and acidic pharmaceuticals belonging to different therapeutic classes. Recent advances in gas chromatography (GC) and liquid chromatography (LC) coupled to mass spectroscopy (MS) have allowed researchers to analyse quite a large number of pharmaceuticals simultaneously over the years [61]. These approaches are versatile, selective and specific. However, GC is only limited to a few non-polar and volatile pharmaceuticals. The majority of pharmaceuticals are polar and lack volatility. Analysis of such pharmaceuticals using GC therefore requires a derivatization step which is

always time-consuming and irreproducible [61]. GC for pharmaceuticals in marine environments has only been used about 2 decades ago [6,62].

The LC especially coupled to tandem MS remains a perfect choice for comprehensive analysis of pharmaceuticals in complex samples. In this regard, it is observed that almost always, the LC-MS/MS mainly the triple quadrupole (QqQ) [36,49,67–72,50–52,54,63–66] and the ion trap (IT) [3,53,57,58,73–78] both equipped with an electrospray ionization (ESI) source is a preferred approach for pharmaceuticals in marine environments while other hybrid techniques such as the quadrupole and its combination with time-of-flight mass spectroscopy [60], Orbitrap/HRMS [79] and hybrid quadrupole-linear ion trap [53,73–78] have also been mentioned. The traditional LC with diode array detection and ultraviolet-visible spectroscopy have appeared in recent literature for analysis of 8 sulfonamides [80], 4 non-steroidal anti-inflammatory drugs (NSAIDs) [39] and chloramphenicol [56]. Their limits of quantitation (LOQs) which were 60 - 160, 25 - 36 and 5 ng L^{-1} respectively are much higher than those reported using LC-MS which are as low as 0.04 ng L^{-1} found during analysis of 56 antibiotics using UHPLC-ESI-QqQ-MS/MS [63]. Notably, the LOQs still vary across different studies regardless of employing similar analytical methods which are mostly based on SPE-LC-MS/MS. This variation is associated with different pre-concentration factors achieved by various authors as a consequence of sample volume percolated on SPE cartridge against the resulting sample size available for chromatographic analysis.

The LC-ESI-MS/MS instrumentation has several advantages in multi-residue analysis of pharmaceuticals in environmental samples. While it has always been advisable to achieve complete separation in chromatographic analysis to avoid signal interference, the MS/MS approach does not require a complete LC separation for selective detection [81]. In this regard, shorter LC columns are used to achieve very fast analysis times. The C18 column preferably packed with sub 2 micron particles remains the column of choice for separation with some studies reporting separation of 56 antibiotics in 14 min using a C18 column of 1.7 μm particle diameter [63]. In the MS/MS systems, fragmentation using ESI is achieved either in positive or negative mode depending on the sensitivity of the pharmaceutical. Generally, the negative mode is preferred for acidic pharmaceuticals while positive

ionization is applied for neutral and basic pharmaceuticals. For example, in one study that analysed 7 pharmaceuticals in the Gran Canaria Island, only the acidic diclofenac gave better fragmentation response in the negative ionization mode [50]. Elsewhere, all the 4 acidic pharmaceuticals (diclofenac, ibuprofen, gemfibrozil and naproxen) were all ionized in the negative mode deprotonating to the $[M-H]^-$ ions [66].

Another advantage of the MS/MS approach is its ability to positively confirm presence of compounds based on the precursor and product ions [81,82]. This is achieved through multiple reaction monitoring (MRM, also called selective reaction monitoring (SRM)) of two transitions between the precursor and the product ions to achieve the four identification points (IPs) as the minimum requirement for positive identification and confirmation criteria defined by the EU Commission Decision 2002/657/EC [83]. The first MRM transition is prone to false positive identification, therefore, the results of the first MRM transition are verified using a second MRM transition leading to correct identification of the analyte. In this regard, most of the studies on pharmaceuticals in marine environments use the two MRM transitions quantitation approach for accurate identification of the targeted pharmaceuticals. Another advantage of the LC-MS/MS which has not yet been utilized in analysis of pharmaceuticals in marine environments is structure elucidation of unknown degradation and transformation products of pharmaceuticals in the environment [84].

3.4 Validation of analytical methods and quality assurance

Prior to applications in environmental monitoring, the efficacy of the optimized analytical methods is often evaluated by spiking the environmental samples with analytes using the environmentally relevant concentrations. The performance of the analytical methods are evaluated based on sensitivity using the detection (LOD) and quantitation (LOQ) limits, accuracy by determining the percent recoveries and precision based on relative standard deviations (RSD) [39]. Investigating field blanks and surrogate recovery checks using deuterated standards are common in some studies [48,59]. In general, the LOD and LOQ are computed as the lowest concentration that give a signal-to-noise ratio (S/N) of 3 and 10, respectively [50]. For accurate measurements, the concentrations of analytes in the environment should fall within the linear dynamic range. Therefore, several studies report the linearity close to the value of

1 that has been achieved in a plot of different concentrations versus the corresponding detector responses [57]. In some cases, matrix effects were examined for quality assurance and quality control [52]. Evaluation of matrix effects by evaluating signal suppression and enhancement is conducted to ensure minimal quantitative bias that may result from the competition of the analyte and co-extracted matrix components [53]. Several studies report that the correct analyte peaks and peak purity were assigned using the retention times as well as characteristic ions [68]. In one case, signal suppression was dominant in a study of 40 compounds with the exception of sulfamethoxazole and sotalol that had signal enhancements [53]. Percent recoveries in the range of 80 to 120% indicate the high accuracy of the analytical method, while satisfactory precision is achieved when RSD values are lower than 20% [57,59]. In some cases, the newly established analytical methods yield lower percent recoveries for certain analytes due to variations in physicochemical properties [60,85]. Elsewhere, the extraction efficiencies for bag-SPE ranged from 10.6 to 64.5% [60], an indication for further improvement.

4 Occurrence of pharmaceuticals in the seawater

In 2016, Fabbri and Franzellitti presented a review article on the occurrence human pharmaceuticals in the marine environment which focused primarily on the exposure and biological effects in animal species [11]. Their review article clearly indicated non-existence of the analytical data in Africa, while there was one scientific study conducted in South America. Currently, there are four articles reporting the occurrence of pharmaceuticals in the African coastal environment. Two of these studies were conducted in Tunisia [51,63] while others are reported in South Africa [35,39]. Africa has always been lagging behind in environmental monitoring of any pollutants. The scientific data on the occurrence of pharmaceuticals in the African aquatic environment only emerged in the last decade [86,87], with the recent review article observing a steady increase in the number of published articles in the last 3 years [88]. Therefore, more investigations in the African coastal waters are expected to emerge soon.

4.1 Antibiotics

Antibiotics found in the marine environment are listed alongside their environmental concentrations in Table 1. Among the detected antibiotics; trimethoprim, erythromycin,

253 sulfamethoxazole and sulfadiazine were the most abundant having been detected in not less than 10
254 study sites each. Trimethoprim alongside quinolones and sulphonamides were reported as the most
255 investigated and detected antibiotics in the European aquatic environment [89]. An African viewpoint
256 reported sulfamethoxazole, ciprofloxacin and ofloxacin as the prominent antibiotics in water resources,
257 while trimethoprim was singled out as having the highest concentration of 230 ng L^{-1} in a river water
258 from Egypt [88]. Therefore, there are some similarities concerning the observations made during
259 antibiotics studies performed inland and those done in the coastal waters.

260 High antibiotic quantities observed in the Tunisian coast (Table 1) is in accordance to the
261 observation reported in a review article [87] where the authors found the pharmaceutical levels in
262 African waters to be approximately 20 000 times higher than those found in Europe. A suitable example
263 is that of trimethoprim with the highest concentration of 3500 ng L^{-1} in Tunisia [63], while the maximum
264 amount found in Europe was 10.6 ng L^{-1} recorded in the Gulf of Cadiz (Spain) [54]. Some other
265 antibiotics with the highest concentrations in the Tunisian coastline were norfloxacin, spiramycin,
266 enrofloxacin and nalidixic acid. The highest observed concentration for norfloxacin in Tunisia was
267 20700 ng L^{-1} [63], while 3551 and 6800 ng L^{-1} were the closest levels found in Gran Carania Island
268 (Spain) [50] and Bohai Bay (China) [90], respectively. In three observed cases for spiramycin, its
269 concentrations reached 2.1, 7.24 and 66400 ng L^{-1} in Spain [54], Korea [70] and Tunisia [63],
270 respectively. Nalidixic acid was found in two coasts, the Mediterranean Sea of Tunisia with a highest
271 concentration of 16700 ng L^{-1} [63] and the Yellow Sea of China reaching 28.9 ng L^{-1} [67]. Therefore,
272 the highest concentrations of antibiotics were found in a Tunisian coast. But, China [67,68,90–93] and
273 European countries [40,50,52,54,57,71,77,94] were more active in monitoring antibiotics in the marine
274 environment with more than 5 scientific studies available in the literature in each scenario. Variations
275 of concentration levels of antibiotics and other pharmaceuticals in general in the Mediterranean Sea in
276 an interesting situation suggesting the influx of pharmaceuticals from different sources with notably
277 differences in consumption patterns. Variations in concentrations of antibiotics and other
278 pharmaceuticals (presented in Tables 2-8) could also be linked to the dilutions in the marine
279 environment (taking into account the different sampling locations) and comparing the data published in

different years due to the likelihood that the antibiotic or other pharmaceuticals consumption rates varies in different years, thus resulting in deviations in environmental pollution loads.

282 **Table 1**

283 Concentrations (ng L^{-1}) of antibiotics found in seawater samples

Antibiotic	Study site	Sampling year	Concentration	MDL (ng L^{-1})	Reference
Amoxicillin	Eastern Mediterranean Sea, Greece	2013	<128	5.0	[52]
Ampicillin	Southwestern Taiwan	2010	Nd – 88.7	2	[64]
	Gulf of Cadiz, South Western Spain	2015	Nd – 2.0	0.0001	[54]
Novobiocin	Gulf of Cadiz, South Western Spain	2015	Nd – 0.8	0.0001	[54]
Clarithromycin	Eastern Mediterranean Sea, Greece	2013	<1 – 1.5	1.0	[52]
	Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	16	7.5*	[71]
	Baltic Sea, Germany	2009-2011	14	7.5*	[71]
	Gulf of Cadiz, South Western Spain	2015	0.2 – 9.4	0.0001	[54]
	Mediterranean coastal lagoon, Spain	2010-2011	9.6	0.6	[77]
	Pacific Ocean, USA	2009-2011	130	7.5*	[71]
	Laizhou Bay, China	2009	Nd – 0.82	0.25*	[7]
	Bohai Sea and Yellow Sea, China	2010	Nd – 0.51	0.10*	[91]
	Yellow Sea, North China	2010	2.6	0.25*	[68]
Trimethoprim	Eastern Mediterranean Sea, Greece	2013	<0.4 – 3	0.4	[52]

	Gulf of Cadiz, South Western Spain	2015	Nd – 10.6	0.0001	[54]
	Mediterranean coastal lagoon, Spain	2010-2011	1.5	0.1	[77]
	Southern Baltic Sea, Polish coastal zone	2012	Nd – 2.9	0.2	[57]
	Mediterranean Sea, Tunisia	2012-2013	Nd – 3500	0.01	[63]
	Southern California Bight, USA	2006-2007	Nd – 2.1	2.5 RL	[36]
	California coast, USA	2009-2010	Nd - 2	-	[48]
	Baltic Sea, Poland	2011-2012	Nd – 3.4	0.2	[58]
	Mediterranean Sea, Southeast of Spain	2005-2006	0.03	30	[40]
	Antarctica	2016-2017	<0.1	1*	[95]
	Bohai Bay, China	2008	Nd - 120	<20*	[90]
	Bohai Sea and Yellow Sea, China	2010	<LOQ – 16.6	0.10*	[91]
	Yellow Sea, North China	2010	14.1	0.24*	[68]
	Laizhou Bay, China	2009	1.3 - 330	0.24*	[7]
	Hong Kong coastal waters	2006	Nd – 21.8	<13	[69]
	Korean seawater	2012	Nd – 5.30	0.069	[70]
Norfloxacin	Gran Canaria Island, Spain	2011-2012	Nd – 3551	2.5	[50]
	Gulf of Cadiz, South Western Spain	2015	Nd – 207.5	0.00004	[54]
	Mediterranean sea, Tunisia	2012-2013	Nd - 20700	0.1	[63]
	Yellow Sea coast, China	2010	Nd - 109	0.002	[67]

	Laizhou Bay, China	2009	7.5 -103	4.2*	[7]
	Bohai Bay, China	2008	Nd - 6800	<20*	[90]
	Victoria Harbour, Hong Kong	2004-2005	20.1	3.2	[96]
	Hong Kong coastal waters	2006	Nd - 8	<13	[69]
	Korean seawater	2012	Nd – 0.512	0.205	[70]
Ciprofloxacin	Gran Canaria Island, Spain	2011-2012	Nd – 303	1.0	[50]
	Gulf of Cadiz, South Western Spain	2015	Nd – 211.7	0.00006	[54]
	Yellow Sea coast, China	2010	Nd - 26	0.00113	[67]
	Laizhou Bay, China	2009	Nd - 66	3.3*	[7]
	Bohai Bay, China	2008	Nd - 390	<20*	[90]
	Korean seawater	2012	Nd – 1.25	0.082	[70]
	Antarctica	2016-2017	4-218	50*	[95]
Clindamycin	Antarctica	2016-2017	<0.1	1*	[95]
	Gulf of Cadiz, South Western Spain	2015	Nd – 4.2	0.0001	[54]
Enoxacin	Laizhou Bay, China	2009	Nd - 209	3.8*	[7]
Ofloxacin	Bohai Bay, China	2008	Nd - 5100	<20*	[90]
	Laizhou Bay, China	2009	Nd – 6.5	3.5*	[7]
	Victoria Harbour, Hong Kong	2004-2005	16.4	2.6	[96]
	Korean seawater	2012	Nd – 12.4	0.048	[70]

	Gulf of Cadiz, South Western Spain	2015	Nd – 34.4	0.00001	[54]
Erythromycin	Mediterranean Sea, Southeast of Spain	2005-2006	0.01 – 0.03	10	[40]
	Gulf of Cadiz, South Western Spain	2015	Nd – 2.3	0.00004	[54]
	Mediterranean coastal lagoon, Spain	2010-2011	78.4	0.3	[77]
	Northern Adriatic Sea, Italy	2009-2011	5.8	7.5*	[71]
	San Francisco Bay, USA	2009-2011	217	7.5*	[71]
	Pacific Ocean, USA	2009-2011	86	7.5*	[71]
	Mediterranean Sea, Tunisia	2012-2013	Nd - 3900	0.1	[63]
	Bohai Bay, China	2008	Nd - 150	<20*	[90]
	Bohai Sea and Yellow Sea, China	2010	0.13 – 6.7	0.10*	[91]
	Yellow Sea, North China	2010	25.2	0.23	[68]
	Laizhou Bay, China	2009	0.9 – 8.5	0.23	[7]
	Hong Kong coastal waters	2006	16 - 486	<13	[69]
	Victoria Harbour, Hong Kong	2004-2005	5.2	2.0	[96]
	Korean seawater	2012	Nd – 0.196	0.259	[70]
	Southwestern Taiwan	2010	Nd – 26.6	2	[64]
Spiramycin	Gulf of Cadiz, South Western Spain	2015	Nd – 2.1	0.00014	[54]
	Mediterranean Sea, Tunisia	2012-2013	Nd - 66400	0.01	[63]

	Korean seawater	2012	Nd – 7.24	0.261	[70]
Neospiramycin	Mediterranean Sea, Tunisia	2012-2013	Nd - 4100	0.01	[63]
Josamycin	Mediterranean Sea, Tunisia	2012-2013	Nd - 1500	0.01	[63]
Roxithromycin	Laizhou Bay, China	2009	<LOQ – 1.5	0.62*	[7]
	Bohai Sea and Yellow Sea, China	2010	Nd – 0.26	0.09*	[91]
	Yellow Sea, North China	2010	6.9	0.62*	[68]
	Victoria Harbour, Hong Kong	2004-2005	30.6	2.0	[96]
	Gulf of Cadiz, South Western Spain	2015	Nd – 1.3	0.00001	[54]
	Baltic Sea, Germany	2009-2011	16	9.5*	[71]
	Pacific Ocean, USA	2009-2011	141	9.5*	[71]
Azithromycin	Laizhou Bay, China	2009	Nd – 1.2	0.26*	[7]
	Bohai Sea and Yellow Sea, China	2010	Nd – 0.39	0.10*	[91]
	Yellow Sea, North China	2010	2.5	0.26*	[68]
	Gulf of Cadiz, South Western Spain	2015	Nd – 17.8	0.00001	[54]
	Mediterranean coastal lagoon, Spain	2010-2011	163.8	3.3	[77]
Lomefloxacin	Yellow Sea coast, China	2010	Nd – 1.2	0.00046	[67]
Danofloxacin	Yellow Sea coast, China	2010	Nd - 30	0.00048	[67]
	Gulf of Cadiz, South Western Spain	2015	Nd – 157.5	0.00005	[54]
Enrofloxacin	Yellow Sea coast, China	2010	0.78 – 5.1	0.00058	[67]

	Laizhou Bay, China	2009	Nd – 7.6	4.4	[7]
	Gulf of Cadiz, South Western Spain	2015	Nd - 122	0.00001	[54]
	Southern Baltic Sea, Polish coastal zone	2012	Nd - <LOQ	3.3	[57]
	Mediterranean Sea, Tunisia	2012-2013	Nd - 40200	0.01	[63]
Marbofloxacin	Yellow Sea coast, China	2010	Nd - 22	0.00068	[67]
Fleroxacin	Yellow Sea coast, China	2010	Nd – 1.4	0.00047	[67]
Orbifloxacin	Yellow Sea coast, China	2010	Nd – 2.7	0.00045	[67]
Difloxacin	Yellow Sea coast, China	2010	Nd – 20.7	0.00048	[67]
Sarafloxacin	Yellow Sea coast, China	2010	Nd – 14.6	0.00053	[67]
	Mediterranean Sea, Tunisia	2012-2013	Nd - 5300	0.1	[63]
Sparfloxacin	Yellow Sea coast, China	2010	Nd – 0.79	0.00052	[67]
	Gulf of Cadiz, South Western Spain	2015	Nd – 14.9	0.00001	[54]
Lincomycin	Korean seawater	2012	Nd - 438	0.203	[70]
	Gulf of Cadiz, South Western Spain	2015	Nd – 6.1	0.00001	[54]
Cefalexin	Southwestern Taiwan	2010	Nd – 9.19	1.5	[64]
	Hong Kong coastal waters	2006	Nd - 182	<13	[69]
Cefaclor	Gulf of Cadiz, South Western Spain	2015	Nd – 9.4	0.00001	[54]
Cefdinir	Gulf of Cadiz, South Western Spain	2015	Nd – 15.8	0.0001	[54]

Cefquinome	Gulf of Cadiz, South Western Spain	2015	Nd – 44.9	0.00002	[54]
Ceftiofur	Gulf of Cadiz, South Western Spain	2015	Nd – 1.7	0.00002	[54]
Sulfadiazine	Eastern Mediterranean Sea, Greece	2013	<0.1 – 2	0.1	[52]
	Gulf of Cadiz, South Western Spain	2015	Nd – 1.8	0.00001	[54]
	Mediterranean sea, Tunisia	2012-2013	Nd - 29100	0.01	[63]
	Mahdia coastal, Tunisia	2017-2018	6 – 11	<1	[51]
	Dalian coast, China	2011	Nd – 2	0.47	[92]
	Yellow Sea, North China	2010	0.24	0.24*	[68]
	Yellow Sea coast, China	2010	Nd – 3.0	0.00459	[67]
	Bohai Bay, China	2008	Nd - 41	<20*	[90]
	Bohai Sea and Yellow Sea, China	2010	Nd – 0.36	0.10*	[91]
	Laizhou Bay, China	2009	Nd – 0.43	0.24*	[7]
Sulfamerazine	Mediterranean Sea, Tunisia	2012-2013	Nd - 4500	0.1	[63]
	Southern Baltic Sea, Polish coastal zone	2012	Nd - <LOQ	1.7	[57]
Sulfamoxole	Mediterranean Sea, Tunisia	2012-2013	Nd - 800	0.1	[63]
Sulfamethoxazole	Eastern Mediterranean Sea, Greece	2013	<0.1 – 6	0.1	[52]
	Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	11	2.6*	[71]
	Northern Adriatic Sea, Italy	2009-2011	4.1	2.6*	[71]

Mediterranean Sea, Tunisia	2012-2013	Nd - 2400	0.1	[63]
Gulf of Cadiz, South Western Spain	2015	Nd - 99	0.00001	[54]
Mediterranean coastal lagoon, Spain	2010-2011	94	0.3	[77]
Baltic Sea, Germany	2009-2011	42	2.6*	[71]
Southern Baltic Sea, Polish coastal zone	2012	Nd – 20.0	1.7	[57]
Baltic Sea, Poland	2011-2012	Nd – 10.8	3.3	[58]
Mahdia coastal, Tunisia	2017-2018	2 – 6	<1	[51]
Red Sea, Saudi Arabian coastal waters	2016	63	0.8	[72]
Dalian coast, China	2011	Nd – 2.2	0.83	[92]
Yellow Sea coast, China	2010	Nd - 212	0.0362	[67]
Bohai Bay, China	2008	Nd - 140	<20*	[90]
Bohai Sea and Yellow Sea, China	2010	<LOQ – 8.3	0.10	[91]
Yellow Sea, North China	2010	50.4	0.24*	[68]
Laizhou Bay, China	2009	1.5 - 82	0.24*	[7]
Korean seawater	2012	Nd – 2.20	0.469	[70]
San Francisco Bay, USA	2009-2011	61	2.6*	[71]
Pacific Ocean, USA	2009-2011	6.4	2.6*	[71]
Southern California Bight, USA	2006-2007	Nd – 3.4	2.5 RL	[36]
German Baltic Sea	2015	1.5	0.5	[94]

Sulfathiazole	Mahdia coastal, Tunisia	2017-2018	Nd – 3	<1	[51]
	Bohai Sea and Yellow Sea, China	2010	Nd – 0.17	0.10*	[91]
	Dalian coast, China	2011	Nd – 1.2	0.89	[92]
	Korean seawater	2012	7.01 – 18.6	0.125	[70]
Sulfaphenazole	Mediterranean Sea, Tunisia	2012-2013	Nd - 600	0.01	[63]
Sulfamethizole	Mahdia coastal, Tunisia	2017-2018	4 – 11	<1	[51]
	Mediterranean Sea, Tunisia	2012-2013	Nd - 2800	0.1	[63]
	Dalian coast, China	2011	Nd – 1.3	0.92	[92]
	Gulf of Cadiz, South Western Spain	2015	Nd – 67.1	0.00002	[54]
Metronidazole	Mediterranean Sea, southeast of Spain	2005-2006	13.4	8	[40]
	Gulf of Cadiz, South Western Spain	2015	Nd – 2.3	0.00003	[54]
Nitrofurantoin	Gulf of Cadiz, South Western Spain	2015	Nd – 21.7	0.0015	[54]
Ornidazole	Gulf of Cadiz, South Western Spain	2015	Nd – 1.9	0.00001	[54]
Sulfamethazine	Mahdia coastal, Tunisia	2017-2018	Nd – 3	<1	[51]
	Dalian coast, China	2011	Nd – 2.8	0.98	[92]
	Yellow Sea coast, China	2010	Nd - 37	0.00313	[67]
	Bohai Bay, China	2008	Nd - 130	<20*	[90]
	Laizhou Bay, China	2009	Nd – 1.5	0.24*	[7]
	Gulf of Cadiz, South Western Spain	2015	Nd – 9.1	0.00002	[54]

	Southern Baltic Sea, Polish coastal zone	2012	Nd - <LOQ	1.7	[57]
Sulfadimidine	Bohai Sea and Yellow Sea, China	2010	Nd – 0.16	0.10*	[91]
	Yellow Sea, North China	2010	0.35	0.24*	[68]
	Mediterranean Sea, Tunisia	2012-2013	Nd - 1800	0.1	[63]
Sulfaquinoxaline	Mediterranean Sea, Tunisia	2012-2013	Nd - 1900	0.01	[63]
Sulfaguanidine	Mediterranean Sea, Tunisia	2012-2013	Nd - 200	0.01	[63]
Sulfamethoxypyridazine	Mahdia coastal, Tunisia	2017-2018	Nd – 5	<1	[51]
	Yellow Sea coast, China	2010	0.35 – 15.2	0.0334	[67]
Sulfacetamide	Dalian coast, China	2011	Nd – 1.5	1.02	[92]
	Yellow Sea coast, China	2010	Nd – 4.3	0.00320	[67]
	Bohai Sea and Yellow Sea, China	2010	Nd – 0.12	0.10*	[91]
Sulfameter	Dalian coast, China	2011	Nd – 1.9	1.05	[92]
	Yellow Sea coast, China	2010	Nd – 1.2	0.00290	[67]
Sulfamonomethoxine	Dalian coast, China	2011	Nd – 2.3	0.66	[92]
	Yellow Sea coast, China	2010	Nd – 4.6	0.00343	[67]
Sulfadimethoxine	Dalian coast, China	2011	Nd – 1.9	0.51	[92]
	Yellow Sea coast, China	2010	Nd – 1.9	0.00338	[67]
	Gulf of Cadiz, South Western Spain	2015	Nd – 0.9	0.00001	[54]
	Southern Baltic Sea, Polish coastal zone	2012	Nd – 1.0	0.2	[57]

	Baltic Sea, Poland	2011-2012	Nd – 0.8	1.7	[58]
Sulfapyridine	Mediterranean Sea, Tunisia	2012-2013	Nd - 400	0.1	[63]
	Southern Baltic Sea, Polish coastal zone	2012	Nd – 33.2	1.7	[57]
Chloramphenicol	Dalian coast, China	2011	Nd – 1.4	0.04	[92]
	Gulf of Cadiz, South Western Spain	2015	Nd – 8.1	0.00001	[54]
Timulin	Gulf of Cadiz, South Western Spain	2015	Nd – 0.8	0.00001	[54]
Florophenicol	Dalian coast, China	2011	Nd – 2.3	0.07	[92]
Oxytetracycline	Dalian coast, China	2011	1.1 – 6.3	1.02	[92]
	Yellow Sea coast, China	2010	Nd – 13.0	0.00797	[67]
	Bohai Bay, China	2008	Nd - 270	<20*	[90]
	Gulf of Cadiz, South Western Spain	2015	Nd – 25.1	0.00004	[54]
Doxycycline	Dalian coast, China	2011	Nd – 1.6	0.29	[92]
	Yellow Sea coast, China	2010	Nd – 3.2	0.00064	[67]
	Gulf of Cadiz, South Western Spain	2015	Nd – 10.3	0.0002	[54]
Tetracycline	Dalian coast, China	2011	Nd – 3.8	0.63	[92]
	Yellow Sea coast, China	2010	Nd – 5.3	0.00145	[67]
	Bohai Bay, China	2008	Nd - 30	<20*	[90]
	Hong Kong coastal waters	2006	Nd - 122	<13	[69]
	Gulf of Cadiz, South Western Spain	2015	Nd – 63.3	0.001	[54]

Chlortetracycline	Dalian coast, China	2011	1.0 – 3.0	0.43	[92]
	Yellow Sea coast, China	2010	Nd – 2.7	0.00076	[67]
	Gulf of Cadiz, South Western Spain	2015	Nd - 22	0.00002	[54]
Sulfisoxazole	Yellow Sea coast, China	2010	Nd – 16.5	0.00340	[67]
	Mediterranean Sea, Tunisia	2012-2013	100 - 700	0.1	[63]
Sulfachloropyridazine	Yellow Sea coast, China	2010	Nd – 5.9	0.00339	[67]
Oxolinic acid	Yellow Sea coast, China	2010	29-105	0.00187	[67]
Pyrrole acid	Yellow Sea coast, China	2010	0.95 – 17.5	0.00046	[67]
Nalidixic acid	Yellow Sea coast, China	2010	Nd – 28.9	0.00227	[67]
	Mediterranean Sea, Tunisia	2012-2013	Nd - 16700	0.01	[63]
Pefloxacix	Yellow Sea coast, China	2010	Nd – 14.6	0.00099	[67]
Flumequine	Yellow Sea coast, China	2010	Nd – 7.0	0.00105	[67]
	Mediterranean Sea, southeast of Spain	2005-2006	0.13	30	[40]
	Gulf of Cadiz, South Western Spain	2015	Nd – 3.6	0.00001	[54]
Dapsone	Mediterranean Sea, Tunisia	2012-2013	Nd - 2800	0.1	[63]

MDL: method detection limit. Nd: no detection. <LOQ: the compound was found with a concentration that is below the quantitation level. The single concentrations given represent the mean or maximum detected values. In such cases, the concentration ranges were not available. RL: reporting limit (defined as three to five times the method detection limit). * LOQ. The same applies to all Tables.

4.2 Non-steroidal anti-inflammatory drugs and analgesics

Pharmaceuticals belonging to NSAIDs and analgesics are commonly detected in environmental samples. NSAIDs and analgesics found in the marine environment are summarized in Table 2. Based on Table 2, acetaminophen is regarded as the most abundant analgesic in various seawater samples having been quantified in 14 different study sites. Its highest concentration was 2893 ng L^{-1} found in investigations conducted in Aegean Sea & Dardanelles (Greece and Turkey) [71]. In the case of NSAIDs, diclofenac and ibuprofen appeared prominently with the highest concentrations of 14020 ng L^{-1} and 2094 ng L^{-1} found in Red Sea (Saudi Arabian coastal waters) [72] and Santos Bay (São Paulo, Brazil) [73], respectively. High amounts of diclofenac in seawater and its frequent detection could be due to the poor removal during the sewage treatment processes. The observations of negative removal efficiencies in WWTPs for diclofenac have been linked with the discharge of supplementary diclofenac molecules by de-conjugation of glucuronidated or sulfated diclofenac and/or its desorption from solid particles [33,97,98]. Detection of phenylbutazone, propyphenazone, indomethacin, tramadol, nimesulide, oxycodone, acetylsalicylic acid and fenoprofen in single study sites demands further investigations in order to fully understand the spread of these drugs in the marine environment.

The concentrations found for NSAIDs and analgesics in the marine environment for the developing countries (South Africa and Brazil) were generally comparable with those reported in the developed countries. For example, the naproxen concentrations in South Africa (Durban coast) and Portuguese seawater reached 160 ng L^{-1} [39] and 178 ng L^{-1} [65], respectively. Highest concentrations for ibuprofen in the seawaters from Brazil and Spain were 2094 ng L^{-1} [73] and 1219 ng L^{-1} [54], respectively. The exceptions could be linked to episodic events such as spillages and direct disposal of poorly treated WWTP effluent into the oceans (marine outfalls). These have resulted in higher concentrations reaching 310 and 14020 ng L^{-1} for phenazone in the Gulf of Cadiz (Spain) [54] and diclofenac in the Red Sea (Saudi Arabia) [72], respectively.

311 **Table 2**

312 Maximum concentrations (ng L^{-1}) of NSAIDs and analgesics found in seawater samples.

Pharmaceutical	Study site	Sampling year	Concentration	MDL (ng L^{-1})	Reference
Mefenamic acid	Mahdia coastal, Tunisia	2017-2018	Nd – 0.6	<1	[51]
	Eastern Mediterranean Sea, Greece	2013	<0.2 – 11	0.2	[52]
	Gulf of Cadiz, South Western Spain	2015	Nd – 4.5	0.00001	[54]
Phenylbutazone	Mahdia coastal, Tunisia	2017-2018	Nd – 2	<1	[51]
Phenazone	Gulf of Cadiz, South Western Spain	2015	Nd – 309.8	0.0008	[54]
	Baltic Sea, Germany	2009-2011	5.9	2.0	[71]
	Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	2	2.0	[71]
Propyphenazone	North Seawater, Germany	1998	0.6	<0.7	[6]
Indomethacin	Gulf of Cadiz, South Western Spain	2015	Nd – 4.5	0.0006	[54]
Tramadol	Eastern Mediterranean Sea, Greece	2013	<0.1 – 1	0.03	[52]
Nimesulide	Portuguese seawaters	2013	Nd – 7.3	0.06	[65]
Codeine	Southwestern Taiwan	2010	Nd – 63.6	2.25	[64]
	Mediterranean coastal lagoon, Spain	2010-2011	1.8	0.3	[77]
Oxycodone	Mediterranean coastal lagoon, Spain	2010-2011	6.8	0.4	[77]

Acetylsalicylic acid	Portuguese seawaters	2013	Nd – 534	0.10	[65]
Acetaminophen	Gran Canaria Island, Spain	2011-2012	Nd – 297	0.6	[50]
	Gulf of Cadiz, South Western Spain	2015	Nd – 41.5	0.0005	[54]
	Baltic Sea, Germany	2009-2011	48	3.7*	[71]
	Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	2893	3.7*	[71]
	Eastern Mediterranean Sea, Greece	2009-2011	<41	3.7*	[52]
	Mediterranean Sea, Israel	2009-2011	12	3.7*	[71]
	Victoria, BC, Canada seawater	2009-2011	44.7	3.7*	[37]
	San Francisco Bay, USA	2009-2011	85	3.7*	[71]
	Southern California Bight, USA	2006-2007	Nd – 11	0.5 RL	[36]
	Portuguese seawaters	2013	51-584	0.3	[65]
	Southwestern Taiwan	2015	2.6 – 16.7	0.0005	[64]
	Korean seawater	2012	Nd – 48	0.276	[70]
	Red Sea, Saudi Arabian coastal waters	2016	2363	4.8	[72]
	Santos Bay, Brazil	2014	<LOQ – 34.6	1.4	[73]
Ketoprofen	Gran Canaria Island, Spain	2011-2012	Nd – 106	0.1	[50]
	Gulf of Cadiz, South Western Spain	2015	Nd – 2.6	0.0001	[54]
	Southern Baltic Sea, Polish coastal zone	2012	Nd – 72.7	0.2	[57]

	Mahdia coastal, Tunisia	2017-2018	Nd – 76	<1	[51]
	Portuguese seawaters	2013	10 - 90	0.30	[65]
	Southwestern Taiwan	2010	Nd – 23.3	3.5	[64]
	Northern Taiwan seawater	2009	<1.7 – 6.59	-	[32]
Diclofenac	Gran Canaria Island, Spain	2011-2012	Nd – 344	1.4	[50]
	Gulf of Cadiz, South Western Spain	2015	Nd – 31.9	0.0001	[54]
	Baltic Sea, Germany	2009-2011	9.2	2.0*	[71]
	Mahdia coastal, Tunisia	2017-2018	Nd – 23	<1	[51]
	Eastern Mediterranean Sea, Greece	2013	<1.4 – 16	1.4	[52]
	Mediterranean Sea , Israel	2009-2011	6.1	2.0*	[71]
	Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	9.7	2.0*	[71]
	Southern California Bight, USA	2006-2007	Nd – 0.6	0.25 RL	[36]
	Portuguese seawaters	2013	Nd - 241	0.02	[65]
	Santos Bay, Brazil	2014	<LOQ – 19.4	1.0	[73]
	Red Sea, Saudi Arabian coastal waters	2016	14020	1.60	[72]
	Singapore seawater	2011	<2 – 12	1.5	[53]
	Marina Bay, Singapore	2010	4 - 38	0.93	[66]
	Northern Taiwan seawater	2009	<2.5 – 53.6	-	[32]

Naproxen	Eastern Mediterranean Sea, Greece	2013	<0.01 – 0.8	0.01	[52]
	Gulf of Cadiz, South Western Spain	2015	Nd – 95.8	0.0003	[54]
	Portuguese seawaters	2013	Nd - 178	0.02	[65]
	Singapore seawater	2011	<0.9 – 7	0.9	[53]
	Marina Bay, Singapore	2010	13 - 30	0.95	[66]
	Durban coast, South Africa	2018	<LOD – 160	7.6	[39]
	Southern California Bight, USA	2006-2007	Nd – 26	5 RL	[36]
Fenoprofen	Gulf of Cadiz, South Western Spain	2015	Nd – 7.5	0.0001	[54]
Ibuprofen	Singapore seawater	2011	<2 – 9	2.2	[53]
	Marina Bay, Singapore	2010	41 - 121	1.0	[66]
	Red Sea, Saudi Arabian coastal waters	2016	508	26.7	[72]
	Santos Bay, Brazil	2014	326 - 2094	35	[73]
	Durban coast, South Africa	2018	<LOD – 166	11	[39]
	San Francisco Bay, USA	2009-2011	12	3.6*	[71]
	Southern California Bight, USA	2006-2007	Nd – 30	5 RL	[36]
	Portuguese seawaters	2013	Nd - 222	0.08	[65]
	Gulf of Cadiz, South Western Spain	2015	Nd – 1219.7	0.001	[54]
	Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	35	3.6*	[71]

	Baltic Sea, Germany	2009-2011	109	3.6*	[71]
	Seawater from Tromsø/Norway	2002	Nd – 0.7	-	[62]
	Mediterranean Sea, Israel	2009-2011	7.1	3.6*	[71]
	Southwestern Taiwan	2010	Nd – 12.1	2.5	[64]
	Northern Taiwan seawater	2009	<2.5 – 57.1	-	[32]

313

4.3 Beta-blockers

Seven pharmaceuticals belonging to the therapeutic class of β-blockers have been found present in the coastal environment, with atenolol and metoprolol being identified as the most prominent drugs (Table 3). While pindolol occurred in one study conducted in South Western Spain with a highest concentration of 0.7 ng L^{-1} [54]. A highest concentration of 194 ng L^{-1} was recorded for atenolol in a study that investigated β-blockers in Aegean Sea and Dardanelles of Greece and Turkey [71]. Variations of atenolol concentrations from 0.4 to 139 ng L^{-1} were observed in the Gulf of Cadiz (Spain) [54], signifying a wide distribution of the environmental levels. Thus, the atenolol levels did not exceed the quantitation limits in Brazil [73], while the reported average concentrations in other studies were 13 ng L^{-1} in Baltic Sea (Germany) and 57 ng L^{-1} in San Francisco Bay (USA) [71]. The maximum values of 11 ng L^{-1} in Southern California Bight (USA) [36] and 86 ng L^{-1} in Korea [70] were reported. Wide variations for the environmental concentrations of metoprolol were also observed. Its highest concentration was 158 ng L^{-1} in Baltic Sea (Germany) [71], while in some studies the reported amount did not exceed 10 ng L^{-1} [54,71,77]. Comparable levels were only found for timodol and nadolol.

328 **Table 3**

329 Maximum concentrations (ng L^{-1}) of β-blockers found in seawater samples.

β-blocker	Study site	Sampling year	Concentration	MDL (ng L^{-1})	Reference
Timolol	Mahdia coastal, Tunisia	2017-2018	Nd – 0.3	<1	[51]
	Gulf of Cadiz, South Western Spain	2015	Nd – 1.1	0.00001	[54]
Nadolol	Mahdia coastal, Tunisia	2017-2018	Nd – 0.8	<1	[51]
	Gulf of Cadiz, South Western Spain	2015	Nd – 1.6	0.00001	[54]
Atenolol	Southern California Bight, USA	2006-2007	Nd – 11	2.5 RL	[36]
	Korean seawater	2012	Nd – 85.7	0.214	[70]
	Gulf of Cadiz, South Western Spain	2015	0.4 – 138.9	0.00001	[54]
	Baltic Sea, Germany	2009-2011	13	3.5*	[71]
	Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	194	3.5*	[71]
	San Francisco Bay, USA	2009-2011	57	3.5*	[71]
	Santos Bay, Brazil	2014	Nd - <LOQ	6.9	[73]
Propanolol	Korean seawater	2012	Nd – 11.9	0.106	[70]
	Mediterranean coastal lagoon, Spain	2010-2011	0.5	0.1	[77]
	Gulf of Cadiz, South Western Spain	2015	Nd – 5.9	0.00002	[54]

Metoprolol	Mediterranean coastal lagoon, Spain	2010-2011	0.73	0.02	[77]
	Gulf of Cadiz, South Western Spain	2015	Nd – 5.1	0.00007	[54]
	Baltic Sea, Germany	2009-2011	158	4.1*	[71]
	Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	6	4.1*	[71]
	San Francisco Bay, USA	2009-2011	32	4.1*	[71]
	Mediterranean Sea, Israel	2009-2011	6.7	4.1*	[71]
Sotalol	Mediterranean coastal lagoon, Spain	2010-2011	0.8	0.1	[77]
	Baltic Sea, Germany	2009-2011	65	4.8*	[71]
	Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	67	4.8*	[71]
	San Francisco Bay, USA	2009-2011	12	4.8*	[71]
Pindolol	Gulf of Cadiz, South Western Spain	2015	Nd – 0.7	0.00003	[54]

330

4.4 Anti-epileptics

Table 4 shows carbamazepine as the only anti-epileptic drug detected in the coastal environment. Carbamazepine is the most studied and reported antiepileptic in the aquatic environment [99,100]. This could be in accordance to epilepsy being recognised as the second most common disease of the central nervous system after a stroke [101]. Therefore, the treatment of epilepsy through the human consumption of carbamazepine is imperative. Carbamazepine highest concentration of 157 ng L^{-1} was reported in the Baltic Sea of Germany [71]. Besides this maximum level, trace amounts of carbamazepine not exceeding 110 ng L^{-1} were found in other seawater samples. This could be influenced by its poor removal efficiencies observed in most WWTPs. One review article noted the removal efficiency of carbamazepine in most WWTPs to be less than 20% [102]. Also, carbamazepine undergo metabolic reactions on humans with a possibility of forming thirty-three metabolites, two of them (10,11-dihydro-10-11-dihydroxycarbamazepine and 10,11-dihydro-10-11-epoxycarbamazepine) being the most excreted and detected in the aquatic environment [103].

344 **Table 4**

345 Maximum concentrations (ng L^{-1}) of anti-epileptics found in seawater samples.

Anti-epileptic	Study site	Sampling year	Concentration	MDL (ng L^{-1})	Reference
Carbamazepine	Eastern Mediterranean Sea, Greece	2013	<1.4	0.05	[52]
	French coast on the Mediterranean Sea	2012-2013	0.05 – 0.71	-	[79]
	Mediterranean coastal lagoon, Spain	2010-2011	4.9	1.1	[77]
	Mediterranean Sea, Israel	2009-2011	8.8	2.2*	[71]
	Gulf of Cadiz, South Western Spain	2015	Nd – 31.1	0.00001	[54]
	North Seawater, Germany	1998	2	<0.7	[6]
	Baltic Sea, Germany	2009-2011	157	2.2*	[71]
	Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	22	2.2*	[71]
	Northern Adriatic Sea, Italy	2009-2011	3.1	2.2*	[71]
	Southwestern Taiwan	2010	Nd – 3.83	2	[64]
	Red Sea, Saudi Arabian coastal waters	2016	110	0.60	[72]
	San Francisco Bay, USA	2009-2011	13	2.2*	[71]
	Southern California Bight, USA	2006-2007	Nd – 0.9	0.5 RL	[36]
	California coast, USA	2009-2010	Nd – 21	-	[48]

	Mahdia coastal, Tunisia	2017-2018	Nd – 0.5	<1	[51]
	Korean seawater	2012	4.58 – 38.6	0.064	[70]
	Singapore seawater	2011	<0.3 – 11	0.3	[53]

346

4.5 Antidepressants

The cited literature (Table 5) attest the occurrence of pharmaceuticals used as human antidepressants in the coastal environment of the European countries (Greece and Spain), Israel in Middle East, USA and Tunisia in Africa. Citalopram and fluoxetine were the most common drugs in seawaters. The highest concentration for fluoxetine at 90 ng L^{-1} was found in the Pacific Ocean of USA [71]. The highest value for citalopram was 93 ng L^{-1} found in Rías Baixas coastline (North-western Spain) followed by 27 ng L^{-1} in the Pacific Ocean (USA) (Table 5). This could be ascribed to the consumption amounts in the USA, with the literature suggesting antidepressants as the third most common prescription drugs consumed by Americans over a decade ago, while 11% of the population aged above 11 years were consuming antidepressant medication [104]. Importantly; fluoxetine, sertraline, venlafaxine and duloxetine are the most prescribed anti-depressants worldwide [105]. Therefore, their appearance in the coastal waters with the exception of duloxetine and venlafaxine is not surprising. Although venlafaxine did not appear in the coastal waters based on the reviewed literature, its major active metabolite (norvenlafaxine) was detected in Greece [52] and Spain [78]. Interestingly, norvenlafaxine recorded the highest concentration of 291 ng L^{-1} in this group of pharmaceuticals found in Rías Baixas coastline (North-western Spain) [78]. This is an indication that the investigation of pharmaceuticals in environmental waters should be accompanied by the analysis of their metabolites in the same samples.

365 **Table 5**

366 Maximum concentrations (ng L^{-1}) of anti-depressants found in seawater samples.

Anti-depressant	Study site	Sampling year	Concentration	MDL (ng L^{-1})	Reference
Norvenlafaxine	Eastern Mediterranean Sea, Greece	2013	<0.01 – 2	0.01	[52]
Venlafaxine	Rías Baixas coastline, North-western Spain	2015	Nd - 291	0.19	[78]
Citalopram	Eastern Mediterranean Sea, Greece	2013	<0.06 – 8	0.06	[52]
	Rías Baixas coastline, North-western Spain	2015	Nd – 92.5	0.27	[78]
	Mediterranean Sea, Israel	2009-2010	4.3	3.2*	[71]
	Pacific Ocean, USA	2009-2011	27	3.2*	[71]
Fluoxetine	Mahdia coastal, Tunisia	2017-2018	Nd – 41	<1	[51]
	Gulf of Cadiz, South Western Spain	2015	Nd – 0.6	0.00001	[54]
	Rías Baixas coastline, North-western Spain	2015	Nd – 10.6	0.18	[78]
	Pacific Ocean, USA	2009-2011	90	16*	[71]
Amitriptyline	Mahdia coastal, Tunisia	2017-2018	Nd – 10	<1	[51]
	Gulf of Cadiz, South Western Spain	2015	Nd – 0.4	0.00002	[54]
Hydroxyzine	Rías Baixas coastline, North-western Spain	2015	Nd – 0.57	0.14	[78]
Sertraline	Rías Baixas coastline, North-western Spain	2015	Nd – 15.3	0.35	[78]

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4.6 Lipid regulators

The most monitored and detected lipid regulator in the marine environment is gemfibrozil (Table 6), with the highest concentration of 43 ng L^{-1} found in St Francisco Bay (USA) [71]. Gemfibrozil is not completely removed in WWTPs with selected studies reporting conflicting information such as the removal efficiencies of less than 16% [106], 55% [107] and greater than 75% [108]. However, these few cases serve as an indication to conduct more monitoring studies of gemfibrozil in river water and seawater. Other lipid regulators found in the coastal waters were fenofibrate, bezafibrate and atorvastatin (Table 6). Fewer detection and levels of these pharmaceuticals in the marine environment is in agreement with the general observation made by Sui et al. (2015) where they reported that lipid regulators have lower detection frequencies than some antibiotics, NSAIDs and carbamazepine [109]. Therefore, there is great focus directed towards the analysis of antibiotics, NSAIDs and carbamazepine in environmental waters rather than the monitoring of lipid regulators.

380 **Table 6**

381 Maximum concentrations (ng L^{-1}) of lipid regulators found in seawater samples.

Lipid regulator	Study site	Sampling year	Concentration	MDL (ng L^{-1})	Reference
Fenofibrate	Mahdia coastal, Tunisia	2017-2018	Nd – 14	<1	[51]
	Gulf of Cadiz, South Western Spain	2015	Nd – 1.1	0.00002	[54]
Bezafibrate	Gulf of Cadiz, South Western Spain	2015	Nd – 0.5	0.00001	[54]
	Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	3.5	3.5*	[71]
	Mediterranean Sea, Israel	2009-2011	3.8	3.5*	[71]
Gemfibrozil	Singapore seawater	2011	<0.09 – 20	0.09	[53]
	Marina Bay, Singapore	2010	1 - 9	0.4	[66]
	Pacific Ocean, USA	2009-2011	6.2	2.0*	[71]
	San Francisco Bay, USA	2009-2011	43	2.0*	[71]
	Southern California Bight, USA	2006-2007	Nd – 13	2.5 RL	[36]
	Southwestern Taiwan	2010	Nd – 3.67	1	[64]
	Mediterranean coastal lagoon, Spain	2010-2011	3.3	0.04	[77]
	Gulf of Cadiz, South Western Spain	2015	Nd – 5.7	0.00001	[54]
	Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	18	2.0*	[71]

Atorvastatin	Southern California Bight, USA	2006-2007	Nd – 0.4	0.25 RL	[36]

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4.7 Steroid hormones

Steroid hormones are common pollutants of environmental waters [86,88]. Their detection in the river water [110,111] is an indication that they escape the wastewater treatment process and get transported into the marine environment. Seven of these compounds have been found present in the coastal environment of Asia, Europe and North America (Table 7). The reviewed literature shows estrone, estradiol and 17α-ethinylestradiol as the most investigated steroid hormones in the marine environment with higher detection frequencies. These compounds also appear prominently in wastewater and river water samples [111,112]. However, the detection of coprostanol, coprostanol, cholesterol and equilin in a single study conducted in USA [113] demands more monitoring of these compounds in the marine environment. This is important as cholesterol had the concentration reaching 2896 ng L^{-1} (Table 7) which is much higher than any of the chemicals in this group including the common ones.

Table 7

Maximum concentrations (ng L^{-1}) of steroid hormones found in seawater samples.

Steroid hormone	Study site	Sampling year	Concentration	MDL (ng L^{-1})	Reference
Estrone	Singapore seawater	2011	<0.8 – 11	0.8	[53]
	Dublin bay, Ireland	2010	0.76	0.07	[74]
	Key Largo Harbor, USA	2004-2006	0.66 – 5.2	-	[113]
	Inner Wismar Bay, German Baltic Sea	2003-2004	0.45 – 0.53	0.02	[49]
	Eggers Wiek, German Baltic Sea	2003-2004	0.36 – 0.54	0.02	[49]
	Outer Wismar Bay, German Baltic Sea	2003-2004	0.13 -0.35	0.02	[49]
	Salzhaff, German Baltic Sea	2003-2004	0.27 0.37	0.02	[49]
	Darss Peninsula, German Baltic Sea	2003-2004	0.08 – 0.26	0.02	[49]
Estradiol	Halifax Harbour, Nova Scotia, Canada	2005	Nd – 0.57	0.10	[114]
	Key Largo Harbor, USA	2004-2006	Nd – 1.8	-	[113]
17α-ethinylestradiol	Halifax Harbour, Nova Scotia, Canada	2005	Nd - <0.14	0.14	[114]
	Inner Wismar Bay, German Baltic Sea	2003-2004	2.1 – 17.9	0.45	[49]
	Eggers Wiek, German Baltic Sea	2003-2004	Nd – 14.1	0.45	[49]
	Outer Wismar Bay, German Baltic Sea	2003-2004	Nd – 3.9	0.45	[49]

	Salzhaff, German Baltic Sea	2003-2004	1.6 – 4.0	0.45	[49]
	Darss Peninsula, German Baltic Sea	2003-2004	1.7 – 3.2	0.45	[49]
Coprostanol	Key Largo Harbor, USA	2004-2006	0.46 – 3.1	-	[113]
Coprostanone	Key Largo Harbor, USA	2004-2006	Nd – 5.5	-	[113]
Cholesterol	Key Largo Harbor, USA	2004-2006	<150 – 2896	-	[113]
Equilin	Key Largo Harbor, USA	2004-2006	Nd – 5.5	-	[113]

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4.8 Other pharmaceuticals

In this study, other pharmaceuticals refer to those compounds that are less monitored in the aquatic environment. Herein, such pharmaceuticals have been monitored in the marine environment but detected in five occasions or less. The reported concentrations for these pharmaceuticals in the marine environment are given in Table 8. Five antipsychotic drugs were detected in three investigations conducted in Greece [52] and USA [36,71], with haloperidol having the highest concentration of 56 ng L^{-1} found in the Pacific Ocean (USA) [71]. An antidiabetic drug, metformin, is noted for its high concentration of 4801 ng L^{-1} found in Saudi Arabia [72], while lower levels of up to 33 ng L^{-1} were reported in Germany [76]. Unusual occurrence of four antihelmintics was only observed in the Korean seawater [70]. All detected benzodiazepines are reported in Rías Baixas coastline (North-western Spain) [78] with lorazepam also found with a concentration of 40 ng L^{-1} at the Mediterranean coastal lagoon of the same country [77]. Similarly, the contrast media pharmaceuticals were reported in a single study [71] conducted in Aegean Sea & Dardanelles (Greece and Turkey), Baltic Sea (Germany), Mediterranean Sea (Israel) and St Francisco (USA). The occurrence of pharmaceuticals given in Table 8 should be investigated in other coastal regions in order to understand their spread in the marine environment.

414 **Table 8**

415 Maximum concentrations (ng L^{-1}) of other pharmaceuticals (not frequently detected / monitored in the aquatic environment) found in seawater samples.

Therapeutic class	Drug name	Study site	Sampling year	Concentration	MDL (ng L^{-1})	Reference
Antipsychotics	Sulpiride	Eastern Mediterranean Sea, Greece	2013	<0.06 – 0.5	0.06	[52]
	Chlorpromazine	Eastern Mediterranean Sea, Greece	2013	<0.05 – 0.6	0.05	[52]
	Amisulpride	Eastern Mediterranean Sea, Greece	2013	<0.2 – 6	0.2	[52]
	Risperidone	Southern California Bight, USA	2006-2007	Nd – 1.4	0.25 RL	[36]
	Haloperidol	Pacific Ocean, USA	2009-2011	56	4.0	[71]
Anti-hypertensives	Valsartan	Eastern Mediterranean Sea, Greece	2013	<0.8 – 4	0.8	[52]
		Mediterranean coastal lagoon, Spain	2010-2011	38	0.3	[77]
		Santos Bay, Brazil	2014	<LOQ – 75	7.7	[73]
	Irbesartan	Mediterranean coastal lagoon, Spain	2010-2011	16.8	0.05	[77]
	Losartan	Mediterranean coastal lagoon, Spain	2010-2011	104	2.3	[77]
		Santos Bay, Brazil	2014	Nd – 32	6.1	[73]
		Santos Bay, Brazil	2017	0.2 – 8.7	0.01	[75]
Nasal decongestants	Pseudoephedrine	Southwestern Taiwan	2013	0.71 – 2.65	0.5	[64]
Anesthetic	Lidocaine	Eastern Mediterranean Sea, Greece	2013	<0.01 – 13	0.01	[52]

Diuretics	Hydrochlorothiazide	Eastern Mediterranean Sea, Greece	2013	1.3 – 1.4	0.02	[52]
		Gulf of Cadiz, South Western Spain	2015	Nd – 155.5	0.00001	[54]
	Torasemide	Mediterranean coastal lagoon, Spain	2010-2011	1.8	0.3	[77]
HR antagonist	Ranitidine	Mahdia coastal, Tunisia	2017-2018	Nd – 53	<1	[51]
		Gulf of Cadiz, South Western Spain	2015	Nd – 1.7	0.00004	[54]
	Famotidine	Gulf of Cadiz, South Western Spain	2015	Nd – 0.2	0.00002	[54]
NMDA receptor antagonist	Ketamine	Southwestern Taiwan	2010	Nd – 21.1	1	[64]
Sulfonylurea	Glibenclamide	Mahdia coastal, Tunisia	2017-2018	Nd – 2	<1	[51]
Tranquilizers	Meprobamate	Southern California Bight, USA	2006-2007	Nd – 1.5	0.25	[36]
	Azaperol	Mediterranean coastal lagoon, Spain	2010-2011	0.8	0.2	[77]
Calcium channel blocker	Diltiazem	Singapore seawater	2011	<0.9 – 1.7	0.9	[53]
Sedation and muscle relaxation	Xylazine	Mediterranean coastal lagoon, Spain	2010-2011	13.8	1.2	[77]
Antihistamin	Diphenhydramine	Singapore seawater	2011	< 0.3 – 4.6	0.3	[53]
	Loratadine	Baltic Sea, Germany	2009-2011	4.1	2.7*	[71]
		Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	4.3	2.7*	[71]
		Pacific Ocean, USA	2009-2011	57	2.7*	[71]

Antihelmintics	Thiabendazole	Korean seawater	2012	0.585 – 2.84	0.027	[70]
	Fenbendazole	Korean seawater	2012	0.487 – 9.69	0.027	[70]
	Fenbendazole-SO	Korean seawater	2012	Nd – 4.98	0.190	[70]
	Praziquantel	Korean seawater	2012	2.78 – 22.7	0.065	[70]
Scabicide	Crotamiton	Korean seawater	2012	2.92 - 10.5	0.066	[70]
Antidiabetics	Metformin	German Bight and North Sea	2012	Nd – 33	2*	[76]
		Red Sea, Saudi Arabian coastal waters	2016	4801	0.98	[72]
	Glyburide	Gulf of Cadiz, South Western Spain	2015	<LOQ – 13.5	0.00001	[54]
Asthma treatment	Albuterol	Gulf of Cadiz, South Western Spain	2015	Nd – 2.5	0.00003	[54]
Cancer treatment	Methotrexate	Gulf of Cadiz, South Western Spain	2015	Nd – 3.5	0.00002	[54]
Contrast media	Iohexol	Baltic Sea, Germany	2009-2011	861	21*	[71]
		Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	76	21*	[71]
		Mediterranean Sea, Israel	2009-2011	26	21*	[71]
		San Francisco Bay, USA	2009-2011	162	21*	[71]
	Iomeprol	Baltic Sea, Germany	2009-2011	1159	19*	[71]
		Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	145	19*	[71]

		Northern Adriatic Sea, Italy	2009-2011	29	19*	[71]
	Iopamidol	Baltic Sea, Germany	2009-2011	1027	19*	[71]
		Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	145	19*	[71]
		Northern Adriatic Sea, Italy	2009-2011	61	19*	[71]
		San Francisco Bay, USA	2009-2011	783	19*	[71]
		Pacific Ocean, USA	2009-2011	32	19*	[71]
	Iopromide	Baltic Sea, Germany	2009-2011	109	19*	[71]
		Aegean Sea & Dardanelles, Greece and Turkey	2009-2011	199	19*	[71]
Anti-estrogen	Tamoxifen	Pacific Ocean, USA	2009-2011	93	19*	[71]
Benzodiazepines	Alprazolam	Rías Baixas coastline, North-western Spain	2015	Nd – 10.8	0.30	[78]
	Diazepam	Rías Baixas coastline, North-western Spain	2015	Nd – 5.22	0.16	[78]
	Lorazepam	Rías Baixas coastline, North-western Spain	2015	Nd – 95.9	2.55	[78]
		Mediterranean coastal lagoon, Spain	2010-2011	40.2	0.6	[77]

	Lormetazepam	Rías Baixas coastline, North-western Spain	2015	Nd – 42.8	0.21	[78]
	Temazepam	Rías Baixas coastline, North-western Spain	2015	Nd – 23.6	1.55	[78]
	Oxazepam	Rías Baixas coastline, North-western Spain	2015	Nd - 59	0.70	[78]
Sedatives or hypnotics	Zolpidem	Rías Baixas coastline, North-western Spain	2015	Nd – 1.46	0.10	[78]

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5 Occurrence of pharmaceutical metabolites in seawater

Pharmaceuticals are excreted by humans and animals as original drugs and metabolites. Therefore, some studies have investigated the occurrence of both pharmaceuticals and their metabolites in the marine environment [52,71]. Salicylic acid, a deacylated and more active form of acetylsalicylic acid also known as aspirin has been commonly detected in marine waters. It is indicated in literature that 10% of a low dose of acetylsalicylic acid is released as salicylic acid in the urine [115]. The concentrations of salicylic acid have reached 130, 53, 11, 18 and 977 ng L^{-1} in seawater samples from Tunisia [51], Greece [52], Germany [77], Mediterranean Sea (Spain) [54] and Gulf of Cadiz (Spain) [94], respectively. In a different case, guanylurea, a transformation product of metformin was found having a maximum concentration of 32 ng L^{-1} in German Bight and North Sea [76]. Notably, the main drug (metformin) had similar concentrations reaching 33 ng L^{-1} in the same study sites [76]. Two main transformation products (10,11-dihydro-10,11-trans-dihydroxycarbamazepine and 10-hydroxy-10,11-dihydrocarbamazepine) for carbamazepine have been found present in the French coast of the Mediterranean Sea with mean concentrations of 0.60 and 0.31 ng L^{-1} at one sampling location, respectively [79]. In the same study, 5 metabolites (*O*-desmethylvenlafaxine, *N*-desmethylvenlafaxine, *N,O*-didesmethylvenlafaxine, *N,N*-didesmethylvenlafaxine, and *N,N*-didesmethyl-*O*-desmethylvenlafaxine) of an antidepressant (venlafaxine) were all detected [79]. Ibuprofen metabolites, hydroxy-ibuprofen and carboxy-ibuprofen in seawater samples from Tromsø (Norway) had concentrations of up to 1.5 and 7.0 ng L^{-1} respectively [62]. In the same study, ibuprofen did not exceed 0.7 ng L^{-1}, which is an indication that the occurrence of pharmaceuticals is seawater should be investigated alongside their metabolites. This is important as the concentrations of some metabolites exceed or are similar to those recorded for their corresponding pharmaceuticals (parent compound) [62,65,76]. To elaborate further, a maximum concentration of 222 ng L^{-1} was found for ibuprofen in Portuguese seawater, while the levels of its metabolites, hydroxy-ibuprofen and carboxy-ibuprofen reached 287 and 1227 ng L^{-1}, respectively [65].

6 Health effects and associated risks

The levels of pharmaceuticals found in the oceans are much lower than those normally reported in the inland. This is due to large dilution of pharmaceuticals by seawater. Therefore, the detected concentrations of pharmaceuticals in the coastal environment are unlikely to cause any direct harm to humans, however, conflicting results have been presented for aquatic organisms. For example, Feo et al. (2020) used risk quotients to show that the presence of pharmaceuticals in the seawater of the Augusta Bay (southern Italy) was of no risk for aquatic organisms with the risk quotients less than 0.01 for all targeted pharmaceuticals even though the aqueous concentrations were up to 281 ng L^{-1} [116]. A recent study has indicated no detection of pharmaceuticals in fish tissues despite the presence of these drugs in seawater samples from the Gulf of Uraba (Colombia) [117]. On the other hand, the antibiotic, erythromycin has been classified as medium risk, while clarithromycin and sulfamethoxazole as high risk pharmaceuticals in German marine waters [118]. The possibility of raising moderate to severe risks to aquatic organisms (algae, crustaceans and fishes) due to the presence of acetaminophen, diclofenac, losartan and valsartan in Brazil marine waters has been reported [119]. Lincomycin and ofloxacin posed high risks to the relevant aquatic organisms in Jiaozhou Bay (China) [120].

Some pharmaceuticals are reported to be taken-up from seawater by marine organisms and bio-accumulate in their tissues. However, some pharmaceuticals are reported to be taken-up from seawater by marine organisms and bio-accumulate in their tissues [13,14,21,116,121,122]. As an example, oxytetracycline and flumequine were found to accumulate in marine invertebrates at concentrations between 60 - 380 and 2500 - 2900 μg kg^{-1} respectively [122]. In certain studies, the occurrence of pharmaceuticals in marine organisms is documented [35,70,101,123]. Hormones (progesterone and levonorgestrel) had concentrations reaching 15 ng g^{-1} in mussels [124]. In seafood muscles from Bay of Biscay (Southern France), acetaminophen had a concentration of 1.4 ng g^{-1} in hake while azithromycin and clarithromycin in red mullet were 1 ng g^{-1} [125]. Venlanfaxine and azithromycin were found in mussels (2.7 ng g^{-1}) and oyster (3.0 ng g^{-1}) [126]. This is a concern as some marine organisms are regarded as important food sources for humans. Therefore, this could cause an un-intentional over dosage of pharmaceuticals by humans. Consequently, this indirect uptake of pharmaceuticals by

humans through the consumption of marine organisms is likely to pose health risks. Although McEneff et al. (2014) suggested low risk of pharmaceutical exposure to humans through the consumption of exposed mussels [127], the effects of continuous intake of contaminated seafood by humans are not understood. In addition, a recent study reported the presence of citalopram and alprazolam in octopus and pod razor tissues exceeding the chosen hazard limits (HQ > 0.1) for children, with HQ values between 0.18 and 0.27 [128]. Research has indicated that the cooking of seafood, particularly mussel has the ability to increase the pharmaceutical concentration in tissues and cooking water [129]. But Alvarez-Munoz found no variations in pharmaceutical concentrations between the steam cooked and uncooked sole, plaice, seabream, mackerel, tuna and mussels [130]. Therefore, further research is required in order to provide more information regarding the effect of cooking on contamination of seafood.

It is clearly documented in literature that some marine organisms react negatively to the presence of pharmaceuticals in water. The health effects of various classes of pharmaceuticals on aquatic organisms is summarized in a review by Prichard and Granek (2016) [21]. Extreme cases include foot detachment of the marine snail due to citalopram, venlafaxine, fluvoxamine and fluoxetine [21,131]. This has a potential to reduce the population of marine organisms, thus affect the availability of seafood for humans. For example, mussels exposed to diclofenac, ibuprofen and propranolol were found to have lower growth, lower byssus strength and lower abundance of byssus threads, compared to controls which resulted in reduced ability to attach to the underlying substrate [132]. In a different study, it was suggested that carbamazepine can accumulate and consequently cause negative physiological and biochemical changes to wild *Daphnia magna* populations [133]. An antidepressant, amitriptyline has been reported to significantly reduce the hatching time and body length of zebrafish embryos after exposure in a concentration-dependent manner [134]. A potential chronic risk on *Phaeodactylum tricornutum* was observed from propranolol at Belgian harbours [135]. Therefore, it is important to prevent the pharmaceutical contamination of oceans as some drugs such as prochlorperazine have been found to be more stable in seawater than in freshwater [136]. Overall, this article provided the overview of the health effects and risks associated with the occurrence of

pharmaceuticals in the marine environment. Further studies and/or reviews are necessary to provide more information in this regard.

7 Predicted future studies and concluding remarks

Detection of pharmaceuticals at trace levels in seawater is an indication that more monitoring of detected drugs in required. Such monitoring should also be extended in the analysis of drugs in estuaries and WWTP effluents as these are regarded as the main feed of pharmaceuticals into the oceans. Focus should be directed to those WWTPs that discharge their effluents directly into the marine surface water. This will give more information on the main contributors (land-based activities vs swimming and bathing in the oceans) of pharmaceutical occurrence in seawater.

Analyte isolation and pre-concentration remains a crucial step in environmental analysis. SPE is regarded as the best sample preparation technique for these purposes. However, massive dilution of pharmaceuticals in the oceans and concoction of water contaminants require modification of simple existing SPE procedures. The increased SPE sorbent (Oasis HLB) mass to 4 g and sample volumes to 50 L has been reported in order to achieve greater pre-concentration factors, thus leading to a more sensitive analytical method [49]. But most SPE sorbents including HLB are known for their single use followed by the disposal. Therefore, this useful analytical procedure could be too costly for implementation in countries with poor economy. Also, discarding the sorbent after single use is against the green analytical chemistry principles discussed in a previous study [137]. Therefore, the battle to find suitable sample preparation methods that adhere to green analytical chemistry principles remains a challenging task. However, for a more specific research towards a single pharmaceutical or drugs with similar chemical structures and size, MIPs are regarded as promising SPE sorbents. In addition, other sample preparation techniques that use small volumes of organic solvents (as required for green chemistry applications) such as SPME, liquid-phase microextraction, and stir-bar sorptive extraction are likely to be explored in future. Under the same sentiments of adhering to green chemistry principles, solvents that are normally utilized in sample preparations such as conditioning and elution solvents in SPE can be replaced with greener chemicals such as ionic liquids and deep eutectic solvents. The same

greener solvents can be investigated as desorption solvents in SPME and stir-bar sorptive extraction, while they can also be used liquid-phase microextraction.

Identification of more pharmaceuticals in seawater can be achieved through the utilization of a non-target and suspect screening approach. This approach which is common in qualitative determination of water pollutants involves the utilization of non-selective SPE procedures for the extraction of pharmaceuticals prior to their identification using LC-MS [138,139]. Application of HLB SPE cartridges is common in this task as the HLB sorbent is known for its ability to extract a wide range of compounds with different functionalities from the aqueous phase. For the same purpose, Rimayi et al. (2019) utilized the Chemcatcher passive sampler deployed in environmental waters over a period of 14 days [140]. This resulted in the identification of over 200 compounds which included pesticides, pharmaceuticals and personal care products, drugs of abuse and their metabolites in environmental waters [140]. In a different study, while performing the quantitative analysis for carbamazepine and its transformation products using POCIS passive sampling (HLB sorbent) technique with LC-HRMS, 20 additional compounds belonging to herbicides, stimulants, β-blockers, lipid regulators, analgesics, antibiotics, and antidepressants were found present in the French coast on the Mediterranean Sea [79]. Almost two decades ago, non-target screening of organic contaminants in seawater was conducted using SPE allowing a large sample volume percolation of 10 L and GC-MS analysis [6]. Pesticides and industrial chemicals were detected in German seawaters with two pharmaceuticals, carbamazepine as well as propyphenazone with concentrations of 2 and 0.6 ng L^{-1} respectively. Therefore, related research that is focussing mainly on the identification of the wide range of pharmaceuticals in seawater is required.

As demonstrated in this review paper, the information on the occurrence of metabolites of pharmaceuticals in the marine environment is limited. In this regard, there is even lack of eco-toxicity studies performed for these compounds. Future studies should be devised to provide more information on the status of pharmaceutical metabolites in the marine environment.

Carbamazepine and pharmaceuticals belonging to therapeutic classes of antibiotics, NSAIDs and analgesics are the most monitored drugs in coastal waters. Therefore, more research is required on

549 the monitoring of other pharmaceuticals in the coastal environment. Focus should be directed on
550 intensive monitoring of those pharmaceuticals that were only reported in single occasions. Examples
551 include antibiotics (cefaclor, cefdinir, cefquinome, ceftiofur, nitrofurantoin, ornidazole) found in Gulf
552 of Cadiz, Spain [54]; NSAID (phenylbutazone) detected in Mahdia coastal waters, Tunisia [51] and
553 anti-depressants (hydroxyzine and sertraline) reported in Rías Baixas coastline, North-western Spain
554 [78]. Also, the information presented in this study shows that most of the monitoring data for
555 pharmaceuticals and their metabolites was recorded in the coastal environment of the high income and
556 developed nations such as European countries. Hence, there is a need to conduct more research in
557 coastal areas of developing countries such as those found in Africa and Asia. Recent work has already
558 reported that Asia showed the greatest contamination of coastal environment followed by Europe, North
559 America, and Australia in regard to the priority pharmaceuticals and personal care products [141].

560 Antiretroviral drugs are the chemicals of emerging concern in environmental waters. In recent
561 years, there has been an intensive monitoring of these pharmaceuticals in WWTPs and surface water
562 with most studies being conducted in Africa (Kenya and South Africa) where there is high number of
563 people infected with HIV/AIDS [86,88]. Hence, the occurrence of these drugs in river water has been
564 reported [142–144]. Therefore, there is a strong need to monitor antiretroviral drugs in the marine
565 environment as these drugs have already been detected in environmental waters of the coastal cities
566 such as Durban in South Africa [142].

567 In conclusion, literature revealed the occurrence of pharmaceuticals and their metabolites in
568 seawater mostly near the estuaries and marine outfalls. This means pharmaceutical contamination in the
569 seawater is mostly attributed to land-based activities. In this case, pharmaceuticals are generally
570 transferred from households and industrial effluents or spillages into WWTPs which discharge these
571 chemicals into rivers and marine environment. Pharmaceuticals flows with river water and enter into
572 the sea through the estuaries. Swimming and bathing in the beaches contribute to a lesser extent.

Funding

This work was financially supported under the project, SANOCEAN which is South Africa – Norway Cooperation on ocean research including blue economy, climate change, the environment and sustainable energy (UID 118757).

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