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## CRITICAL REVIEW

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# Non-steroidal anti-inflammatory drugs, analgesics, and their metabolites in the coastal environment: the escape to seawater and concerns

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Recent literature shows NSAIDs and analgesics as some of the most studied pharmaceuticals in the environment. These drugs, which are readily accessible as over-the-counter medications, have been detected in various environmental samples, including wastewater and surface water. Consequently, these chemicals are transferred to marine and coastal environments, entering marine organisms that play significant roles in the food chain, thereby posing toxic effects on human health. Therefore, the present review aims to comprehensively assess the occurrence, distribution, and environmental impact of a wide range of NSAIDs and analgesic medications in the marine environment worldwide. Marine outfalls and estuaries were viewed as significant sources of pharmaceuticals found in seawater, resulting in their presence in marine organisms considered as seafood. Transformation of the investigated drugs into metabolites is evident, as some transformation products were previously detected in estuaries, seawaters, and fish. In this context, carboxy ibuprofen and hydroxy ibuprofen have been reported in seawater and estuarine waters with concentrations reaching 1227 ng L<sup>-1</sup> and 70 ng L<sup>-1</sup>, respectively. Meanwhile, the parent compound, ibuprofen, has been extensively studied in marine organisms, mussels, with the highest concentration reported to be 730 ng g<sup>-1</sup>. These findings suggest a need to monitor the occurrence of pharmaceutical metabolites in environmental samples routinely. Therefore, the present review is an important resource for the scientific community as it discusses crucial issues related to seawater contamination and the quality of food products.

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### Environmental significance

Non-steroidal anti-inflammatory drugs are widely consumed all over the world and channelled to various waterways after excretion. Due to their physico-chemical properties, they escape the water and wastewater treatment facilities and make their way into the estuaries and eventually seawater. This review examined their occurrence in seawater and marine resources, with extensive critical review on their effects in marine organisms. Their detection in seafood is an indication of potential unintentional consumption by humans. At the same time, their toxic effects on marine organisms are well documented, showcasing their potential to disrupt the food chain. Therefore, the contents of this review have environmental significance considering its scope which covers the occurrence of NSAIDs in estuaries and seawater together with the associated risks.

## 1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics are two categories of medications used to relieve various types of pain, such as headaches, muscle aches, joint pain, menstrual cramps, and pain associated with inflammation or injury, thereby improving the quality of human life. These drugs are highly monitored in the environment, mainly because they are easily accessible and are highly consumed drugs in the world.<sup>1</sup> The steady increase in the aging population and climate change are key drivers increasing the global demand for NSAIDs and analgesic drugs. This is because as the global population ages,

they start to encounter chronic conditions that often require them to consume multiple medications at once. Furthermore, the global market size of NSAIDs was valued at USD 15.58 billion in 2021 and is anticipated to reach USD 24.35 billion by 2027.<sup>2</sup> Therefore, constantly monitoring these drugs in the environment is crucial for establishing mitigative measures to keep these pollutants out of the environment, subsequently protecting the ecosystem and human health.

In recent decades, there has been a significant increase in reports on the presence of NSAIDs and analgesic drugs in the environment worldwide. Notably, most of these studies have focused on monitoring the occurrence of these pharmaceuticals in wastewater,<sup>3</sup> sewage sludge,<sup>1</sup> river water,<sup>4</sup> and sediments.<sup>5</sup> However, there is currently a lack of sufficient data on the presence of pharmaceuticals in coastal and marine

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environments. Given that these environments also receive inflows from inland rivers, which are often highly contaminated with drugs, further research is urgently needed to understand the extent of pharmaceutical contamination in coastal and marine ecosystems. Moreover, coastal and marine environments host diverse aquatic species, some of which are integral to the human food chain. Consequently, the presence of pharmaceuticals in these environments can lead to bioaccumulation in aquatic organisms, which are consumed by humans. For instance, a study by Wolecki *et al.* 2019 reported the presence of naproxen, ibuprofen, diclofenac, paracetamol, and ketoprofen in mussels. Another study reported the occurrence of NSAIDs and analgesic drugs in hake, red mullet, sole, and shrimp.<sup>6</sup> This accumulation poses potential risks not only to human health but also to the overall health of marine ecosystems. Additionally, the presence of pharmaceuticals in coastal and marine environments can disrupt the natural behaviour, reproduction, and growth of marine species, further threatening biodiversity.<sup>7</sup> Therefore, it is crucial to expand research efforts to monitor and assess the impact of pharmaceutical contamination in these environments and develop strategies for mitigating the associated risks to marine life and human populations.

To date, several review articles focusing on the occurrence of NSAIDs and analgesic drugs in coastal environments have been published worldwide.<sup>8–12</sup> However, most of these studies only focus on a limited number of NSAIDs and analgesic drugs, with acetaminophen, diclofenac, and ibuprofen being the most extensively studied drugs due to their high prevalence in the environment. For instance, a review study by Blasco and Trombini<sup>9</sup> specifically examined the occurrence of diclofenac and ibuprofen in marine environments.<sup>13</sup> Another recent study reviewed the occurrence of eight NSAIDs (diclofenac sodium, fenoprofen, ibuprofen, ketoprofen, mefenamic acid, naproxen, paracetamol, and salicylic acid). Similarly, Madikizela *et al.* provided an overview of the distribution of 16 NSAIDs and analgesic drugs in marine environments; however, their study included only one African study.<sup>14</sup> Thus, highlighting a significant gap in the data on pharmaceutical contamination in the marine environments of African nations and other developing countries. The present review aims to provide a comprehensive analysis of the occurrence, distribution, and environmental impact of a wide range of NSAIDs and analgesic medications in the marine environment worldwide. Thus, enabling comparison across continents and identifies regional differences in sources, concentrations, and environmental risks. It further seeks to enhance understanding of the health risks, fate, transport, and transformation of these pharmaceutical pollutants within marine ecosystems and their potential effects on marine organisms, particularly those that are integral to the human food chain.

## 2. Routes of non-steroidal anti-inflammatory drugs and analgesics to seawater

Pharmaceuticals enter the coastal and marine environment through various pathways, with the most significant route being

the discharge of contaminated inland rivers. Rivers are heavily loaded with pharmaceuticals, which eventually flow into the sea *via* estuaries, introducing these pollutants to marine ecosystems.<sup>15</sup> As illustrated in Fig. 1, pharmaceutical contamination of inland rivers primarily results from various anthropogenic activities. These activities include the improper disposal of unwanted medications, which are often deposited at municipal dumping sites. Rainwater runoff then carries these pharmaceuticals into rivers. In developing countries such as South Africa, some areas are densely populated with informal settlements that lack proper sanitation facilities. As a result, residents often use indoor buckets for nighttime urination and dispose of the urine during the day on land, which can sometimes be closer to the rivers. This practice contributes to the pharmaceutical contamination of the nearby rivers, as the discarded urine may contain drug residues taken by the residents. Given that pharmaceuticals are only partially metabolized in the human body,<sup>1</sup> these residues contribute to the pollution of nearby water bodies.

The other significant source of contamination is WWTPs, which receive loads of pharmaceuticals from pharmaceutical manufacturers, hospitals, and households. Since WWTPs are not designed to eliminate pharmaceuticals during wastewater treatment processes, they are then released into the surface water, ultimately depositing into the ocean.<sup>16</sup> Some South African WWTPs are located near the sea to discharge treated wastewater into the ocean. However, these facilities frequently experience breakdowns, leading to the release of untreated wastewater into the marine environment. Open beaches offer a range of attractions and activities, drawing visitors with their scenic beauty, opportunities for swimming, sunbathing, and water sports, as well as for relaxation and social gatherings. However, during these activities, drugs may be accidentally dropped onto the sand and subsequently seep into the ocean. All these practices result in the occurrence of pharmaceuticals in the coastal and marine environments, potentially posing significant health risks to aquatic species, which are integral to human food chains. Lately, the establishment of desalination water treatment plants has emerged as a solution to increase drinking water accessibility. However, if the seawater is contaminated with pharmaceuticals, these substances could end up in human drinking water, potentially leading to the unintentional consumption of certain drugs.

These pathways have been reported as significant sources of pharmaceuticals to the coastal environment in other countries. For instance, Afsa *et al.* documented that discharges from hospitals and urban wastewater contributed to the occurrence of 40 pharmaceutical compounds, including analgesics, in coastal seawater from Mahdia, Tunisia.<sup>17</sup> In South America, Roveri *et al.* identified the presence of acetaminophen, diclofenac, and orphenadrine in the South Atlantic Ocean *via* inland rivers in Brazil, with maximum concentrations reaching 22.44 ng L<sup>-1</sup>.<sup>18</sup> Another Brazilian study reported coastal water concentrations of ibuprofen and acetaminophen of 2094 and 34.6 ng L<sup>-1</sup>, respectively.<sup>19</sup> Overall, the global occurrence of NSAIDs and analgesics in coastal environments is driven primarily by wastewater discharges and riverine inputs. Thus, reinforcing the need for improved wastewater management strategies.





Fig. 1 Various sources and routes through which pharmaceuticals enter the coastal and marine environment.

### 3. Marine outfalls as the source of non-steroidal anti-inflammatory drugs, analgesics, and their metabolites in the marine environment

Continuous sewage discharges into the sea through the WWTP marine outfalls are expected to increase the contamination levels in seawater and marine organisms.<sup>20</sup> Reports indicate that under certain conditions, sewage discharged into the sea finds its way back into the shore at levels that could be harmful, releasing some toxic chemicals, and thus affecting marine life.<sup>21</sup> Besides this, the concentrations of NSAIDs (clofibric acid, diclofenac, ibuprofen, and ketoprofen) were found to be higher in areas closer to the ocean outfalls.<sup>22,23</sup> In seawater around the coastal submarine sewage outfall in Guarujá, São Paulo State of Brazil, diclofenac and paracetamol had concentrations of 3.6–85.7 and 1.2–1.4 ng L<sup>-1</sup>, respectively.<sup>23</sup> Similarly, the discharge of wastewater in Athens to the Inner Saronikos Gulf was linked

to the contamination levels of NSAIDs and analgesics.<sup>24</sup> Although various sources of pharmaceuticals in seawater are well-described in section 2 of this paper, wastewater discharges remain the focal point of environmental contamination. Arguments could arise that a big waterbody, such as an ocean, could dilute these drugs to levels that are below the detection limits of many analytical instruments. However, these drugs could present significant risks to marine life as they can bioaccumulate in organisms considered as seafood. Therefore, stringent measures should be put in place to govern the quality of treated wastewater, which is expected to be directly discharged into the ocean.

### 4. Occurrence of non-steroidal anti-inflammatory drugs, analgesics, and their metabolites in estuaries

Estuaries remain a significant source of these pharmaceuticals and their metabolites in seawaters. Their presence in major



estuaries across the world is documented in Table 1. The concentrations of these drugs in estuaries are generally higher than the levels found in the open oceans. This observation is expected considering large water bodies, such as oceans, where dilution is significant. The occurrence of these drugs in the estuaries demonstrates their transfer through the rivers into the

**Table 1** Concentrations (ng L<sup>-1</sup>) of non-steroidal anti-inflammatory drugs and analgesics found in estuarine water<sup>a</sup>

Compound	Study location	Sampling year	Concentration	Reference
Naproxen	Weser estuary, Bremerhaven, southern North Sea	2023	Nd-1.87	27
	Garonne River, South-West of France	2011–2012	2.9–14	28
	Australian east coast estuaries; Sydney, Yarra, and Brisbane	2013 and 2017	Nd	29
	Golden Horn Estuary, Sea of Marmara, Turkey	2019–2020	Nd-270	30
	Quenera River and Gonubie River estuaries, South Africa	2023	Nd	20
	Umgeni estuary, South Africa	2018	130–192	31
Ibuprofen	Weser estuary, Bremerhaven, southern North Sea	2023	36.6–51.9	32
	Garonne River, South-West of France	2011–2012	Nd-28	33
	Australian east coast estuaries; Sydney, Yarra, and Brisbane	2013 and 2017	Nd	34
	Golden Horn Estuary, Sea of Marmara, Turkey	2019–2020	Nd-2046	35
	UK estuaries	2002	Nd-928	36
	Quenera River and Gonubie River estuaries, South Africa	2023	55–71	20
	Umgeni estuary, South Africa	2018	Nd-261	31
	Jiulong River estuary, China	2014	Nd-20.7	37
	Tejo estuary	2016	<MQL	38
Diclofenac	Weser estuary, Bremerhaven, southern North Sea	2023	2.95–4.92	32
	Garonne River, South-West of France	2011–2012	7.6–14	33
	Golden Horn Estuary, Sea of Marmara, Turkey	2019–2020	Nd-1046	35
	UK estuaries	2002	Nd-195	39
	Jiulong River estuary, China	2014	0.819–11	40
	Yangtze estuary, China	2009	Nd	41
	Klang River estuary, Malaysia	2016	0.47–10.8	42
	Tejo estuary	2016	1.60–51.8	43
	Estuaries along the Portuguese coast	2017	Nd-346	44
	Estuarine waters along the São Paulo coast, Brazil	2021	0.76–3.93	45
	Umgeni estuary, South Africa	2018	Nd	31
Ketoprofen	Weser estuary, Bremerhaven, southern North Sea	2023	Nd	32
	Garonne River, South-West of France	2011–2012	25–144	33
	Golden Horn Estuary, Sea of Marmara, Turkey	2019–2020	Nd-260	35
	Jiulong River estuary, China	2014	Nd-36.6	40
Fenoprofen	Weser estuary, Bremerhaven, southern North Sea	2023	Nd	32
	Golden Horn Estuary, Sea of Marmara, Turkey	2019–2020	Nd-1128	35
	Jiulong River estuary, China	2014	Nd-241	40
Paracetamol	Weser estuary, Bremerhaven, southern North Sea	2023	Nd	32
	Garonne River, South-West of France	2011–2012	11–395	33
	Australian east coast estuaries; Sydney, Yarra, and Brisbane	2013 and 2017	Nd-33.9	34
	Sydney estuary, Australia	2013	5.0–67.1	46
	Danshue River estuary, Northern Taiwan	2015	5.63–44.9	47
	Jiulong River estuary, China	2014	Nd-12.5	40
	Yangtze estuary, China	2013	Nd	48
	Clyde estuary, Scotland	2019	<MQL-509	49
	Tejo estuary	2016	0.12–10.6	43
	Estuarine waters along the São Paulo coast, Brazil	2021	<MQL-22.2	18
Indomethacin	Weser estuary, Bremerhaven, southern North Sea	2023	1.99–3.61	32
	Jiulong River estuary, China	2014	Nd-2.67	40
	Yangtze estuary, China	2013	Nd-0.89	50
	Yangtze estuary, China	2009	159–352	51
Tramadol	Estuaries along the Portuguese coast	2017	Nd-56.5	44
Salicylic acid	Weser estuary, Bremerhaven, southern North Sea	2023	7.43–45.4	32
	Australian east coast estuaries; Sydney, Yarra, and Brisbane	2013 and 2017	<LOQ	34
Mefenamic acid	Weser estuary, Bremerhaven, southern North Sea	2023	0.05–1.11	32
	UK estuaries	2002	Nd-196	39
	Jiulong River estuary, China	2014	Nd-3.14	40
	Weser estuary, Bremerhaven, southern North Sea	2023	Nd	32
Codeine	Australian east coast estuaries; Sydney, Yarra, and Brisbane	2013 and 2017	Nd-9.5	34
	Sydney estuary, Australia	2013	Nd-9.5	52
	Jiulong River estuary, China	2014	Nd-0.356	40
Hydroxy ibuprofen	Garonne River, South-West of France	2011–2012	Nd-70	33

<sup>a</sup> Nd, not detected.



sea. However, many studies have monitored the occurrence of these drugs along the major rivers into the estuaries but have excluded the extensive analysis of the receiving seawaters.<sup>25,26</sup> This could have been necessitated by the lack of sensitive analytical facilities for the analysis of these pharmaceuticals in seawater, and probably the application of the analytical methods that have not been validated for complex samples such as seawater which have high salt content and numerous contaminants.

The concentrations found in some estuaries for these pharmaceuticals are high and comparable to some levels reported for some rivers across the world (Table 1). This suggests that the concentrations of these chemicals can sometimes be higher in the river upstream than in estuaries, possibly due to dilution effects as river water mixes with seawater. In the Umgeni estuary (South Africa), ibuprofen had the maximum concentration of 261 ng L<sup>-1</sup>,<sup>31</sup> which is much smaller than 62 000 ng L<sup>-1</sup>, which was previously reported for the same pharmaceutical in the upstream of the Umgeni River.<sup>53</sup> Although such trends are true in different locations, estuaries are still considered the sink of environmental contaminants, with higher concentrations sometimes found in estuaries than elsewhere in rivers. Ibuprofen concentration in Golden Horn Estuary (Turkey) with a maximum concentration of 2046 ng L<sup>-1</sup> (Table 1) is higher than the maximum level of 17.6 ng L<sup>-1</sup>, which was detected in Ceyhan River (still in Turkey).<sup>54</sup> Similarly, indomethacin found in the Yangtze Estuary (China) was previously not detected in the central and lower parts of the same river.<sup>25</sup>

## 5. Occurrence of non-steroidal anti-inflammatory drugs, analgesics, and their metabolites in seawater

A list of NSAIDs, analgesics, and their metabolites found in seawater worldwide is provided alongside the detected concentrations in Table 2. NSAIDs such as ibuprofen and diclofenac, which are mostly detected in the aquatic environment, seem to be constantly detected in seawater samples. This indicates that domestic activities contribute largely to the contamination of the coastal and marine environments. These two pharmaceuticals (ibuprofen and diclofenac) were also detected in high quantities, with their concentrations in seawater samples from the Sea of Marmara (Turkey) and Santos Bay (São Paulo, Brazil) exceeding 1 µg L<sup>-1</sup>.<sup>55,56</sup> Notably, compounds such as phenazone, propylphenazone, codeine, and oxycodone were investigated and not detected in any of the samples (Table 2). In the case of codeine, such results could be expected as this drug is usually found in smaller quantities in the medications. Table 2 shows two studies that investigated the occurrence of tramadol resulting in positive detections in seawater.<sup>44,57</sup> The environmental fate of tramadol is of interest to investigate, as this drug has been recently found to be rapidly taken up by plants, including aquatic plants such as water hyacinth.<sup>58,59</sup> The occurrence of tramadol in coastal waters indicates its ability to be transferred to the coastline, even though it can be taken by plants from the surface water (limiting its availability in water

resources). It is believed that fenoprofen is a less consumed NSAID when compared to ibuprofen, diclofenac, and naproxen, hence the least interest in its environmental monitoring.

As shown in Table 2, few studies evaluated the occurrence of the metabolites of NSAIDs and analgesics in seawater. This observation could be a result of the lack of interest and limited infrastructure available in research-intensive institutions to monitor these metabolites. The occurrence of the metabolites of these compounds was already discovered in the last two decades, with the ibuprofen metabolites found in seawater bordering Tromsø in Norway.<sup>73</sup> In this case, the metabolites of ibuprofen were found with their concentrations mostly exceeding the levels seen for the parent compound.<sup>73</sup> In one study, hydroxy ibuprofen was among the compounds with the highest concentrations in seawater.<sup>74</sup> Despite these findings, research on the metabolites of pharmaceuticals in environmental samples remains minimal. Besides the metabolites of ibuprofen, residues of the metabolites of diclofenac have been found in seawater (Table 2). These findings indicate the rapid transformation of ibuprofen and diclofenac, which need to be further studied. Furthermore, there is a clear need to monitor the occurrence of the metabolites in the marine and coastal environment. Overall, this review has established that the most studied pharmaceuticals in surface water and wastewater are also constantly detected in seawater. Therefore, this highlights a need to further investigate the occurrence of these drugs in marine organisms and seawater where swimming activities are dominant.

## 6. Occurrence of non-steroidal anti-inflammatory drugs, analgesics, and their metabolites in marine organisms

Based on the information presented in Table 3, there are plenty of reports on the occurrence of NSAIDs and analgesics in sea-food and marine species. Diclofenac and ibuprofen seem to be the most investigated drugs from this therapeutic group, which correlates well with investigations conducted in wastewater and river water.<sup>75,76</sup> In various environmental compartments, these two drugs have been documented with high concentrations in some surface water samples.<sup>77</sup>

In comparison with other NSAIDs and analgesics, it is both ibuprofen and diclofenac that have been found with high concentrations in different marine organisms (Table 3). For example, ibuprofen was found with the highest concentration of 730 ng g<sup>-1</sup> in mussels from the Gulf of Gdansk (Southern Baltic Sea).<sup>98</sup> At the same time, diclofenac had concentrations ranging from 68 to 780 ng g<sup>-1</sup> in various samples from South Africa, which included limpets, sea snails, mussels, starfish, and sea urchins.<sup>89</sup> Despite the discovery of fenoprofen with concentrations reaching 323 ng g<sup>-1</sup> in marine biota from the Sea of Marmara, Turkey,<sup>80</sup> there seems to be a lack of studies investigating the occurrence of this drug in marine organisms from other coastal areas.

Notably, several drugs were investigated in different marine organisms without any detection, and detection with



Table 2 Concentrations (ng L<sup>-1</sup>) of non-steroidal anti-inflammatory drugs and analgesics found in seawater<sup>a</sup>

Compound	Study location	Sampling year	Concentration	Reference	
Naproxen	Southern North Sea coastal waters	2023	Nd	32	
	Inner Saronikos Gulf and Elefsis Bay (Greece)	2013	<0.01–0.8	57	
	Southern Baltic Sea	2012	Nd-135	60	
	Augusta Bay (Sicily, Italy)	2017–2018	Nd	61	
	Sea of Marmara, Turkey	2019	Nd-340	56	
	Atlantic Ocean along the North Portuguese coast	2013	Nd-178	62	
	Western Mediterranean Sea	2014	0.47–1.68	63	
	Mediterranean Sea	2015–2016	Nd	64	
	Xiamen Bay	2019–2020	15–84	65	
	Indian Ocean (East London, South Africa)	2023	Nd-57	20	
	Indian Ocean (Durban, South Africa)	2018	160	31	
	Ibuprofen	Southern North Sea coastal waters	2023	1.23–15.8	32
		Southern Baltic Sea	2012	Nd-34.9	60
Sea of Marmara, Turkey		2019	Nd-2130	56	
Augusta Bay (Sicily, Italy)		2017–2018	Nd	61	
Atlantic Ocean along the North Portuguese coast		2013	Nd-222	62	
Western Mediterranean Sea		2014	Nd-1.08	63	
Mediterranean Sea		2015–2016	Nd-23.9	64	
Mediterranean coastal lagoon		2018–2019	Nd	66	
Mahdia coastal seawater		2017–2018	Nd	17	
Indian Ocean (East London, South Africa)		2023	52–90	20	
Indian Ocean (Durban, South Africa)		2018	170	31	
Xiamen Bay		2019–2020	Nd-9.4	65	
Diclofenac		Gulf of Uraba, Colombia	2018–2019	Nd-460	67
	Santos Bay (São Paulo, Brazil)	2014	326–2094	55	
	Southern North Sea coastal waters	2023	Nd-1.4	32	
	Mahdia coastal seawater	2017–2018	Nd-23	17	
	Indian Ocean (Durban, South Africa)	2018	Nd	31	
	Red Sea coastal waters	2018	Nd-26.9	68	
	Portuguese coast	2017	Nd	44	
	Inner Saronikos Gulf and Elefsis Bay (Greece)	2013	<1.4–16.3	57	
	Sea of Marmara, Turkey	2019	Nd-1300	56	
	Atlantic Ocean along the North Portuguese coast	2013	Nd-241	62	
	Augusta Bay (Sicily, Italy)	2017–2018	Nd	61	
	Southern Baltic Sea	2012	Nd-92.6	60	
	Western Mediterranean Sea	2014	Nd	63	
Ketoprofen	Mediterranean Sea	2015–2016	Nd	64	
	Eastern Gulf of Finland (Russia)	2019	0.9–4.5	69	
	Gulf of Uraba, Colombia	2018–2019	Nd-570	67	
	Santos Bay (São Paulo, Brazil)	2014	<LOQ-19.4	55	
	Guarujá, São Paulo State, Brazil	2018	1.7–17.4	70	
	Jiaozhou Bay, North China	2017	Nd-0.88	71	
	Southern North Sea coastal waters	2023	Nd	32	
	Southern Baltic Sea	2012	Nd-135	60	
	Atlantic Ocean along the North Portuguese coast	2013	10.3–89.7	62	
	Augusta Bay (Sicily, Italy)	2017–2018	Nd-1.6	61	
	Sea of Marmara, Turkey	2019	Nd-370	56	
	Western Mediterranean Sea	2014	Nd-0.18	63	
	Mediterranean Sea	2015–2016	Nd	64	
Fenoprofen	Mediterranean coastal lagoon	2018–2019	Nd-2.0	66	
	Eastern Gulf of Finland (Russia)	2019	1.5–4452	69	
	Mahdia coastal seawater	2017–2018	Nd-76	17	
	Southern North Sea coastal waters	2023	Nd	32	
	Mahdia coastal seawater	2017–2018	Nd	17	
Paracetamol	Sea of Marmara, Turkey	2019	Nd-1320	56	
	Inner Saronikos Gulf and Elefsis Bay (Greece)	2013	Nd-40.5	57	
	Atlantic Ocean along the North Portuguese coast	2013	51.2–584	62	
	Western Mediterranean Sea	2014	0.03–0.11	63	
	Mediterranean Sea	2015–2016	Nd-13.7	64	
	Xiamen Bay	2019–2020	Nd-0.64	65	
	Jakarta Bay, Indonesia	2017–2018	Nd-610	72	
Santos Bay (São Paulo, Brazil)	2014	<LOQ-34.6	55		
Guarujá, São Paulo State, Brazil	2018	<1.4–18.3	70		



Table 2 (Contd.)

Compound	Study location	Sampling year	Concentration	Reference
Mefenamic acid	Southern North Sea coastal waters	2023	Nd-1.72	32
	Inner Saronikos Gulf and Elefsis Bay (Greece)	2013	<0.2–10.9	57
	Mahdia coastal seawater	2017–2018	Nd-0.6	17
Indomethacin	Jiaozhou Bay, North China	2017	Nd-0.12	71
	Southern North Sea coastal waters	2023	Nd-0.81	32
	Mediterranean Sea	2015–2016	Nd	64
Phenylbutazone	Mahdia coastal seawater	2017–2018	Nd	17
	Jiaozhou Bay, North China	2017	Nd-0.26	71
	Southern North Sea coastal waters	2023	Nd	32
Salicylic acid	Mahdia coastal seawater	2017–2018	Nd-2	17
	Southern North Sea coastal waters	2023	10.1–127	32
	Mahdia coastal seawater	2017–2018	3–130	17
Phenazone	Inner Saronikos Gulf and Elefsis Bay (Greece)	2013	<0.4–53.3	57
	Mediterranean coastal lagoon	2018–2019	Nd	66
	Mediterranean Sea	2015–2016	Nd-18.0	64
	Mahdia coastal seawater	2017–2018	Nd	17
Propylphenazone	Mediterranean Sea	2015–2016	Nd	64
	Mediterranean Sea	2015–2016	Nd	64
Tramadol	Inner Saronikos Gulf and Elefsis Bay (Greece)	2013	<0.1–1.0	57
	Portuguese coast	2017	Nd-1327	44
Codeine	Mediterranean Sea	2015–2016	Nd	64
Oxycodone	Mediterranean Sea	2015–2016	Nd	64
<b>Transformation products</b>				
9 <i>H</i> -Carbazole-1-acetic acid	Red Sea coastal waters	2018	Nd-3.3	68
8-Chloro-9 <i>H</i> -carbazole-1-acetic acid	Red Sea coastal waters	2018	Nd-1.9	68
Carboxy ibuprofen	Atlantic Ocean along the North Portuguese coast	2013	Nd-1227	62
Hydroxy ibuprofen	Atlantic Ocean along the North Portuguese coast	2013	22.4–287	62

<sup>a</sup> Nd; not detected.

concentrations not exceeding the method quantitation limits (Table 3). These drugs include codeine, phenazone, and piroxicam, among others. There is scientific evidence indicating that some pharmaceuticals are transformed into other substances within the human body, while in some cases, the transformation can occur after excretion.<sup>99</sup> This is highlighted by the detection of hydroxyl- and carboxyibuprofen, *O*-desmethylnaproxen, and hydroxydiclofenac, which are metabolites of ibuprofen, naproxen, and diclofenac, respectively, in environmental water.<sup>62,100</sup> A critical analysis of these metabolites remains scarce in the existing literature. Nevertheless, the traces of 4'-hydroxydiclofenac (a phase I metabolite of diclofenac) have been reported in fishes and bivalves from the Brazilian coastal areas, with concentration reaching 9.6 ng g<sup>-1</sup>.<sup>78</sup> Another study reported the presence of this metabolite in mussels when evaluating its uptake and environmental fate.<sup>101</sup> Also, hydroxyibuprofen and carboxyibuprofen, metabolites of ibuprofen, were reported in the Atlantic Ocean along the North Portuguese coast with concentrations of 287 ng L<sup>-1</sup> and 1227 ng L<sup>-1</sup>, respectively.<sup>102</sup> This information suggests a need to conduct more surveys in the coastal and marine environments where pharmaceutical presence in samples is investigated alongside their metabolites.

The bioavailability of pharmaceuticals in cooked seafood has also been observed through an increase in pharmaceutical quantities in cooked seafood, while the residues of the same drugs have been detected in the cooking water.<sup>103</sup> One study

reported the increase of diclofenac and mefenamic acid residues by more than a factor of 20 in mussel tissues.<sup>104</sup> The same study found an increase of mefenamic acid from 1.6 (in raw mussels) to 89.5 µg g<sup>-1</sup> in cooked mussels.<sup>104</sup> A recent study showcased that the effect of cooking on NSAIDs and analgesics concentrations in seafood could be influenced by the nature of the seafood and the preparation procedures for consumption.<sup>105</sup> In this case, the cooking of fish was found to decrease the bioaccessibility of diclofenac by up to 40% in seabass and 25% in white mullet.<sup>106</sup> Furthermore, the same study revealed that the cooking process does not transform diclofenac to its metabolites. Since these findings could also depend on the nature of the compound under investigation, there is a need to conduct more research in this area which can be extended to the understanding of potential risks that could be associated with the consumption of contaminated seafood.

## 7. Health risks associated with the occurrence of non-steroidal anti-inflammatory drugs, analgesics, and their metabolites in marine organisms

Pharmaceuticals belonging to the classes of NSAIDs and analgesics have not only been found in marine organisms and seafood, however these drugs have also been documented to harm marine species and pose health risks. For example,



Table 3 Non-steroidal anti-inflammatory drugs and analgesics quantified in marine organisms<sup>a</sup>

Compound	Study location	Marine organism	Study year	Detected concentration (ng g <sup>-1</sup> )	Reference	
Naproxen	Gulf of Gdansk (southern Baltic Sea)	Mussels	Not provided	Nd-473	6	
	Brazilian coastal areas	Fishes and bivalves	2019	Nd-10.5	78	
Ibuprofen	Gulf of Gdansk (southern Baltic Sea)	Mussels	Not provided	Nd-730	6	
	Portonovo Bay (Central Adriatic Sea)	Mussels	2014	Nd-9.4	79	
	Brazilian coastal areas	Fishes and bivalves	2019	Nd-22	78	
	Sea of Marmara, Türkiye	Marine biota	2019	<3.0–1225	80	
	Gulf of Uraba, Colombia	Fish	2018–2019	Nd	81	
	Adriatic and Tyrrhenian Sea	Mussels	2014–2017	<8.0–144	82	
	Bay of Biscay (southern France)	Seafood (hake, red mullet, sole, and shrimp)	Not provided	Nd	83	
	Diclofenac	Gulf of Gdansk (southern Baltic Sea)	Mussels	Not provided	Nd-560	6
Diclofenac	Portonovo Bay (Central Adriatic Sea)	Mussels	2014	Nd-16	84	
	Portuguese Atlantic coast	Mussels	2015	0.5–4.5	85	
	Pulau Kukup, Johor of Malaysia	Mariculture fish	Not provided	Nd-4.11	86	
	Brazilian coastal areas	Fishes and bivalves	2019	Nd-5.6	78	
	English and Welsh coast	Bivalve molluscs	2017–2018	0.03–0.04	87	
	Mar Menor lagoon (Spain)	Cockle, noble pen shell, sea snail, golden grey mullet, and black goby	2010	Nd-2.2	88	
	False Bay, Cape Town, South Africa	Limpets, sea snails, mussels, starfish, and sea urchins	2018	68–780	89	
	Bay of Biscay (southern France)	Seafood (hake, red mullet, sole, and shrimp)	Not provided	Nd	90	
	Different European regions	Seafood	2014–2015	Nd-<MQL	91	
	Gulf of Uraba, Colombia	Fish	2018–2019	Nd	67	
Ketoprofen	Adriatic and Tyrrhenian Sea	Mussels	2014–2017	<1.4–280	92	
	Gulf of Gdansk (southern Baltic Sea)	Mussels	Not provided	Nd	6	
	Portonovo Bay (Central Adriatic Sea)	Mussels	2014	Nd	84	
	Brazilian coastal areas	Fishes and bivalves	2019	Nd-12.0	78	
Fenoprofen	Bay of Biscay (southern France)	Seafood (hake, red mullet, sole, and shrimp)	Not provided	Nd	90	
	Sea of Marmara, Türkiye	Marine biota	2019	<3.6–323	80	
	Gulf of Gdansk (southern Baltic Sea)	Mussels	Not provided	Nd	6	
	Portonovo Bay (Central Adriatic Sea)	Mussels	2014	Nd	84	
	Belgian coastal zone	Blue mussels	2008	Nd-115	93	
	Southern Sea of Korea	Cultured fish	2012	Nd	94	
	False Bay, Cape Town, South Africa	Limpets, Sea snails, Mussels, Starfish, and Sea urchins	2018	18–131	89	
	Bay of Biscay (southern France)	Seafood (hake, red mullet, sole, and shrimp)	Not provided	Nd-1.40	90	
	Codeine	Mar Menor lagoon (Spain)	Cockle, noble pen shell, sea snail, golden grey mullet, and black goby	2010	Nd	95
	Nimesulide	Spanish Mediterranean	Bivalves	2013–2014	Nd	96
Portonovo Bay (Central Adriatic Sea)		Mussels	2014	3.0–6.0	84	
Phenazone	Adriatic and Tyrrhenian Sea	Mussels	2014–2017	<2.0–81	92	
	Spanish Mediterranean	Bivalves	2013–2014	Nd-<MQL	97	
	Bay of Biscay (southern France)	Seafood (hake, red mullet, sole, and shrimp)	Not provided	Nd	90	
Propyphenazone	Spanish Mediterranean	Bivalves	2013–2014	Nd	97	
Piroxicam	Spanish Mediterranean	Bivalves	2013–2014	Nd	97	
Methadone						



Table 3 (Contd.)

Compound	Study location	Marine organism	Study year	Detected concentration (ng g <sup>-1</sup> )	Reference
Acetylsalicylic acid	Bay of Biscay (southern France)	Seafood (hake, red mullet, sole, and shrimp)	Not provided	Nd	90
Mefenamic acid	Bay of Biscay (southern France)	Seafood (hake, red mullet, sole, and shrimp)	Not provided	Nd	90
Niflumic acid					
4'-Hydroxydiclofenac	Brazilian coastal areas	Fishes and bivalves	2019	Nd-9.6	78

<sup>a</sup> Nd; not detected, MQL; method of quantification.

acetylsalicylic acid is one of three drugs that were found to affect the embryonic development of the sea urchin at different concentrations including the environment-relevant levels.<sup>107</sup> The same drug exposed to a sea snail resulted in a positive response with the marine organism showing a mild response to the oxidative stress.<sup>108</sup> The same study reported the toxic effects of paracetamol on the same species, but such effects were only observed at unrealistic concentrations (higher levels than those found in seawater). The toxicity of pharmaceuticals present in seawater is not only influenced by the concentrations of such drugs as the climate and environmental changes have also the ability to induce the toxicity. For example, some studies have reported that seawater acidification is detrimental to marine wildlife, due to its ability to enhance toxic effects caused by environmentally realistic concentrations of pharmaceuticals.<sup>109–111</sup> Although this information has been presented in the literature, there is a need to conduct more investigations on various factors that could affect the toxicity of pharmaceuticals toward marine organisms. The authors of the present paper are of the view that the conditions affecting the toxic effects cannot be generalized as such effects could be related to a selected group of pharmaceuticals.

Numerous studies have reported the presence of NSAIDs and analgesics in mussels (Table 3). Similarly, the toxic effects of these drugs on mussels are well-documented in the literature. Paracetamol has been associated with the potential to cause several major changes related to the reproductive system of mussels.<sup>112</sup> Diclofenac, which is an NSAID that has always been linked to more toxic effects, has been found to cause oxidative stress to mussels and enhance their lipid peroxidation.<sup>113,114</sup> These observations were not influenced by the changes in temperature. Similarly, ibuprofen was found to exert oxidative stress in the gills of the mussels.<sup>115</sup> The toxic effects of ibuprofen in mussels were observed in exposure concentrations that are as low as 250 ng L<sup>-1</sup>.<sup>116,117</sup> Some studies have already found the concentrations of ibuprofen exceeding 250 ng L<sup>-1</sup> in seawater for ibuprofen.<sup>56,67</sup> This demonstrates the potential toxicity of this drug towards mussels in different regions. In a similar context, the environmentally relevant concentrations of diclofenac were observed not to affect the condition of mussels.<sup>118</sup> However, it is not understood if the prolonged exposure of diclofenac at environmentally relevant concentrations to mussels could induce toxic effects. One study reported an impaired

regulatory capacity of rainbow trout when exposed to salicylate and ibuprofen in seawater.<sup>119</sup> Some of these pharmaceuticals cause oxidative stress to the seaweeds as well.<sup>120</sup>

Although there are toxic effects recorded for NSAIDs and analgesics in seawater toward marine organisms,<sup>121,122</sup> this information cannot be generalized to other pharmaceuticals. Issues such as the concentrations of these drugs in seawater, long-term exposure, and the type of marine species could have effects on toxicity. The accumulation of pharmaceuticals in marine organisms is drug-specific.<sup>123</sup> For example, one study observed the accumulation of diclofenac and nimesulide in mussels while compounds such as paracetamol, ibuprofen, and ketoprofen remained undetected.<sup>124</sup> Even drugs bound to the marine sediments are reported to have toxic effects, thereby, resulting in disturbing the marine ecosystem.<sup>125</sup>

## 8. Occurrence of non-steroidal anti-inflammatory drugs and analgesics in marine sediments

The information presented in Table 4 shows the occurrence and quantities of NSAIDs and analgesics in marine sediments. Although there seems to be a lesser interest in the monitoring of these drugs in marine sediments, the presented data shows that these compounds sink from the oceanic waters into the sediments. Thus far, the monitored drugs seem to be those that are mostly consumed and already well-known as environmental contaminants. Furthermore, the most consumed and environmentally widespread NSAID, ibuprofen, has been observed to contain a higher concentration of 49.0 ng g<sup>-1</sup> in marine sediments<sup>126</sup> compared to other drugs. Notably, NSAIDs and analgesics quantities in marine sediments of Augusta Bay (Southern Italy) were found to pose negligible risks to the health of the ecosystem.<sup>127</sup>

The extensive literature search conducted for the present study showed limited investigations on the occurrence of the drugs under this study in marine sediments. However, the limited information available shows the sediments as the potential sink of these drugs which could present severe health risks over time. This is because the drugs sorbed into the sediments could be released back into the oceanic waters over time, thus prolonging their presence in such conditions. The available information can be expanded by conducting more research in



Table 4 Concentrations (ng g<sup>-1</sup>) of non-steroidal anti-inflammatory drugs and analgesics found in marine sediments

Compound	Study location	Sampling year	Concentration (ng g <sup>-1</sup> )	Reference
Naproxen	Augusta Bay, Southern Italy	2017–2018	Nd-0.3	61
Ibuprofen	Todos os Santos Bay and the north coast of Salvador, Brazil	Not provided	0.77–18.8	128
	Puget Sound, Washington, USA	2010	21.7	129
	Santos Bay, Sao Paulo, Brazil	2015	49.0	130
Diclofenac	Todos os Santos Bay and the north coast of Salvador, Brazil	Not provided	<0.1–1.06	131
	Augusta Bay, Southern Italy	2017–2018	Nd-1.1	61
Ketoprofen	Augusta Bay, Southern Italy	2017–2018	Nd-8.8	61
	Jiaozhou Bay, North China	2018	0.98–3.32	132
Indomethacin	Jiaozhou Bay, North China	2018	0.01–0.19	132
Paracetamol	Masan Bay, Korea	2009	<MQL-2.21	133
	Augusta Bay, Southern Italy	2017–2018	Nd-5.10	61
	Capbreton Submarine Canyon, North Atlantic Ocean	2017	<MQL-7.90	134
Codeine	Masan Bay, Korea	2009	<MQL-4.15	135
Salicylic acid	Mediterranean coastal lagoon, SE Spain	2010	Nd	136

different parts of the world where non-target analysis or suspect screening could avail more information on unknown drugs present in marine sediments. The application of this approach in sediment samples from Qatar has resulted in the discovery of other organic compounds such as those belonging to plasticizers, which were not going to be discovered when performing the targeted screening of just pharmaceuticals.<sup>137</sup>

Overall, due to the scarcity of analytical data on the analysis of NSAIDs and analgesics in marine sediments, the fate of these drugs in marine ecosystems remains poorly understood. It is crucial to close such research gaps as some pharmaceuticals bound to marine sediments have been reported to have toxic effects on some organisms.<sup>138</sup> In this case, ibuprofen is one of the drugs that have been linked to DNA damage after the exposure of amphipods to sediment spiked with a mixture of these drugs and other compounds.<sup>139</sup> However, the binding of pharmaceuticals into sediments has been reported to be influenced by several factors which include the nutrients of the overlying water, the total organic carbon, and the clay of the sediments.<sup>140</sup> This means understanding these dynamics in marine environments could assist in the estimation of the affinity of pharmaceuticals between the aqueous phase and the sediments.

## 9. Major knowledge gaps and future outlook

Similarly to the other environmental matrices and other pharmaceutical classes, there is little focus on the analysis of the metabolites in the marine and coastal environments. The present review discovered little evidence presented on the metabolites of NSAIDs and analgesics, where the focus was directed to the well-known water contaminants in the form of ibuprofen and diclofenac. Although the metabolites of ibuprofen and diclofenac were discovered in seawater, their potential transformation back to the parent compounds under environmental conditions is not understood. However, the presence of such compounds in seawater indicates a need to screen the seawater for the occurrence of the metabolites of other NSAIDs and analgesics.

The scarcity of information on the occurrence of metabolites of NSAIDs and analgesics in marine organisms and seafood was observed. Similarly, the scientific information on the occurrence of parent compounds and their metabolites in cooked seafood is lacking. This means there is insufficient information on the potential transformation of the investigated drugs during the preparation of seafood for human consumption. Therefore, this knowledge gap showcases a need to conduct studies that will provide more information to the body of scientific knowledge about the influence of cooking seafood on the occurrence of NSAIDs and analgesics in marine organisms. At the same time, there seems to be a lack of interest in evaluating the presence of some drugs (such as phenazone, fenoprofen, *etc.*) in marine organisms. This could be easily solved by conducting the non-target analysis to establish the occurrence of these drugs in a wide range of samples (including seawater). Once such information is available, a more detailed analysis can be conducted.

Marine sediments have been shown to sorb some investigated drugs from oceanic waters. However, there is still limited work conducted in this regard. Future work should focus on non-target analysis or suspect screening, where a wide range of organic contaminants can be investigated in marine sediments. This approach would provide more information on which pharmaceuticals need to be monitored in marine sediments. Furthermore, such an investigation needs to be conducted in other geographical areas, as the presented data seems to focus on marine environments in areas around Europe and America.

## 10. Overview and perceptions

In this paper, we critically reviewed the available information in the literature which has reported on the occurrence of NSAIDs, analgesics, and their metabolites in the coastal environment. The notable routes of these drugs to the coastal environment include transfer from the rivers through the estuaries to the oceans and disposal into the oceans *via* the effluents of the WWTPs which are discharged directly into the marine environment. Hence, various pharmaceuticals under investigation have been detected in seawater and seafood. In some cases,



these pharmaceuticals have been detected in marine sediments which could extend their availability in marine waters due to desorption from sediments to surrounding water bodies. Based on the reviewed literature, there are no clear trends in relation to the concentrations of these compounds in the coastal environment across different continents. In this review, several research gaps have been identified that could influence the direction of future research. Notably, most studies focused on measuring the parent compounds rather than the transformation products. Future research is expected to focus largely on investigating the transformation of pharmaceuticals in the coastal environment, including marine organisms and to monitor the occurrence of metabolites in a wide range of sample matrices, including seafood. This is necessary to understand the fate of these contaminants.

## Author contributions

Both authors contributed to the study's conception and design. Most sections were originally drafted by Lawrence M. Madikizela, edited and approved by Ronewa Netshithothole. The graphics materials were conceptualized by Lawrence M. Madikizela and crafted by Ronewa Netshithothole. Therefore, approximately 80% of the first draft of the manuscript was written by Lawrence M. Madikizela, with Ronewa Netshithothole drafting the rest of the paper. Both authors read the entire manuscript and approved the final manuscript.

## Conflicts of interest

The authors declare no competing financial interest.

## Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

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