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Sources, impacts and trends of pharmaceuticals in the marine and coastal environment

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There has been a significant investment in research to define exposures and potential hazards of pharmaceuticals in freshwater and terrestrial ecosystems. A substantial number of integrated environmental risk assessments have been developed in Europe, North America and many other regions for these situations. In contrast, comparatively few empirical studies have been conducted for human and veterinary pharmaceuticals that are likely to enter coastal and marine ecosystems. This is a critical knowledge gap given the significant increase in coastal human populations around the globe and the growth of coastal megacities, together with the increasing importance of coastal aquaculture around the world. There is increasing evidence that pharmaceuticals are present and are impacting on marine and coastal environments. This paper reviews the sources, impacts and concentrations of pharmaceuticals in marine and coastal environments to identify knowledge gaps and suggests focused case studies as a priority for future research.

1. Introduction

Over the last 15 years increasing attention has been paid to understanding the presence and impacts of pharmaceuticals entering or detected in freshwater ecosystems [1]. By contrast, significantly less attention has been paid to understanding releases of pharmaceuticals from sewage and other routes into coastal environments and their potential marine impacts. There is now widespread recognition of the need for a cradle-to-grave stewardship of medicines for minimizing environmental exposure while promoting human and animal health [2]. Large centres of human population are often found in coastal areas and pharmaceutical releases via municipal effluent discharges are probable. For example, Martínez *et al*. [3] reported that based on 2003 data, over 2.3 billion people live within coastal limits (representing 41% of world global population) and more than 50% of coastal countries have 80–100% of their total population within 100 km of the coastline. Twenty-one of the world's 33 megacities (cities with more than 8 million inhabitants) are on the coast and face a range of environmental management issues [4]. Global demographic trends towards coastal conurbations suggest increasing numbers of people living along coastlines, while waste management from coastal megacities is increasingly recognized as a major challenge [3,5,6]. These trends suggest the potential for increasing inputs of human pharmaceuticals into coastal environments and therefore the need to address potential exposure scenarios and implications for marine risk assessments of drug residues and their transformation products [7–9]. Marine risk assessments for pharmaceuticals are also relevant to veterinary medicines used in aquaculture [10–12].

More broadly, if releases of pharmaceuticals into coastal ecosystems are high enough to induce biological impacts, they may act as additional stressors on marine ecosystems already impacted by climate change, eutrophication and over-fishing [13]. It is estimated that 49% of marine ecosystems worldwide are strongly impacted by anthropogenic stressors with significant economic implications [3,14]. If unmanaged, multiple anthropogenic impacts on marine

ecosystems may also affect coastal fisheries and aquaculture. For example, human health concerns linked to aquaculture include exposure to pharmaceuticals through consumption of seafood and the induction and spread of antibiotic resistance [15,16]. This paper reviews the sources, concentrations and potential impacts of human and veterinary pharmaceuticals in coastal environments to support risk assessments and to identify key knowledge gaps as priorities for future research. The scope of the review has been limited to human pharmaceuticals and antibiotics used as veterinary medicines.

2. Sources of pharmaceuticals in marine environments

(a) Sewage

Sewage effluent is recognized as a major source of multiple pharmaceuticals, including their metabolites, entering aquatic environments. Removal rates for pharmaceuticals in wastewater treatment plants (WWTPs) range from less than 10 to almost 100% and depend on the physico-chemical characteristics of the pharmaceutical and type of treatment technology [17]. Sources of human pharmaceuticals in sewage include patient use in the community, discharges from hospitals and, in some cases, wastewater from pharmaceutical manufacturing [18]. Sewage can be discharged into marine environments through coastal and ocean outfalls for WWTPs combined sewer overflows and via rivers receiving WWTP effluents [19,20]. For example, the Yangtze River in China transports sewage from 400 million people out to sea and releases an estimated 152 tonnes of pharmaceuticals annually [21]. Sewage may also be discharged into the marine environment from boats. Ships, including cruise liners, may discharge (under Annex IV of MARPOL 73/78 ships) treated sewage into the sea 4 nautical miles from the nearest land and 12 nautical miles for untreated sewage [22]. The volumes of sewage discharged can be significant as cruise liners can have passenger numbers equivalent to populations found in small towns. Sewage effluents from small boats, on the other hand, may not receive any treatment prior to being discharged. Typhoon shelters for small boats were a point source of antibiotics in Victoria Harbour, Hong Kong [23]. As discussed by Kookana *et al.* [24] in this issue, many large cities in Asia still rely on septic tanks with poorly managed septage which can contaminate surface and groundwaters with pharmaceuticals and ultimately be discharged into coastal areas.

Sewage impacted groundwater can also be a source of pharmaceuticals entering coastal waters. Pharmaceuticals have been detected in a coastal aquifer on the Yucatan Peninsula, Mexico injected with municipal sewage discharges [25]. Reuse of treated domestic wastewater for irrigation contributed to pharmaceutical contamination in groundwater on Mallorca [26]. Throughout the world rural and peri-urban areas including popular coastal holiday areas are reliant on septic tanks or small decentralized systems for sewage treatment disposal [27]. Depending on their treatment efficiency and the capacity of the local soils, these systems are a potential source of pharmaceuticals in coastal waters via leakage to ground and surface waters [28,29].

(b) Aquaculture

Globally the production of seafood through aquaculture is rapidly increasing with over 90% of aquaculture based in Asia [30]. A range of veterinary medicines including antibiotics, also registered for human use, is used prophylactically and to control disease outbreaks in marine aquaculture. Up to 75% of the administered dietary dose of a veterinary medicine can be lost to the surrounding environment. The loss mechanisms include dispersal of non-ingested pellets, gill and renal excretion of the unprocessed drug, and renal and faecal excretion of drug metabolites [31]. Other marine organisms in the vicinity including wild fish feed on leftover food and faecal material from marine aquaculture potentially further spreading pharmaceuticals and their transformation products. Pond-based farms located in coastal areas are also a source of antibiotics entering coastal waters through leaks and discharge of wastewaters which can contain elevated concentrations of pharmaceuticals. Extremely high antibiotic concentrations of up to 2.5 mg l^{-1} were measured in water samples from shrimp ponds in Vietnamese mangroves [32]. The ancient practice of wastewater- (human and animal) fed aquaculture, although declining, still occurs in some parts of Asia [30]. Aquaculture practices including the use of antibiotics vary greatly between countries [33].

(c) Animal husbandry and horticulture

Animal husbandry and horticulture along rivers and in coastal areas may also contribute to loadings of pharmaceuticals entering coastal waterways [17,34]. Antibiotics are added to animal feeds and in some cases drinking water to treat disease particularly in feedlots housing large numbers of animals [35]. The use of low doses of antibiotics in feed as growth promoters still occurs in some regions of the world despite being banned in Europe [36]. Some countries permit the use of antibiotics including oxytetracycline and streptomycin on horticultural crops [17]. Application of municipal biosolids to farmland as fertilizer is a further source of pharmaceuticals entering agricultural systems [37].

(d) Waste disposal

Waste disposal in coastal areas is a further source of pharmaceuticals entering the marine environment. Leachate from coastal landfills and seafills may be a pathway for pharmaceuticals disposed of in household and clinical wastes to enter coastal waters. Landfill leachate on the island of Mallorca contained up to 27 000 ng l^{-1} total concentration of pharmaceuticals [26]. Historically, in some regions drug manufacturing waste, sewage sludge and animal manure were dumped at sea [38,39].

(e) Environmental fate of pharmaceuticals in marine environments

Once discharged into aquatic environments, pharmaceuticals and their metabolites can undergo biotic and abiotic transformation (degradation) and sorb to suspended particulate matter (SPM) and sediments, and in some cases accumulate in the tissues of aquatic organisms [40]. Existing data for the environmental fate of pharmaceuticals generated for freshwater environments may not necessarily be transferable to marine environments. The differences in physico-chemical conditions including salinity, pH and organic matter between freshwater and seawater can impact on the environmental fate of pharmaceuticals [41]. The environmental fate of ionizable pharmaceuticals may be altered by the increased pH of seawater. Photodegradation may be a less important removal

mechanism in coastal waters compared with more shallow freshwater environments due to light attenuation. Indirect photodegradation mechanisms may differ to those occurring in freshwater due to differences in water composition [42,43]. There is some evidence to suggest that the environmental fate of pharmaceuticals can differ between fresh and saline environments. The transformation behaviour of ibuprofen differed between freshwater and seawater [44] and prochlorperazine was more stable in seawater than freshwater [43].

3. Current state of knowledge of pharmaceutical concentrations in marine environments

(a) Seawater

The assessment of the concentrations of pharmaceuticals in coastal environments has been limited. Forty-nine studies have reported concentrations for individual pharmaceuticals and metabolites detected in estuarine and coastal waters. Only studies published since 2000 are considered. Seventy per cent of these studies have been published since 2010. The geographical breakdown for the studies is Europe (20), Asia (21), North America (6), South America (1) and Oceania (1). The studies included those investigating the presence of 30 or more pharmaceuticals over a wide spatial area [45] studies targeting specific classes of compounds, for example, sulfonamide antibiotics [34] and method validation studies screening only a limited number of 'real' samples [46].

To date, 113 pharmaceuticals and pharmaceutical metabolites have been detected in coastal waters at concentrations ranging from 0.01 to 6800 ng l^{-1} with the maximum concentrations for 69 of these compounds exceeding the European Medicines Agency threshold for predicted environmental concentrations for surface waters of 0.01 μg l^{-1} [47] (electronic supplementary material, tables S1–S3). Data were most frequently reported for antibiotics (41 compounds) followed by non-steroidal anti-inflammatories (8) and analgesics (8). Twenty compounds were reported in five or more studies (table 1) including acetaminophen, atenolol, carbamazepine, clarithromycin, diclofenac, 17α-ethinyloestradiol, erythromycin-H_2O, gemfibrozil, ibuprofen, ketoprofen, naproxen, norfloxacin, oxafloxacin, propanolol, roxithromycin, sulfadiazine, sulfadimidine, sulfamethoxazole, tetracycline and trimethoprim. The higher frequency of reporting for concentrations of antibiotics and painkillers for the marine environment are consistent with Hughes *et al*. [1] synthesis of pharmaceutical data for freshwater environments.

Current methodologies targeting the dissolved fraction of pharmaceuticals may be underestimating the environmental concentrations and the potential impacts on aquatic ecosystems [49]. The majority of the studies published to date have reported pharmaceutical concentrations in seawater for the dissolved fraction only with filtering being the first step in sample extraction methods. Two studies have investigated pharmaceutical concentrations in SPM. Mean concentrations of pharmaceuticals in SPM (more than 0.7 μm) from the Long Island Sound Estuary ranged from 7 to 44 ng g^{-1}. The pharmaceuticals detected in the SPM were either hydrophobic, for example, tamoxifen, or positively charged, for example, clarithromycin, and up to 47% of the total concentration was sorbed to the SPM [19]. Yang *et al*. [19] compared concentrations of pharmaceuticals in the sediment, SPM and the colloidal and soluble phases in the Yangtze River Estuary and adjacent coastal areas. SPM concentrations were up to 5 times higher than that in the sediments. The colloidal phase had sorption affinities of 2–4 orders magnitude greater for pharmaceuticals than the SPM and contributed up to 45% of the target pharmaceuticals in the Yangtze system.

Pharmaceutical metabolites and transformation products can be more persistent and more toxic than the parent compound [50]. Twenty-one studies reported data for pharmaceutical transformation products in coastal waters with erythromycin-H_2O the most commonly reported transformation product. Transformation products can be present in WWTP effluents and surface waters at concentrations equivalent to or exceeding the parent compound. For example, concentrations of metabolites of carbamazepine (carbamazepine epoxide), diclofenac (4′- and 5-hydroxy diclofenac) and atorvastin (*o*- and *p*-hydroxy atorvastin) in wastewater discharged into the Oslofjord were present at higher concentrations than the parent compounds [51]. Similarly the concentrations of sulfonamide metabolites measured in Liaodong Bay, China were comparable to those of the parent compounds [34].

Pharmaceuticals have been detected significant distances from their source(s). Pharmaceuticals were detected at a reference site approximately 9 km downstream from the WWTP outfall in Halifax Estuary [52]. Similarly, pharmaceuticals in the Baltic Sea were detected 17 km downstream of WWTP outfalls [53]. Zhang *et al*. [54] detected antibiotics including erythromycin-H_2O, sulfamethoxazole and trimethoprim (0.1–16.7 ng l^{-1}) 400 km offshore of the coast of China.

(i) Seasonal trends

Identifying seasonal trends for pharmaceutical concentrations in marine and coastal waters is crucial for determining time periods during which sensitive ecosystems may be at greater risk from exposure [55,56]. To date only a handful of studies have investigated seasonal trends for pharmaceutical concentrations in the marine environment. Pharmaceutical concentrations in the Yangtze River and Pearl River Estuary were higher in the dry season than in the wet season [57]. Similarly, heavy rainfall events reduced pharmaceutical concentrations in Jamaica Bay, a wastewater impacted estuary [20]. Conversely, Zheng *et al*. [58] and Qi *et al*. [21] reported increased river water concentrations of antibiotics in China during the wet season and attributed the increased concentrations to increased runoff of veterinary medicines and decreased efficiency of WWTPs due to increased wastewater flow. Temporal trends in pharmaceutical concentrations were not observed in Southern California coastal waters with relatively constant year-round temperatures [59]. By contrast, Hedgespeth *et al*. [55] reported higher probability of detecting acetaminophen in seawater from Charleston Harbor, South Carolina during winter. Pharmaceuticals were transported further downstream when the Aura River (Finland) was covered by snow and ice with the spring snowmelt increasing the speed of transport [60].

Seasonal trends in WWTP effluent pharmaceutical concentrations have also been reported which will in turn influence seawater concentrations. For example, total concentrations of NSAID drugs and bezafibrate were 3–5 times higher in effluent in winter than in summer [60]. Reduced removal rates in WWTPs and in surface seawaters can occur during colder months due to lower temperatures and

Table 1. Summary of seawater and biota concentrations and marine ecotoxicology data for the human and veterinary pharmaceuticals most frequently detected in seawater (ww, wet weight; dw, dry weight).

		seawater		marine biota			marine ecotoxicology data		
					concentration range [ng g^{-1}]				
pharmaceutical	class[a]	no. studies	concentration range [ng L^{-1}]	no. studies	dw	ww	no. studies	organisms tested	most sensitive endpoint reported [µg L^{-1}]
acetominophen	analgesic	7	1.9–1952	1	65–115		1	mussels	feeding rate LOEC = 23
ibuprofen	analgesic	18	0.01–2370				2	algae mussels	biochemical responses 0.25
carbamazepine	anticonvulsant	18	0.4–1400	4	1.3–11		2	algae amphipods	21d ^{geotaxis}NOEC = 1
erythromycin-H_2O	antibiotic metabolite	9	0.1–1900	2	0.1–2				
clarithromycin	antibiotic	8	0.3–17.6						
norfloxacin	antibiotic	8	2.3–6800	3	370	2.7–255			
ofloxacin	antibiotic	7	3.5–5100	3	5–242				
roxithromycin	antibiotic	8	0.1–630						
sulfadiazine	antibiotic	10	0.4–71.8	3	2.7	3.0–5.2			
sulfadimidine	antibiotic	9	0.2–219	3	29.8–430	3.9			
sulfamethoxazole	antibiotic	18	0.6–765	2	20.1	2.3			
tetracycline	antibiotic	7	2.4–313	1		1.9	1	bacteria diatom	^{growth}EC50 = 16000
trimethoprim	antibiotic	20	0.2–870	1	<4–9				
atenolol	anti-hypertensive agent	5	3.8–293	2	0.3–13				
propranolol	anti-hypertensive agent	5	0.3–142	1	19–52		3	mussels	^{Feedingrate}NOEC = 11
gemfibrozil	hypolipidemic agent	11	1–758						
diclofenac	NSAID	11	0.6–843				7	algae amphipods copepods decapods diatoms mussels	biochemical responses 0.25
ketoprofen	NSAID	7	0.6–805						
naproxen	NSAID	8	1.1–130						
17α-ethinylestradiol	SERM	9	0.1–38	2	7.2–38	2.7–3.4[b]	2	copepod echinoderm	^{development}EC50 = 30.3

[a]Class descriptors as used in DrugBank [http://www.drugbank.ca/; [48]].

[b]Units are ng g^{-1} lipid.

resulting in lower rates of biological activity enhancing the persistence of pharmaceuticals in marine ecosystems [43]. Reduced sunlight levels during winter can inhibit removal of pharmaceuticals susceptible to photodegradation [60]. Snowmelt reduced pharmaceutical concentrations in effluent in Norway [61]. Seasonal trends in pharmaceutical usage should also be considered [62]. Antibiotic use patterns can be influenced by a number of factors. High antibiotic use in winter can be due to the inappropriate use for treating respiratory tract infections including the common cold and viral infections [63]. Anti-allergenic medicines may also have a seasonal profile. Wastewater concentrations of over-the-counter anti-allergenic cetirizine peaked in summer and followed the pollen season [64]. Certain disease-specific pharmaceuticals, such as antiviral drugs, will peak during disease outbreaks, as has been demonstrated for oseltamivir (Tamiflu) during the recent influenza A(H1N1)pdm09 outbreak in Europe [65].

(b) Sediment data

Sediments are a reservoir for the accumulation of pharmaceuticals in marine ecosystems and can act as a secondary pollution source from which pharmaceuticals can be released by changes in environmental conditions such as salinity and pH [57]. Sediments can be resuspended during tidal changes and during storm events exposing marine biota to sorbed pharmaceuticals. Twenty-two studies reporting sediment concentrations of pharmaceuticals for estuarine and marine environments have been published since 2000. In total, 62 pharmaceuticals and transformation products have been detected in marine sediments at concentrations up to 2 615 000 ng g^{-1} wet weight (electronic supplementary material, tables S4 and S5). Excluding the extremely high concentrations of antimicrobials measured in marine shrimp aquaculture pond sediments [32], 17α-ethinyloestradiol was the pharmaceutical measured in sediment at the highest concentration (129.8 ng g^{-1}). 17α-ethinyloestradiol was also the pharmaceutical most frequently detected with sediment concentrations reported for nine studies. All other pharmaceutical compounds were reported in a maximum of three studies. Data were most frequently reported for antibiotics (26 compounds) followed by anti-hypertensive agents (6). Marine sediment data for pharmaceutical transformation products and metabolites are currently almost non-existent with only four studies reporting concentrations of pharmaceutical metabolites in marine sediments. Langford & Thomas [51] reported concentrations of α-hydroxy metoprolol (1–3 ng g^{-1}) and simvastatin hydroxy carboxylic acid (2–4 ng g^{-1}) in sediments collected from Oslofjord in Norway. Erythromycin-H_2O was reported in San Francisco Bay (3.4 ng g^{-1} dw) [66] and in the Pearl River Estuary, China (0.7–14 ng g^{-1} dw) [57]. Only nine of the 22 studies analysed both seawater and sediment samples.

(c) Factors influencing pharmaceutical concentrations in seawater and sediment

Factors reported to increase concentrations of pharmaceuticals in seawater and sediment include proximity to WWTP outfalls [67,68], higher effluent outflows [69], size of the urban area and population [11,70,71], the number of rivers discharging into coastal waters [70], the type of wastewater treatment [19], low mixing and dilution rates for WWTP effluents [72], the hydrodynamic flushing and residence time for confined water bodies [61,73,74], the type, scale and density of animal husbandry [34,58] and proximity to aquaculture [74,75]. Higher concentrations of pharmaceuticals have been measured in estuaries during low and incoming tides [76]. Re-suspension of sediments during weather events including monsoons and during incoming tides can increase surface water concentrations of pharmaceuticals. Stratification of pharmaceuticals in the water column with higher concentrations being measured at the surface has been reported in the Long Island Sound Estuary [19] and in Victoria Harbour, Hong Kong [77]. Local conditions may inhibit wastewater treatment resulting in higher surface water concentrations. For example, Arctic permafrost conditions reduce the efficiency of WWTPs [78].

(d) Marine biota

Data for accumulation of pharmaceuticals in marine biota are scant most probably because of the lack of reliable analytical methods for these challenging analytical matrices [66]. Fourteen studies were identified reporting data for concentrations of pharmaceuticals in finfish, crustaceans and shellfish (electronic supplementary material, table S6). Ten of these studies reported results for filter-feeding marine shellfish and five for marine finfish. Tissue concentrations of 60 pharmaceuticals and seven metabolites have been reported with antibiotics being the most frequent class reported (38) followed by anti-hypertensive agents (6). Carbamazepine, ciprofloxacin and enrofloxacin were the most frequently reported compounds each being reported in four studies. Only three studies reported concentrations for pharmaceutical transformation products including erythromycin-H_2O, salicylic acid and metabolites of venlafaxine [62,66,79]. Higher concentrations of venlafaxine metabolites than parent compound were detected in mussels (*Mytilus galloprovincialis*). As some marine organisms also metabolize pharmaceuticals [80], a wide range of metabolites could potentially be present.

Marine organisms can be exposed to pharmaceuticals over widespread geographical areas. The anti-depressant sertraline was detected at 43 of 68 mussels sampling stations along the California Coast [81]. Antibiotics were detected in 142 out of 190 mollusc samples collected from nine cities along the Bohai Sea in China [82]. Detectable concentrations of pharmaceuticals were measured in wild seafood samples purchased from Czech supermarkets including squid caught in the Eastern Central Pacific, herring from the Atlantic Northeast and shark from the Eastern Central Atlantic [83].

Pharmaceuticals have been detected in marine organisms despite not being detected in water or sediment. Ranitidine, sertraline and enlapril were detected in mussels from San Francisco Bay but not in seawater [66]. Diazepam was detected in all liver samples of hornyhead turbot but only infrequently detected in sediments near wastewater outfalls in the Southern Californian Bight [84]. Fluoroquinolone antibiotics were detected less frequently in water than in fish from six sampling sites in two marine aquaculture regions of the Pearl River Delta, China [74].

Pharmaceutical uptake in marine organisms is compound, species and body-tissue specific. Oxytetracycline preferentially accumulated in the viscera and oxolinic acid in the gills of *Mytilus edulis* [85]. Concentrations of fluoroquinolones antibiotics in fish from marine aquaculture regions of the Pearl River Delta were higher in liver tissue than in muscle tissue

[74]. Fluoxetine tissue concentrations in *Mytilus galloprovincialis* followed the order digestive gland > gills > mantle/gonads [86]. Li *et al.* [82] reported differences in uptake of antibiotics between mollusc species harvested from the Bohai Sea, China. In some situations, gender may also influence uptake of pharmaceuticals by marine organisms. Higher concentrations of diazepam were measured in male than female *Pleuronichthys verticalis* (hornyhead turbot) [84]. These preferential uptakes have implications for ecotoxicological impacts and human exposure to pharmaceuticals via consumption of seafood.

Field data for bioaccumulation of pharmaceuticals in marine organisms is limited. Field-derived bioaccumulation factors (BAFs) for pharmaceuticals in mussels from San Francisco Bay included dehydropnifedipine (290–764), carbamezepine (90–322), diphenhydramine (118–218), triamterene (57–71) and erythromycin-H_2O (11–54). The BAFs varied between sites by up to a factor of 7 [66]. Bioconcentration factors (BCFs) ranged from 1300 to 1500 for uptake of 17α-ethinyloestradiol by mussels (*M. galloprovincialis*) harvested from Venice Lagoon, Italy [87]. Field-derived BAFs for antibiotics ranged from 0 to 11 000 in shellfish collected from the coastal environment of Dalian in China. Based on the average BAFs, the authors concluded that sulfamethazine, sulfamethiazole, sulfamonomethoxine and doxycycline are potentially bioaccumulative and that sulfadiazine, sulfameter, sulfamethoxypyridazine and chloramphenicol are bioaccumulative in shellfish [88].

The uptake of pharmaceuticals by marine bivalves has been investigated using laboratory assays. Maximum BCF values in mussels of 100 were reported for tetrazepam and 51 for diazepam [89] and ranged from 200 to 800 for fluoxetine [86]. BAFs for diclofenac and propanolol in mussels (*Mytilus edulis*) ranged between 10 and 180 [90] and from 0.12 to 2 for oxytetracycline and from 0.27 to 0.55 for oxolinic acid [85]. No studies could be found reporting BCFs or BAFs for the uptake of pharmaceuticals by marine finfish.

Only one study has reported pharmaceutical concentrations in higher tropic level marine organisms. Federova *et al.* [83] reported a flumequine concentration of 2.9 ng g^{-1} in an Eastern Central Atlantic shark sample. It is probable that trophic transfer of pharmaceuticals to top level predators including sharks, dolphins and whales is occurring in coastal ecosystems. Six anti-depressants and ethinyloestradiol were measured at trace concentrations (below quantitative limit to 4 ng ml^{-1}) in plasma from bull sharks (*Carcharhinus leucas*) caught in the Caloosahatchee River, a wastewater impacted freshwater tributary of Florida's Charlotte Harbour [91]. The personal care product triclosan has been detected in plasma from wild Atlantic bottlenose dolphins (*Tursiops truncatus*) [92] and UV filters have been detected in Franciscana dolphins (*Pontoporia blainvillei*) [93]. Coastal avian species that feed on fish and shellfish may also be chronically exposed to pharmaceuticals.

4. Biological impacts in marine organisms

(a) Marine ecotoxicology studies

While the body of work on the aquatic ecotoxicology of both human and veterinary pharmaceuticals is steadily growing, there is currently minimal data on the toxicity of pharmaceuticals to marine organisms. Only one study reporting field ecotoxicity data for marine organisms could be found. Exposure of benthic microalgal communities in the North Inlet Estuary (USA) to the antimicrobial tylosin in sediments resulted in reduction of microalgal biomass and primary productivity and retarded diatom growth [94]. Laboratory ecotoxicity data could be found for 22 compounds and for the majority of compounds only one or two studies have been undertaken using marine organisms (electronic supplementary material, table S7). Fluoxetine was the exception, with marine ecotoxicity data reported in seven studies. Marine ecotoxicity laboratory data could be found for only seven of the 20 pharmaceuticals most frequently reported in seawater highlighting the current gap between researchers focusing on environmental presence and researchers focusing on ecotoxicity (table 1). Only one of these studies investigated the toxicity to sediment dwelling organisms [95]. A limited range of marine organisms have been tested to date including primary producers (e.g. microalgae and diatoms), primary consumers (e.g. bivalve molluscs and copepods) and consumers (e.g. crustaceans and fish). It is of great concern that in most studies nominal rather than measured pharmaceutical exposure concentrations were used.

Despite the limited number of studies, a wide variety of adverse effects have been reported for marine organisms with the effects being both test species and pharmaceutical specific. Examples of reported adverse effects for analgesics include reduced feeding rates [96], impacts on survival [97], reduced mussel byssus strength [90] and changes in immune response [96] and biochemical markers [98]. Studies have tended to focus on endpoints related to the therapeutic mode of action of the pharmaceutical. For example, reduced survival and developmental effects have been reported for anti-cancer drugs whereas studies on anti-depressant drugs have focused on neurobehavioural endpoints and spawning [99,100]. The reported no observable effect concentrations (NOECs) and lowest observable effect concentrations (LOECs) ranged from several orders of magnitude above environmental concentrations to comparable to reported environmental concentrations. For example, despite the NOECs for diclofenac for effects on bysuss strength and oxidative stress in mussels of 1000 μg l^{-1}[101], transient tissue-specific changes were reported after a 7 day exposure to 0.25 μg l^{-1} diclofenac [98], a concentration well within the range reported in seawater (table 1).

Pharmaceuticals are present in marine ecosystems as mixtures complicating risk assessments. These complex mixtures may contain a wide variety of pharmaceuticals and other contaminants as well as a number of compounds from the same class (e.g. quinolone antibiotics) or with similar modes of action (e.g. non-steroidal anti-inflammatories) [102]. Additive effects have been reported for mixtures of pharmaceuticals on marine organisms. DeLorenzo & Fleming [103] investigated the toxicity of six pharmaceuticals and personal care products to the marine phytoplankton species *Dunaliella tertiolecta* both singly and in binary mixtures and reported additive toxicity for a mixture containing simvastatin and clofibric acid. As mixture toxicity effects including synergistic effects have also been reported for freshwater organisms and cell lines [104,105], NOECs and LOECs derived from single substance testing may not be sufficient for deriving environmental quality standards [106].

There is a need to assess the impacts of pharmaceuticals on marine food webs. Marine food webs could either be directly affected through bioaccumulation of pharmaceuticals in the food chain to toxic levels or indirectly through the loss of a key species particularly sensitive to pharmaceuticals. The impacts of pharmaceuticals on primary producers such as phytoplankton is a key concern for marine ecosystems due

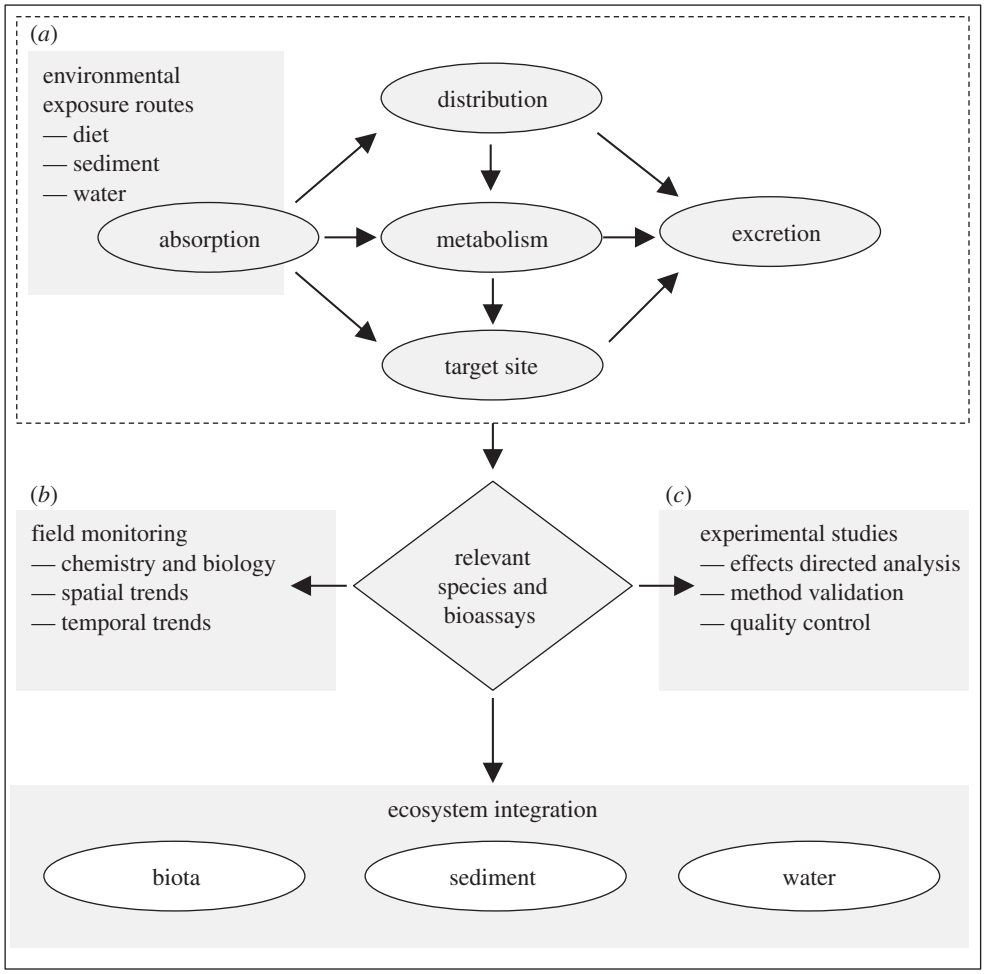

Figure 1. Adverse outcome pathways of chemicals fundamentally reflect patterns of absorption, distribution, metabolism, excretion and target sites in either acute or chronic exposure scenarios pertinent to marine contaminant monitoring. (Adapted from Hutchinson *et al.* [113].)

to the potential follow on effects on nutrient cycling and availability of food for other organisms [103]. Similarly, endocrine disrupting compounds which impact growth and reproduction in fish have the potential to affect predator and prey species [107].

(b) Antibiotic resistance

Exposure of microorganisms to sub-lethal concentrations of antimicrobial compounds including antibiotics can induce antibiotic resistance. The rapid development of antibiotic resistance in bacteria is considered to be a global health security emergency and attention is being focused on mechanisms of transfer of antibiotic-resistant bacteria between species and identifying aquatic environmental reservoirs [108]. As high rates of horizontal gene transfer have been reported for marine bacteria [109], the contribution of contaminants in the marine environment to induction of antibiotic resistance and pathways for dispersal of clinically relevant antibiotic-resistant pathogens warrant further investigation. The development of antibiotic resistance in marine bacteria has been linked with wastewater discharges and the use of antibiotics in aquaculture [33,58]. Widespread antibiotic resistance has been reported in fish, marine mammals and seabirds living in coastal waters including in the North Eastern United States [110]. Higher prevalence of antibiotic-resistant strains of bacteria has been reported for marine wildlife populations exposed to sewage [111] and there is evidence to suggest that the antibiotic-resistant bacteria present in seabirds are of human origin [112]. The presence of antibiotic resistance genes in marine ecosystems may be an indicator of ecological shifts occurring due to the presence of pharmaceuticals [113].

5. Data gaps and priorities for future research

This review has highlighted that human and veterinary pharmaceuticals and their transformation products (including metabolites) are present in coastal ecosystems. Occurrence data for the marine environment are only available for a tiny fraction of the large number of pharmaceuticals currently in global use. There are extremely limited laboratory ecotoxicology data for the impacts of pharmaceuticals on marine organisms and a marked lack of field data. As for other ecosystems, a forward-looking prioritization approach is needed for the marine risk assessment of both generic and novel prescription pharmaceuticals. For example, such an approach has been successfully used for Tamiflu that involved defining both the predicted exposure concentration (PEC_{marine}) and predicted no-effect concentrations ($PNEC_{marine}$) to provide a prospective risk assessment [8]. For the $PNEC_{marine}$ to be reliable, it is important to consider the mode of action of the pharmaceutical, for instance, through the evaluation of Adverse Outcome Pathways in freshwater organisms and to extrapolate this to marine species [114] (figure 1). An Adverse Outcome Pathway is a conceptual framework for the link between exposure, the interaction of a contaminant at the molecular level within a cell and an adverse outcome or toxicological endpoint at the individual or community level.

Mechanisms for the increased sharing of data also need to be developed and a number of schemes have been developed in Europe (see the Swedish scheme www.fass.se and http://www.lif.se/default.aspx?id=29916 and the Norman network's EMPODAT Database www.norman-network.net/empodat) and by individual companies through their Material Safety Data Sheets for specific pharmaceuticals. More widely, Daughton [56] recently proposed the development of a database on pharmaceutical occurrence in the environment, contributed to and curated by the wider science community.

The monitoring of prioritized pharmaceuticals and relevant metabolites in coastal environments should be considered as complementary to prospective risk assessments and include both dissolved and particulate fractions. In Europe, the Water Framework Directive (WFD; Directive 2000/60/EC) covers both freshwaters and transitional waters (the estuarine and coastal area up to one nautical mile, or 1.85 km, from the shore). Two hormones (17α-ethinyloestradiol and 17β-oestradiol) and diclofenac have been placed on a watch list for emerging pollutants under the WFD. In a global context, it would be prudent to develop a monitoring suite of priority pharmaceuticals and transformation products that can be used in conjunction with biological assays to identify marine environments at risk from major centres of pharmaceutical inputs (e.g. WWTPs from megacities, intensive areas of aquaculture and pharmaceutical manufacturing industries).

As highlighted in reviews for pharmaceutical concentrations in freshwater [1] there is a marked absence of data for pharmaceuticals in marine environments in many regions (notably Africa, South America and small island nations in Oceania). These data gaps could easily be overcome by collaboration between well-resourced groups, with access to appropriate technology and validated analytical methods in developed countries, and local scientists in developing countries, at the same time providing valuable scientific and technical training.

The majority of data reported to date for pharmaceutical concentrations in marine organisms are for antibiotics used in aquaculture. In contrast, there are limited data for the accumulation of other classes of pharmaceuticals, their metabolites and transformation products in marine organisms. Further research is required to identify appropriate analytical methods for risk assessments for fish and shellfish to ensure that potentially reversible pharmaceutical metabolite conjugates are accounted for.

There are insufficient data on the potential for impacts on higher trophic levels, either through trophic transfer of pharmaceuticals or indirect effects, such as limited availability of food, due to impacts on lower trophic levels including algae. For high priority pharmaceuticals, it would be desirable to extend the environmental assessment to include fish-eating birds and mammals as recently illustrated by Murray Smith *et al*. [115].

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