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Review

Emerging challenges of the impacts of pharmaceuticals on aquatic ecosystems: A diatom perspective

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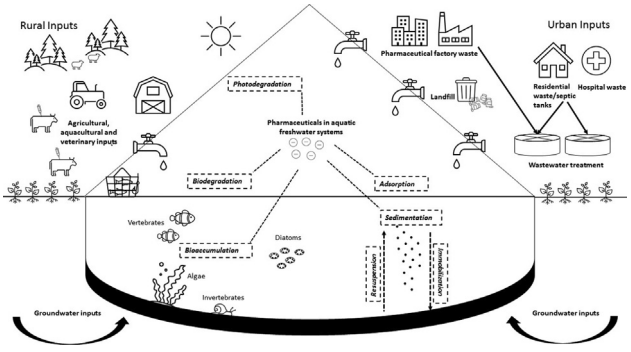
HIGHLIGHTS

- Pharmaceuticals in aquatic systems present a risk to inhabiting species.
- Effects of pharmaceuticals on diatoms represent a key knowledge gap.
- Diatoms have the potential to bioremediate and bio monitor pharmaceutical pollution.
- The North-South research disparity in pharmaceutical pollution needs addressing.

GRAPHICAL ABSTRACT



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ABSTRACT

Pharmaceuticals are a ubiquitous group of emerging pollutants of considerable importance due to their biological potency and potential to elicit effects in wildlife and humans. Pharmaceuticals have been quantified in terrestrial, marine, fresh, and transitional waters, as well as the fauna and macro-flora that inhabit them. Pharmaceuticals can enter water ways through different human and veterinary pathways with traditional wastewater treatment, unable to completely remove pharmaceuticals, discharging often unknown quantities to aquatic ecosystems. However, there is a paucity of available information regarding the effects of pharmaceuticals on species at the base of aquatic food webs, especially on phytoplankton, with research typically focussing on fish and aquatic invertebrates. Diatoms are one of the main classes of phytoplankton and are some of the most abundant and important organisms in aquatic systems. As primary producers, diatoms generate ~40 % of the world's oxygen and are a vital food source for primary consumers. Diatoms can also be used for bioremediation of polluted water bodies but perhaps are best known as bio-indicators for water quality studies. However, this keystone, non-target group is often ignored during ecotoxicological studies to assess the effects of pollutants of concern. Observed effects of pharmaceuticals on diatoms have the potential to be used as an indicator of pharmaceutical-induced impacts on higher trophic level organisms and wider ecosystem effects. The aim of this review is to present a synthesis of research on pharmaceutical exposure to diatoms, considering ecotoxicity, bioremediation and the role of diatoms as bio-indicators. We highlight significant omissions and knowledge gaps which need addressing to realise the potential role of diatoms in future risk assessment approaches and help evaluate the impacts of pharmaceuticals in the aquatic environment at local and global scales.

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Contents

1. Introduction

Pharmaceuticals (excluding recreational substances, such as caffeine) are defined as chemicals used for diagnostic, preventive, and therapeutic purposes in humans and animals (aus der Beek et al., 2016; Xin et al., 2020). Pharmaceuticals are an important pillar in modern medicine, providing benefits to both humans and animals. Worldwide, use of veterinary and human pharmaceuticals is increasing due to ageing and growing populations, economic growth, and the increased demand for animal protein intensifying food production (Lyons, 2014; aus der Beek et al., 2016; Wang et al., 2017a; Kovalakova et al., 2020) with recent estimates suggesting total daily intakes of 5000 and 10,000 pharmaceutical compounds across Europe and the USA respectively (Ngqwala and Muchesa, 2020). Their use directly supports global efforts to achieve the United Nations (UN) Sustainable Development Goals (SDGs) though goals 2 (Zero Hunger), 3 (Good Health and Wellbeing) and 5 (Gender Equality) as well as the World Health Organisation's 'One Health' approach which recognizes that the health of the environment, humans, and animals is closely connected (Destoumieux-Garzón et al., 2018).

However, for >20 years pharmaceuticals have been identified as emerging pollutants of concern (Busfield, 2015; Miller et al., 2018), following reports on the detrimental effects that pharmaceuticals, and their active compounds, pose to the environment, wildlife and humans (Zuccato et al., 2000; Lyons, 2014; Ding et al., 2018; Ding et al., 2020). Over 50 % of the manufactured pharmaceutical chemicals during 2004 and 2018 were found to be harmful to ecosystems, with >70 % of these chemicals observed to have significant environmental impacts (Feijão et al., 2020). The presence of pharmaceuticals in the environment therefore compromises the delivery of other SDG goals including goals 6 (Clean Water and Sanitation), 12 (Responsible Consumption and Production), 14 (Life Below Water) and 15 (Life On Land).

Aquatic ecosystems are an environmental sink for pharmaceuticals (Świacka et al., 2022). However, the chronic long-term impact of pharmaceuticals on ecosystem health is poorly understood with studies focussing on a handful of freshwater and marine target species (Li, 2014; Fabbri and Franzellitti, 2015; Karlsson et al., 2017; Miller et al., 2018; Świacka et al., 2022), using a select number of single pharmaceuticals (Brodin et al., 2013; Brooks et al., 2003; Martin et al., 2019a; Martin et al., 2019b), or focus on specific impacts on target organisms on a molecular (Hampel et al., 2015) and behavioural level (Brodin et al., 2014; Bertram et al., 2018a; Bertram et al., 2018b; Fahlman et al., 2021). Research evaluating the impacts of pharmaceutical pollution on non-target organisms represents a considerable, yet ecologically significant, knowledge gap. Of particular interest are diatoms, which are the lynchpin species for all aquatic ecosystems providing all energy and food for higher, target species. Given their ubiquity, responsiveness to change and critical link to higher tropic species (Wood et al., 2014; Kock et al., 2019; Saxena et al., 2021), diatoms could represent an important biomarker for whole ecosystem health linked to pharmaceutical contamination. Real ecosystem approaches are often lacking with few studies conducting insitu impacts (Kidd et al, 2007; Blanchfield et al, 2015; Fahlman et al., 2021) and therefore the direct impacts of pharmaceuticals on real aquatic ecosystem health remains largely unknown and may underestimate the significance and impact of pharmaceutical pollution. This review synthesises the small body of research that has documented the impacts of pharmaceuticals on diatom species in the aquatic environment. To contextualise this, we briefly summarise the current state of knowledge relating to the fate and effects of pharmaceuticals on the aquatic environment. Knowledge gaps surrounding the exposure of diatoms to pharmaceuticals are discussed and the potential for diatoms to play a role in the future of the environmental risk assessment of pharmaceuticals is considered.

2. Current state of knowledge of pharmaceuticals in the aquatic environment

2.1. Pharmaceutical pathways

Hormones, antibiotics, analgesics, antidepressants and antineoplastics used in human medicine and, hormones, antibiotics and parasiticides used in veterinary medicine are the main pharmaceutical products which are identified as posing an environmental risk (Küster and Adler, 2014). Following use in human and veterinary medicine, pharmaceuticals can be released via different pathways into the aquatic environment either as unchanged compounds, as pharmaceutical derived metabolites or as transformation products, and due to their prevalence they are now considered globally ubiquitous pollutants (Kümmerer, 2009; Lyons, 2014; Rzymski et al., 2017; Ngqwala and Muchesa, 2020; Kovalakova et al., 2020). Human pharmaceuticals are present in excretion products which then end up in municipal wastewater through either hospital effluents or private households (Patel et al., 2019; Ding et al., 2020; Ngqwala and Muchesa, 2020). Humans also directly dispose of unused medicines through domestic wastewater and solid waste disposal. The frequent detection of pharmaceuticals in global water bodies (Liu et al., 2015; aus der Beek et al., 2016; Wang et al., 2017a; Rimayi et al., 2018; Ngqwala and Muchesa, 2020; Kovalakova et al., 2020) is largely due to their continuous input from wastewater discharge and the inability and lack of technology at wastewater treatment plants to remove these chemicals (Roberts et al., 2016; Patel et al., 2019; Ding et al., 2020; Ngqwala and Muchesa, 2020; Gomaa et al.,

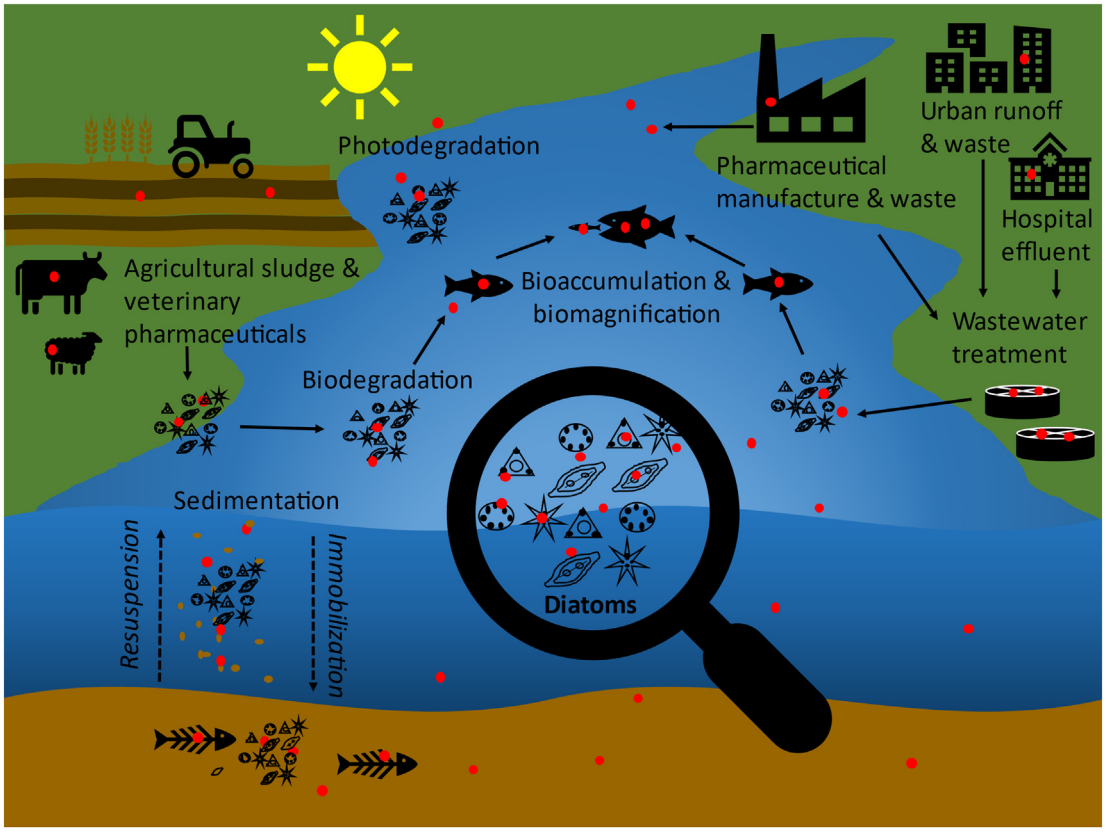

Fig. 1. The sources of rural and urban inputs of pharmaceuticals (solid red circles) into freshwater systems and the processes responsible for the breakdown (photodegradation, biodegradation), accumulation and mobility (sedimentation, immobilisation/adsorption, resuspension/desorption, bioaccumulation) and biological impacts (bioaccumulation, biomagnification) of pharmaceuticals in the aquatic environment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2021). In regions with poor sanitation pharmaceuticals can be directly released into the environment (Fig. 1) (Dalahmeh et al., 2020; Kovalakova et al., 2020; Selwe et al., 2022). In addition, veterinary medicines excreted by livestock animals can also contribute to surface- and groundwater pharmaceutical pollution through surface run off and leaching (Li, 2014; Jaffrézic et al., 2017).

Recent analytical advances (e.g. GC–MS/MS, LC–MS/MS) have enabled detection of pharmaceuticals in drinking water at very low concentrations (ng/L) (Guitart and Readman, 2010; Odendaal et al., 2015; Patel et al., 2019), and antibiotics in the aquatic environment have been found in the range of ng/L–μg/L concentrations (aus der Beek et al., 2016; Wang et al., 2017a; Ding et al., 2020; Kovalakova et al., 2020) and in mg/l (Rzymski et al., 2017; Mylapilli and Reddy, 2019). Globally, antibiotics, antidepressants, NSAIDS and antihypertensives are the most detected types of pharmaceuticals in aquatic systems (Świacka et al., 2022). Differing flow conditions exposes different taxonomic groups within the aquatic system to chronic mixtures of pharmaceuticals over variable time scales. Mixed pharmaceuticals were detected as high as 18 μg/L during flood events in Israel's Alexander micro-estuary during a two-year study compared to 14 μg/L during base flow conditions, with a median annual risk quotient presented as 4.5 for algae highlighting the high risk these pharmaceutical cocktails pose within aquatic ecosystems (Topaz et al., 2020). Pharmaceutical use in aquaculture can also contribute to widespread contamination, for example in Honghu Lake, China (a high-intensity aquaculture lake), 13 antibiotics were present with the concentration of some of these antibiotics reaching up to 2796.6 ng/L (Wang et al., 2017a). Whilst these low concentrations may not be high enough to cause acute toxic effects, there is little data on the non-therapeutic (low concentrations) impacts of the long-term pharmaceutical expose to aquatic organisms. Most ecotoxicological data assesses acute, high concentration doses on large target organisms, however the smaller, primary producers (e.g. diatoms) may be more susceptible to lower concentrations which can have a larger impact on aquatic ecosystem health (Janecko et al., 2016; Kovalakova et al., 2020).

2.2. Pharmaceutical fate

The persistence of pharmaceuticals in the aquatic environment is an important issue which has attracted global concern from the scientific community (Gomaa et al., 2021; Mojiri et al., 2022). Chemical and biological environmental parameters in combination with the pharmaceutical physico-chemical properties have been identified as key drivers in determining the fate, and ultimately the persistence of, pharmaceuticals in the aquatic environment. Physicochemical properties can influence numerous processes in the aquatic environment such as absorption, bio-/catalytic-/photo degradation, distribution, metabolism and can cause biochemical reactions in the environment (Xin et al., 2020). There are numerous reviews which focus in more detail on the fate of pharmaceuticals in aquatic systems (Küster and Adler, 2014; Ngqwala and Muchesa, 2020; Kovalakova et al., 2020; O'Flynn et al., 2021; Caban and Stepnowski, 2021; Duan et al., 2022; Bavumiragira and Yin, 2022).

The reviews on pharmaceuticals in the aquatic environment highlight important processes and reactions which control their fate and occurrence (Bavumiragira and Yin, 2022). Some pharmaceuticals, including cephalosporins, fluoroquinolones, trimethroprim and sulphonamides, can persist in aquatic environments as they are not biodegradable (Buerge et al., 2006; Li, 2014) even under anaerobic conditions Kujawa-Roeleveld et al. (2008). Others, such as fluoroquinolones have a strong adsorption capacity to sediments and organic matter (Ngqwala and Muchesa, 2020). However, sorption to sediments can also aid biodegradation of these compounds due to the presence of microorganisms in the sediments (Li, 2014; Bavumiragira

and Yin, 2022). It is expected that climate change will exacerbate more extreme hot and cold events globally, influence the global water cycle and increase precipitation (IPCC, 2021). Therefore, there is the potential for climate change to influence key processes responsible for the fate of pharmaceuticals in aquatic ecosystems, for example via increased natural attenuation at warmer temperatures (Daneshvar et al., 2010) or increased potential for photodegradation (Boreen et al., 2003; Bavumiragira and Yin, 2022). This is especially true in the Global South where not only is there a paucity in water quality data but these areas are also projected to experience greater extremes in climate changes (Schiedek et al., 2007; Noyes et al., 2009; Landis et al., 2014).

2.3. Effects of pharmaceutical in the aquatic environment

Even though pharmaceuticals are present in the aquatic environment at low concentrations (ng/L or sub-parts-per-billion) they are still pseudo-persistent and bio-accumulate in the aquatic ecosystems due to their relatively low degradation potential, extensive use and continuous release (Ngqwala and Muchesa, 2020). For a review of the impact of pharmaceuticals on aquatic ecosystems, readers are directed to Świacka et al. (2022).

With the exception of antibiotics, enthelmintics and fungicides, pharmaceuticals differ from pesticides as their main purpose is not to regulate or kill organisms, but they are used to modify behaviour or physiology (Arnold et al., 2014). Pharmaceuticals are designed to be biologically active even at very low doses (Fabbri and Franzellitti, 2015; Selwe et al., 2022). To achieve their desired therapeutic effects, they are designed to target specific cell, metabolic or enzymatic signals (Fabbri and Franzellitti, 2015). As all living organisms have these molecular signals their possibility of unintentionally being exposed and effected by the chemicals increases (Fabbri and Franzellitti, 2015).

Pharmaceuticals have recently been included on the EU Water Framework Directive “watch-list” as chemicals that can potentially cause harmful effects on aquatic ecosystems (Miller et al., 2018), yet remain weakly regulated (Miettinen and Khan, 2021). Twenty-five pharmaceutical chemicals are also listed by The Convention for the Protection of the Marine Environment of the North-East Atlantic (OSPAR) as chemicals of possible concern (Miller et al., 2018). The Umweltbundesamt (German Environment Agency) have completed valid Environmental Risk Assessments for a total of 120 human medicine products and concluded that approximately 10 % of these have notable environmental risks with the same trend observed for veterinary medicine (Küster and Adler, 2014). Currently, over 20,000 prescription drug products are approved for marketing by the U.S. Food and Drug Administration (FDA) (FDA, 2021). However, there are considerable uncertainties related to the risk these pharmaceuticals pose to multiple species in the environment, including their functional effects and affinity in non-target biota, as well as their uptake, metabolism and excretion in non-target species (Arnold et al., 2014).

The widely documented global occurrence of pharmaceuticals (Mojiri et al., 2022; Świacka et al., 2022), and their presence in the environment at concentrations as low as ng/L necessitates an evaluation of risk on ecologically relevant species and under realistic exposure scenarios. However, most ecotoxicology studies are under defined laboratory conditions for single pharmaceuticals whereas in the natural world, mixtures of compounds are more likely present (Nallani et al., 2011). Pharmaceutical pollution has already resulted in population-level effects on aquatic organisms stressing the need to take a whole ecosystem approach encompassing multiple species over multiple trophic levels (Miller et al., 2018).

Research evaluating the impacts of pharmaceutical pollution on non-target organisms at the base of the food chain (primary producers – including bacteria, phytoplankton, and algae) represents a considerable knowledge gap. Studies on pharmaceuticals effects in the aquatic environment predominately focusses on fish, crustaceans and molluscs with reported ranges of 0.1–100 ng/g (Huerta et al., 2012). Ecotoxicity bioassays have demonstrated that marine algae are the most sensitive aquatic organisms when exposed to sulfonamides antibiotics, followed by crustaceans and fish (Duan et al., 2022). A small number of studies have reported that select antibiotics are toxic to freshwater algae (Fu et al., 2017; Kovalakova et al., 2020). Non-therapeutic concentrations of antibiotics in the aquatic ecosystem can trigger specific responses to biofilm formation as well as act on signalling molecules (Robson et al., 2020; Kergoat et al., 2021). Aquatic biofilm's function and structure can be modified by environmental concentrations of antibiotics (Kergoat et al., 2021), and studies have also shown ibuprofen (92 ng/L and 920 ng/L), carbamazepine (150 mg/L) and sulfamethoxazole (0–2500 μg/L) can affect the chloroplast and photosynthetic apparatus of algae (Li, 2014). Recently, Robson et al. (2020) identified that pharmaceutical exposure can alter community composition and function which disrupt critical ecosystem processes including photosynthetic capacity, primary production, respiration and chlorophyll *a* concentration, but further research is needed currently to examine the ecological risk on algal, microalgal and microbial assemblages (Gomaa et al., 2021). Xin et al. (2020) reported that fluctuations in nutrient concentrations will affect protein synthesis in algal species' thus influencing the toxicity of pollutants on these organisms, they also noted that pH does affect the growth rates of algae, however, pharmaceuticals did not play a role in altering the growth algae.

There is an urgent need to study the accumulation, fate and chronic long-term impact of pharmaceuticals at the base of the food chain including microbial assemblages (Robson et al., 2020), which are often exposed to a cocktail of pharmaceuticals due to their ubiquitous and often indiscriminate use in rural and urban areas (Fernandes et al., 2020). Investigations into the presence and effects of pharmaceuticals on in-situ riverine biota is particularly scarce (Miller et al., 2018) but needs to be considered due to the dispersive nature of pharmaceutical contaminants and their ability to bioaccumulate and be biomagnified within the food chain (Arnold et al., 2014). This is especially true for diatoms as very limited research has focussed on the effects of pharmaceuticals on diatoms with the majority of research focussing on the effects of specific antibiotics due to the rise in antibiotic resistance. Even with advances in analytical capabilities, the potential for these chemicals to transform and be metabolised further complicates any environmental risk assessment (Rzymski et al., 2017). Environmental factors, such as dilution, pH, light, environmental interactions, nutrients and temperature, can potentially alter the toxicity, fate and mobility of pharmaceuticals in aquatic ecosystems, therefore posing new challenges (Xin et al., 2020). Thus, in a changing climate this poses additional unknowns on the fate, mobility and exposures of pharmaceuticals within aquatic ecosystems and the biota they sustain.

3. Diatoms and their sensitivity to pollutants in aquatic ecosystems

Diatoms are unicellular, photosynthetic organisms present in all aquatic ecosystems that play an important role in the oxygen and carbon cycle (Wood et al., 2014; Kock et al., 2019; Saxena et al., 2021). As phototrophic algae, diatoms are among the major primary producers on which almost all aquatic life depends. Diatoms also play an important role in nutrient cycling and production of organic carbon, producing ~40 % of the world's oxygen through the photosynthesis (Saxena et al., 2021). Diatoms can be planktonic (i.e., free-floating) or periphytic and grow on biological (e.g. macrophyte), sedimentary and rock, and anthropogenic substrates. They can exist as single solitary cells or as long chains in colonies and have a siliceous cell wall (frustule) which varies in size and structure between each species. There are an estimated 100,000 species of diatoms globally (Xin et al., 2020) making them the most abundant algae. Specifically, diatoms comprise 70 % of freshwater algae species of which, 83 % occupy the benthic habitat (Pla-Rabés et al., 2016).

Diatoms have a short generation time and are one of the most widespread groups of algae being reported in all types of water bodies and from all continents; they can directly exchange with nutrients in their environment, and can easily be collected (Wood et al., 2014; Kock et al., 2019; Saxena et al., 2021; Świacka et al., 2022). The distribution of diatoms is influenced by biological, hydrological, climatic and physicochemical properties within the aquatic environment (Mirzahasanlou et al., 2020). As a result of these factors, diatoms respond quickly to environmental and

anthropogenic changes in aquatic systems such as pollution (Schmutz et al., 2006; Fernandes et al., 2020). The influence of pollutants (particularly nutrients and pesticides) on diatom communities has been extensively studied (Ding et al., 2018; Kock et al., 2019; Ding et al., 2020; Fernandes et al., 2020; Kock, 2020; Park et al., 2020). Diatoms have been shown to be more sensitive than macroinvertebrates to pollution arising from metals (Pandey et al., 2017), organic matter, nutrients (e.g., nitrate and phosphate) and PAHs (Romani et al., 2016). Consequently, diatoms assemblages are used as water quality bioindicators for pollution incidences over large geographic areas (Bellinger et al., 2006; Kock et al., 2019; Kock, 2020; Saxena et al., 2021). Over 20 diatom-based indices exist for water quality monitoring including the Biological Diatom Index (Lenoir and Coste, 1996; Zelinka and Marvan, 1961), Nygaard's Algal Index and Palmer's Algal Index (Saxena et al., 2021). However, most traditional indices vastly underutilise the full potential for diatoms to act as bioindicators at the community level in aquatic systems (Saxena et al., 2021).

3.1. Diatoms in ecotoxicity studies

The extent to which pollutants affect diatom species is influenced by a number of factors, including diatom motility, morphology, physicochemical properties of the water body, and pollutant concentration. Due to their limited motility, diatoms have been found to respond more to pollutants than other types of algae (Xin et al., 2020). Diatoms are extremely useful in ecotoxicological studies and are often more responsive to chemical pollution than other aquatic organisms (Pandey et al., 2017). A diatom's key feature is their species-specific, robust silica frustules. However, anthropogenic and environmental stressors can compromise the structure of frustules (Park et al., 2020). Morphological abnormalities and frustule deformation can be identified via simple microscopy techniques. At the community scale, assemblage reorganizations and population size reductions can indicate the presence of pollutants. Diatom motility (ability to move independently) can also be used to determine the health of aquatic ecosystems however this is rarely studied (Park et al., 2020). This was demonstrated by Gupta and Agrawal (2007) who found exposure to several metals influenced the motility rate of *Navicula grimmei* and *Nitzschia palea*. In addition, the unique morphology and lack of motility in *Phaeodactylum tricornutum* led to increased and prolonged exposure to ZnO nanoparticles (commonly found in personal care products, baby lotions, skincare products etc.), which negatively impacted cell surfaces and resulted in membrane damage and oxidative stress (Xin et al., 2020).

Studying the intracellular-component response of diatoms through cytology and cell ultrastructure can provide a robust indication of the effects that pollutants have on these organisms as there is a strong interlink between a diatom's organelles (including the cytoskeleton, nucleus and DNA and siliceous cell wall) (Debenest et al., 2010; Kergoat et al., 2021). Not only do reported toxins negatively affect the diatom's internal structural functions, but they also effect the diatom's growth (biomass and cell diversity) and have various effects on species composition (Debenest et al., 2010; Kergoat et al., 2021; Chia et al., 2021). Interactions and effects of toxins on the different components of the diatom community have considered pesticides, herbicides and metal exposures (Table 1). Fossil diatoms can also aide the investigation of historical aquatic pollutantion events through sediment accumulation in their benthos (e.g. lakes and marine environments). The silica frustules of diatoms will typically not biodegrade, meaning once deposited in benthic sediments they are preserved (Fernandes et al., 2020). The communities that are preserved in lake sediments, and the appearance of individuals within them, are used to infer past environmental conditions. However, the use of fossil diatoms as a tool to investigate and reconstruct historic pharmaceutical concentrations in lake sediments is yet to be explored.

3.2. Impact of pharmaceuticals on diatoms

The role of diatoms as indicators of pharmaceutical presence in aquatic systems is an emerging area of research but has not received as much attention as other pollutants such as heavy metals, nutrients and PAHs. The role of diatoms in monitoring pharmaceuticals is an underutilised area. Studies to understand the impact of pharmaceuticals on diatoms are limited to laboratory based ecotoxicity studies which focus on only a few diatom species and single pharmaceuticals and do not sufficiently represent the aquatic environment (Hagenbuch and Pinckney, 2012; Guo et al., 2016; Ding et al., 2020).

Most studies on single diatom species and single pharmaceuticals suggest high levels of cell deformities and mortality rates at high pharmaceutical concentrations. Additionally, many studies on diatoms emphasise the impact of pharmaceuticals on the physiology of diatoms. For example, a reduction in Chlorophyll α concentrations, reduced assemblage respiration and primary production was noted in periphyton assemblages after exposure to fluoxetine (Robson et al., 2020). Similarly, exposure to the antibiotics tylosin and trimethoprim reduce the light utilization efficiency during photosynthesis of *Navicula pelliculosa* (Guo et al., 2016). After a model diatom (*Phaeodactylum tricornutum*) was exposed to fluoxetine a reduction in cell photosynthesis and cell density was noted (Feijão et al., 2020). The reduction in cell biomass has implications for both freshwater and marine ecosystems as a reduction in primary producer's biomass can result in the reduction of primary oxygen, reduced food source and reduce availability of key fatty acids to higher trophic level organisms (Feijão et al., 2020). There is an absence of studies which consider the impact of pharmaceuticals on entire diatom assemblages and the higher ecosystem which they support.

There is a paucity of studies that include mixtures of pharmaceuticals, or exposure to combined pharmaceuticals and non-pharmaceutical pollutants, as found in the environment. The combination of pharmaceutical

Table 1
Table indicating the impact of chemical pollutants on some key diatom species. Entries in bold represents pharmaceutical exposures.

Species	Chemical	Impact	Reference
Diatom assemblages	Metal pollution	Cytological abnormities	Park et al., 2020
Nitzschia palea	DDT, Deltamethrin	Decreased vitality; increased deformities	Kock, 2020
Navicula grimmeii & Nitzschia palea	Metal pollution	Influenced motility	Gupta and Agrawal, 2007
Phaeodactylum tricornutum	Zinc oxide	Membrane damage; oxidative stress	Xin et al., 2020
Benthic diatoms	Herbicides	Reduce growth	Larras et al., 2013
Skeletonema costatum	Glyphosate	Increased sensitivity	Tsui and Chu, 2003
Benthic diatoms	Atrazine	Decreased vitality	Wood et al., 2014
Diatom assemblages	Herbicides & fungicides	Effects on life-forms and ecological guilds	Rimet and Bouchez, 2011
Diatom assemblages	Herbicides	Decreased chlorophyll-c concentrations and live cell densities	Debenest et al., 2009
Amphora sp. & *Navicula* sp.	Organophosphates & pyrethriods	Inhibited photosynthesis	Shoaib et al., 2011
Diatom assemblages	Herbicides	Nucleus alterations	Debenest et al., 2008
Thalassiosira weissflogii	Oxyfluorfen & copper sulphate	Interfered with growth and nutritive value	Mesquita et al., 2021
Planothidium lanceolatum & Gomphonema gracile	Herbicides & insecticides	Affected growth	Neury-Ormanni et al., 2020
Phaeodactylum tricornutum	**Bezafibrate**	**Shift in metabolism and reduce photosynthesis**	**Duarte et al., 2019**
Navicula pelliculosa	**Antibiotics**	**Reduce photosynthesis**	**Guo et al., 2016**
Diatom assemblages	**Ciprofloxacin**	**Assemblage shifts**	**Robson et al., 2020**
Phaeodactylum tricornutum	**Fluoxetine**	**Reduced cell density and photosynthesis**	**Feijão et al., 2020**

compounds might have a “cocktail effect”, whereby the exposure to a combination of pharmaceuticals can have a different effect (synergistic or antagonistic) on organisms compared to exposure to only one compound (Lyons, 2014; aus der Beek et al., 2016; O'Flynn et al., 2021; Chia et al., 2021). This is highlighted in river systems where inputs of treated effluent may vary in their concentrations and types of pharmaceuticals depending on the primary sources of the water. Chonova et al. (2019) have demonstrated that periphytic, benthic diatom assemblages that receive treated effluent wastewater have fewer diatom genera with polysaprobic preferences, when compared to other river sites that had more diverse diatom assemblages comprising oligotrophic and oligosaprobic genera. Importantly, Chonova et al. (2019) also identified that the source of the treated effluent and as a result the pharmaceuticals within the water influence the diatom assemblages present. The diatom assemblages downstream of urban wastewater treatment plants were influenced by beta-blockers and non-steroidal anti-inflammatory drugs whereas diatom assemblages impacted by hospital treated effluent were influenced by antibiotics and orthophosphate (Chonova et al., 2019).

The potential for synergistic or antagonistic impacts of pharmaceuticals and their active pharmaceutical ingredients (APIs) mixed with other pollutants must also be considered to assess the “mixed effect” on diatom communities (Chia et al., 2021). The influence of substrate (natural or anthropogenic) on the interaction between diatoms and pharmaceuticals is also not known, such as plastic debris on which diatom communities can establish (Smith et al., 2021).

Similarly, there has been a research gap around using ‘natural’ diatom assemblages as found in the real aquatic environments to examine entire diatom assemblage response to a range of environmental stressors and pharmaceuticals. Robson et al. (2020) found that diatom assemblages in freshwater assays showed a significant shift in community structure when exposed to ciprofloxacin. This can also be explored more holistically by looking at community structure changes but also Multiple Trait-Based Approaches (De Castro-Català et al., 2020). Kergoat et al. (2021) adopted a community-based approach by placing cultivated biofilms from natural river systems into mesocosms with exposures to environmentally relevant concentrations of the antibiotics Sulfamethazine and Sulfamethoxazole (500 and 5000 ng/L). The results demonstrated that diatom mortality doubled at higher concentrations relative to the control. Importantly, the results highlighted that the high concentrations led to a decrease in diatom diversity, evenness and richness and teratologies in 3 times as many diatoms compared to the control biofilm. Using the Multiple Trait-Based Approaches on three European river-based systems, De Castro-Català et al. (2020) demonstrated that after river flow, diatom community and structure was determined by pharmaceutical active compounds (PhAC).

Additionally, most ecotoxicity studies fail to recreate the complexity of the natural aquatic environment. For example, diatom growth is mainly influenced by light intensity and nutrient availability (e.g. total nitrogen and phosphorus). Diatoms may therefore respond differently to comparable chemical exposure under different environmental conditions (light and nutrient) (Xin et al., 2020) as seen by diatom responses to pesticide exposure (Debenest et al., 2010). An adequate nutrient supply will result in higher diatom production rates, higher protein content and increased enzyme synthesis rates. The latter is important for ecotoxicological studies as some enzymes may be inhibited by pharmaceutical compounds whilst other enzymes will help metabolise these compounds (Xin et al., 2020). The environmental toxicity of pharmaceuticals to diatoms, and their transport and fate in the aquatic environment are also influenced by the presence of natural organic matter, temperature, and pH (Xin et al., 2020).

Increased light, specifically ultraviolet radiation (UV-A and UV-C), and temperature can damage diatom's photosynthetic system, affect cell integrity, cause DNA damage, influence their ability to fix nitrogen, cause oxidative stress, impact their settle ability and can result in toxin synthesis (Li et al., 2020; Xin et al., 2020). It has also been established that during light exposure (sunlight and UV radiation) diatoms are more sensitive to exposure of specific compounds (e.g. atrazine) (Debenest et al., 2010). In addition to influencing diatom assemblages, natural organic matter can alter a pharmaceutical's ecological effects and influence their environmental behaviour and distribution via physicochemical interactions such as charge transfer, covalent bonding, hydrogen bonding, hydrophobic adsorption and ion exchange (Xin et al., 2020). However, limited studies have considered the combined influence of these parameters on the toxicity of pharmaceuticals, their metabolites and transformation products to diatoms (Chia et al., 2021; Xin et al., 2020).

3.3. Diatoms as bioremediators for pharmaceutical pollution

Selected algae (Norvill et al., 2016), biofilms (i.e., bacteria, algae, protozoa, fungi and inorganic constituents) (Fernandes et al., 2020) and diatoms (Ding et al., 2020) have been used as bioremediators of pharmaceuticals in aquatic systems through the sorption and biodegradation of pharmaceuticals (Mojiri et al., 2022).

Algae are a clean and environmentally friendly way to treat wastewater (Villar-Navarro et al., 2018). Wastewater treatment plants have used algae-based systems to remove emerging contaminants (Mohammed et al., 2014; Fica and Sims, 2016), demonstrating the potential to remove up to 99 % of pharmaceutical and personal care products from aquatic environments (Mojiri et al., 2022). There are four pathways that can be used by algae to remove pharmaceuticals from water; biodegradation, biosorption, photodegradation and sorption (Wang et al., 2017b).

Although compromised by pharmaceutical pollution, there is also potential for diatoms to remediate pharmaceutical pollution. The ability to survive and grow in adverse environments, the high productivity rate, mucilage, nutritional requirements and surface area that diatoms can cover means that diatoms are commonly used in bioremediation of heavy metals from wastewater. However, much less is known about how diatoms could contribute to the bioremediation of pharmaceuticals in freshwater systems. For example, diatoms remove heavy metals by biosorption and subsequent bioaccumulation of inorganic molecules and enzymes (Saxena et al., 2021). Based on the small number of studies on the role of diatoms in bioremediation, it is suggested that pharmaceuticals could bioaccumulate in diatom species by initiating cell growth (i.e., by cell count, cell dry weight, increase in Chl a,) thereby removing them from the aquatic environment. For example, a STP containing the diatom *Chaetoceros muelleri* removed 5.4 % of carbamazepine, 33.1 % of sulfamethazine and 36.5 % of tramadol (Mojiri et al., 2021). The marine diatom *Chaetoceros gracilis* has shown potential for use in the bioaccumulation and bioremediation of estradiol in aquatic systems. Experiments growing *C. gracilis* in estradiol and seawater media demonstrated that increasing concentrations of estradiol (0.5–2.0 mg L^{-1}) produced an increment in cell numbers, and a 1.5-fold increase in the dry cell weight and lipid content (up to 29.5 % DW) (Singh et al., 2022). For example, high concentrations (>30 μg/L) of the lipid-lowering drug Abezafibrate resulted in increased cell density and cell division of the marine diatom *Phaeodactylum tricornutum* (Duarte et al., 2019).

Even at low concentrations there is evidence that pharmaceuticals can stimulate diatom growth rates and uptake pharmaceuticals via biosorption. For example, low concentrations (0.1 mg - 1.0 mgL^{-1}) of Ibuprofen increases growth rates of the freshwater diatom species *Navicula*, but the growth rate rapidly decreases at high concentrations above 50 mgL^{-1}. and photosynthesis can be inhibited with concentrations >1 mgL^{-1} (Ding et al., 2017). These findings also suggest that Ibuprofen metabolites can build up in *Navicula* over time and pose a threat to the aquatic ecosystem at higher concentrations. The impact of bioaccumulation of pharmaceuticals in diatoms as the basis of the food chain in aquatic ecosystems and biogeochemical cycling represent two key areas where much more research is required. Furthermore, many laboratory-based studies use high concentrations of pharmaceuticals that would rarely be found in the natural aquatic environment.

4. Global management of pharmaceutical pollution

Pharmaceutical pollution is a global concern and management approaches should be set in place to minimize the exposure and impact of

pharmaceuticals on the environment. For proper management of these chemicals, collation and dissemination of accurate and consistent information is important (Miller et al., 2018). Worldwide numerous groups and organisations such as NORMAN (organisations for monitoring of emerging environmental substances), Strategic Approach to International Chemicals Management (SAICM), Network of reference laboratories, the United Nations, Education, Scientific and Cultural Organization (UNESCO) and research centres report on the knowledge gathered from environmental pollutants (Miller et al., 2018). This requires the standardisation of reporting units, chemical analysis method validation, reporting guidelines and ensuring that all data are made available to avoid omission of crucial data from research papers and to create an integrated approach to mitigating environmental risk (Miller et al., 2018).

In the lifecycle of pharmaceutical products their environmental fate and impact is often overlooked. The regulation of drugs is not always overseen by environmental scientists (Jones et al., 2001; Miettinen and Khan, 2021). Additionally, standardising analytical methods is a challenge, with different pharmaceuticals potentially polluting different parts of the world due to different prevalence and usage within each countries populations to medicate different public health conditions (Miller et al., 2018). There is therefore a need to understand and monitor each country and/or region for prescribed and administered pharmaceuticals, rather than a set list of pharmaceuticals common in only a few countries. Targeted biomonitoring for only certain pharmaceuticals will fail to reflect unique region-specific mixtures of pharmaceutical pollution. Key to this is consideration of the economic cost of the analytical techniques associated with monitoring pharmaceutical pollution methods, which may not be feasible for developing countries. Biomonitoring for contaminants offers an affordable method but is dependent on a much more advanced understanding of the impacts of pharmaceuticals (individuals and mixtures) on non-target species (Miller et al., 2018), such as diatoms.

To mitigate environmental risk from pharmaceuticals, more integrative approached are required. Coordinated management approaches between pharmaceutical companies, water regulators and environmental bodies should be driven by governmental legislation and supported by research funding. It is important that stakeholders work together internationally and do not only focus on Global North countries (aus der Beek et al., 2016). This can be achieved through training programs and educational programmes across all levels as well as within academia. Educating the public of the increasing threat of pharmaceutical pollution will be a key approach to reducing the impact of pharmaceuticals on the aquatic environment. It is also important to determine what steps are needed to ensure dissemination of findings to governmental, organizational and public sectors; to train and educate the public to better manage pharmaceutical consumption and disposal; and to identify treatment methods to enhance pharmaceutical removal from the environment – particularly wastewater treatment plant effluent.

5. Future research priorities and recommendations

Here, we have highlighted the environmental significance of pharmaceuticals in aquatic ecosystems and the potential for non-target organisms, such as diatoms, as bioindicators of and bioremediators of contamination and environmental change. However, as non-target organisms, diatoms are often overlooked when studying the impacts of pharmaceutical pollution, despite their role as building blocks of all aquatic ecosystems. There are some significant omissions and knowledge gaps, outlined below, which need addressing to realise this potential.

(1) Pharmaceuticals in the aquatic environment

I) Regular monitoring of pharmaceutical pollution should be integrated into national and international assessments of aquatic health.
II) Characterising ecotoxicological effects of individual, mixtures, metabolite derivatives and transformation products of pharmaceuticals at environmentally relevant concentrations and under more environmentally realistic conditions (i.e., natural “mesocosms”).
III) Understanding climate (e.g. temperature, UV, flooding, droughts, etc.) specific and combined impacts on pharmaceutical breakdown, mobility and transport in aquatic ecosystems across different spatial and temporal scales.
IV) Understanding trophic level interactions with pharmaceutical exposures and the influence on aquatic ecosystem functioning, including non-target organisms.
V) Determining interactions between pharmaceuticals and other pollutants (e.g. heavy metals, nanoplastics, nutrients) within aquatic systems and their impacts on whole ecosystem health and function.
VI) Data collection from the Global South must be increased to understand the nature of pharmaceutical pollution at the global scale.

(2) Diatom-pharmaceutical interactions

I) Understanding the effects of single and mixed pharmaceutical exposure on entire diatom assemblages and functional groups (i.e. not single species) in real world aquatic systems (in “Living Laboratory settings”) over a range of time scales.
II) Determining the biomagnification of pharmaceuticals and bioactive compounds to higher trophic levels, and their impacts on organisms across these levels.
III) Exploring the influence of pharmaceuticals on aquatic biogeochemical cycles (i.e., Carbon, Silica and Nitrogen) and direct implications on diatom functioning, especially photosynthesis.
IV) Understanding how environmental and human induced change impacts the toxicity, fate and persistence of pharmaceuticals in the aquatic environment to understand how metabolites and transformation compounds influence diatom health and function.
V) Determining the potential for fossil diatom assemblages from aquatic sediment records (i.e. lakes and estuaries) to reconstruct historic pharmaceutical concentrations.
VI) Investigating diatom-substrate-pharmaceutical interactions to assess how diatom assemblages on anthropogenic substrates (e.g. litter) compare to natural substrate colonisation (i.e, adsorption of pharmaceuticals in biofilms).
VII) Understanding how diatom assemblages in natural and artificial aquatic systems (i.e. wastewater treatment plants) can be optimised to act as successful bioremediators for pharmaceutical pollution.
VIII) Development of a diatom monitoring indices specifically for the monitoring and management of pharmaceutical pollution in aquatic environments.

(3) Future recommendations

In addition to filling the knowledge gaps above, we recommend that scientific research is complemented by appropriate education and dissemination at the policy level. It is important that stakeholders, from members of the public to the pharmaceutical industry and governments, take a collective and integrative approach to generate a comprehensive assessment of pharmaceutical risk that accounts for country specific exposure scenarios. We therefore make the following recommendations:

I) In addition to government and industry, the presence, pathways, and impacts of pharmaceutical pollution on the environment should be a public education priority. This should be supported by organisations including the United Nations and World Health Organisation.
II) Investment should be made in treatment methodologies and technologies for pharmaceutical pollution from wastewaters.

III) The regulation of pharmaceutical use and disposal, in addition to treatment technologies should be improved as part of efforts to minimize the release of pharmaceutical compounds to the environment.
IV) Published data needs to be presented in a transparent manner, adhering to open access policies to improve knowledge exchange between countries so that efforts to address pharmaceutical pollution consider its variability at the global scale. Creation of a reference database for example would ensure long-term accessible data storage (e.g. similar to Pesticide Data Program in the US).
V) Cost effective, reliable and standardised methods to test levels of pharmaceutical pollution must be developed and implemented to increase global capacity to monitor pharmaceutical pollution.

6. Conclusion

There are still major gaps related to our understanding of pharmaceutical pollution in the environment and the effects they might have on wildlife as well as the human population. It is critical for environmental risk assessment in aquatic environments to aid in understanding the distribution, transport and fate of pharmaceuticals. Worldwide there is growing concern surrounding pharmaceutical pollution and increasing pressure to understand the potential risks these pollutants pose to the environment. With increasing global consumption and therefore production of pharmaceutical active compounds there is a timely need to examine environmental risks associated with non-target aquatic ecosystems and the organisms within these habitats. Knowledge on the effects of pharmaceuticals on the aquatic environment will provide vital information to resource managers. It is essential that assessments of pharmaceutical pollution are carried out and appropriate mitigation measures implemented where necessary. Underpinning this will be the development and implementation of appropriate legislation worldwide. Even though most pharmaceuticals degrade over time, the near-constant input into aquatic ecosystems at rates and concentrations that exceed their degradation results in pseudo-persistent and chronic exposure to aquatic organisms to these pollutants. Diatoms, whilst a non-target organism, provide a potentially suitable bio-indicator to test the effects of these pollutants inaquatic systems due to their unique characteristics and position in the food chain. It is important to study the direct effects that pharmaceuticals have on these organisms as well as any alterations to community structure, composition and functioning as impacts to primary production might have considerable and complex negative effects on higher trophic levels. Their relationship with pharmaceuticals must therefore be considered as this field advances, both to establish the value of diatoms as bio-indicators, but also to ensure a comprehensive understanding of the impact of societies use, and misuse, of pharmaceuticals on these keystone communities.

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A. Kock: Conceptualization, Writing – original draft. **H.C. Glanville:** Conceptualization, Writing – review & editing. **A.C. Law:** Conceptualization, Writing – review & editing. **T. Stanton:** Conceptualization, Writing – review & editing. **L.J. Carter:** Conceptualization, Writing – review & editing. **J.C. Taylor:** Writing – review & editing.

Data availability

No data was used for the research described in the article.

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