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Pharmaceuticals in the Aquatic Environment: No Answers Yet to the Major Questions

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Abstract: The presence of pharmaceuticals in the environment, especially the aquatic environment, has received a lot of attention in the last 20 plus years. Despite that attention, the two most important questions regarding pharmaceuticals in the environment still cannot be answered. It is not possible to put the threat posed by pharmaceuticals into perspective with the many other threats (stressors) facing aquatic organisms, such as low flows due to over-abstraction of water, inhibited passage of migratory species due to dams and weirs, diseases, algal blooms causing low oxygen levels and releasing toxins, eutrophication, climate change, and so on. Nor is it possible to identify which pharmaceuticals are of concern and which are not. Not only can these key questions not be answered presently, they have received extremely little attention, despite being identified 10 years ago as the two most important questions to answer. That situation must change if resources and expertise are to be effectively used to protect the environment. *Environ Toxicol Chem* 2022;00:1–6. © 2022 The Authors. *Environmental Toxicology and Chemistry* published by Wiley Periodicals LLC on behalf of SETAC.

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INTRODUCTION

It is now very clear that the environment, especially the aquatic environment, is contaminated with complex mixtures of pharmaceuticals. This is true throughout the world; wherever there are people, they will be excreting the pharmaceuticals they take (and their metabolites) into the environment (Wilkinson et al., 2022). This situation was, in fact, obvious over 20 years ago, based on the ground-breaking research of Thomas Ternes in particular (Daughton & Ternes, 1999; Ternes, 1998). It also became clear over 20 years ago that at least one human pharmaceutical, namely ethinylestradiol (EE2), had dramatic adverse effects on the ability of fish to reproduce when present in the water at extremely low concentrations (Länge et al., 2001). That finding led Caldwell et al. (2008) to propose a predicted-no-effect-concentration (PNEC) for EE2 of 0.35 ng/L, an extremely low concentration, and one that was essentially impossible to measure accurately at the time. Thus, over 20 years ago, two things were certain: (1) that human pharmaceuticals were widely present in the aquatic environment, and (2) there was a significant possibility that at least some of them might be present at concentrations likely to cause adverse effects on some aquatic organisms.

The growing interest on this topic in the first decade of this century from both environmental chemists and ecotoxicologists stimulated Boxall et al. (2012) to seek the opinions of experts on what were the outstanding unresolved questions regarding the presence of pharmaceuticals and personal care products (PPCPs) in the environment. The two highest ranked outstanding questions (Boxall et al., 2012) were:

Question 1: How important are PPCPs relative to other chemicals and nonchemical stressors in terms of biological impacts in the natural environment?

Question 2: What approaches should be used to prioritize PPCPs for research on environmental and human health exposure and effects?

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Although the authors of the present study did not participate in that survey, we would probably have supported its main conclusions.

Focusing on pharmaceuticals alone, we would phrase the two key questions as follows: (1) How important are pharmaceuticals relative to other chemicals, and other stressors, in adversely affecting aquatic biodiversity? and (2) If pharmaceuticals are a significant threat to aquatic biodiversity, which of the very many pharmaceuticals are of the greatest concern?

Below we discuss how much progress has been made towards addressing, and hopefully ultimately answering, these two key questions in the last ten years.

RESULTS AND DISCUSSION

Question 1: How important are pharmaceuticals relative to other chemicals, and other stressors, in adversely affecting aquatic biodiversity?

This is really two questions. One is concerned with comparing any adverse effects of pharmaceuticals on aquatic biodiversity with the well-documented adverse effects of the many other stressors impacting the freshwater environment. The other is concerned with comparing any adverse effects of pharmaceuticals with the known adverse effects of the very many other chemicals known to be present in the aquatic environment.

If the overriding objective of environmental scientists is to protect the environment from the many anthropogenic challenges it faces currently (Johnson & Sumpter, 2014), as it surely is, then one would expect that most scientific effort would be devoted to understanding, addressing, and then mitigating the major threats. The relatively recently published Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services (IPBES) assessment discusses the major declines in biodiversity in different ecosystems and identifies a number of causative factors (IPBES, 2019). For that to happen, it is necessary for the threats to be known, and for them to be ranked in importance. Put another way, before significant scientific effort is devoted to understanding the potential adverse effects of chemicals on aquatic life, it ought to be necessary to know that chemicals are a major threat to aquatic wildlife.

It appears to be widely accepted that freshwater biodiversity is under greater threat, and declining faster, than biodiversity in either the marine or terrestrial environments (World Wide Fund for Nature, 2016). Many different threats, including chemicals, have been identified as posing threats to freshwater biodiversity (Reid et al., 2019; Figure 1). However, documenting real or potential threats is one thing, ranking them in importance is quite another. Although it seems likely that water abstraction from rivers and lakes, and the construction of dams and weirs on rivers (often to provide hydroelectricity), have been, and still are, the two factors most adversely affecting freshwater biodiversity, we are unaware of any effort (i.e., any publication) that has attempted to rank the many known factors definitely, likely, or possibly adversely affecting freshwater biodiversity. There is limited evidence in the scientific literature that some scientists are aware that this task needs to be addressed (see, for example, Johnson & Sumpter [2014] and Sumpter [2009]), but to date its difficulty (see below) appears to have hampered any scientist(s) from attempting such an exercise, despite its crucial importance. This difficulty is highlighted below, where we consider just some of the causes of major fish kills.

Despite being extremely easy to notice, fish kills, even very major ones, are very poorly documented (Boys et al., 2022). Nevertheless, we choose them to illustrate our point because it is unarguable that a fish kill is an adverse event. Enough major fish kills have been documented in the scientific literature to demonstrate that a range of causes can be responsible. The sudden deaths of millions of native fish in the Darling-Baaka

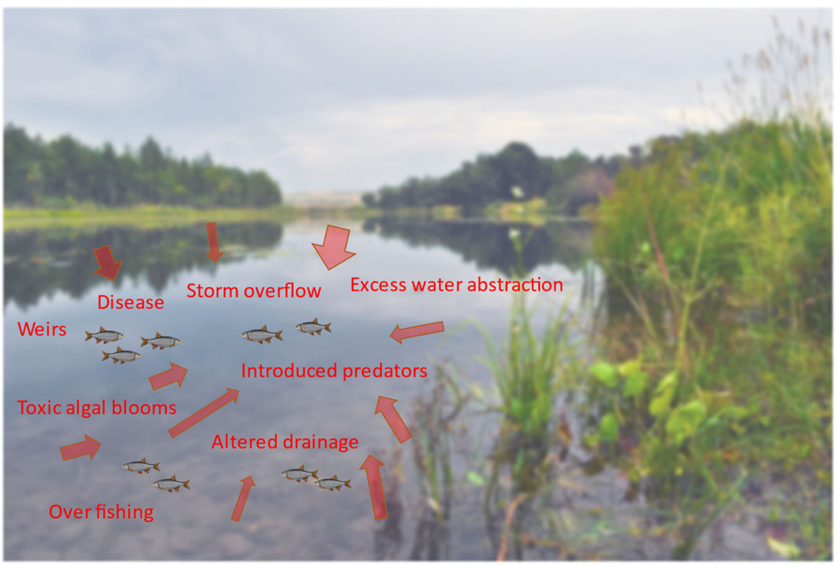

FIGURE 1: An illustration of some of the current threats to the sustainability of freshwater biodiversity.

River in Australia in 2018–2019 was broadcast around the world. The cause was complex: high water temperatures and low dissolved oxygen levels as a consequence of prolonged drought, but exacerbated by water abstraction and a rare storm event (Sheldon et al., 2021). A major fire at a Sandoz warehouse storing mainly pesticides on the banks of the River Rhine in Switzerland led, as a consequence of the escape of firefighting runoff into the river, to a massive fish kill in the river (Giger, 2009) that extended as far as 400 km downstream of the fire itself. The acidification of lakes across the entire northern hemisphere in the 1950s through to the 1970s as a result of sulfur dioxide and nitrogen oxide emissions (acid rain) from industrial and energy-producing facilities (e.g., power stations) led to the total loss of fish in these lakes for decades (Likens & Bormann, 1974). Fortunately, biological recovery in these lakes is now occurring (Warren et al., 2017). Diseases such as proliferative kidney disease have caused large-scale fish kills in a number of countries (e.g., Hutchins et al., 2021). Algal blooms, which appear to be occurring more frequently, can also cause significant fish kills (summarized in Brooks et al., 2016), as can a chemical used in the manufacture of vehicle tires which washes off roads during rainfall events (Tian et al., 2021). Other chemicals have been reported to indirectly lead to loss of fish populations (see, for example, Yamamuro, et al. [2019]). However, to date, no fish kills have been linked to pharmaceuticals, probably because, at least in developed countries, concentrations of pharmaceuticals are not expected to reach lethal levels. Instead, pharmaceuticals could potentially cause adverse effects through sublethal molecular initiation events, with EE2 providing a clear example (see *Introduction*).

These admittedly somewhat arbitrarily selected examples of just some of the factors documented to cause major adverse effects on native fish populations serve to illustrate two things. One is that many different factors (stressors)—not just chemicals—can, and do, lead to loss of fish populations. The other is that whereas pharmaceuticals have not, as yet, been convincingly demonstrated to adversely affect wild fish populations (see Johnson & Sumpter [2014]), other chemicals have. Yet despite this evidence of multifactorial causes behind adverse impacts on fish populations (and freshwater ecology more generally), extremely little effort appears to have been devoted to attempting to rank these factors based on the size of their impacts so that resources can be devoted appropriately, meaning that resources are allocated based on the size of the impacts of each factor. Having said that, there are occasionally signs within the scientific literature that it is important to try to rank the various factors threatening the aquatic environment, rather than just listing them. The study from Brooks et al. (2016) provides an encouraging example.

The authors of this study acknowledge the need to tackle this "seemingly simple question". Although they do not answer it in their study, they do raise the distinct possibility that harmful algal blooms are a greater threat to aquatic ecosystems than current research might suggest. In another study by some of the same authors (Brooks et al., 2013), a call is made "to prioritize global research needs" to, hopefully, achieve a sustainable environment. Thus, there is awareness in at least some of the scientific community that there is a pressing need to identify (the easy bit), then rank (the difficult bit) the threats to the freshwater environment. However, only minimal efforts have been made so far to achieve these goals. We do not underestimate the difficulties associated with doing so, but nevertheless we very strongly encourage the scientific community to conduct such exercises. Even if the obstacles in doing so seem insurmountable, simply by initiating the challenge, progress will have been made. This intellectual challenge needs to be undertaken if the ongoing loss of freshwater biodiversity is to be ended then, hopefully, reversed. It is also important to realize that the rankings of risks might change with time. For example, climate change will affect multiple systems (both natural and human), which in turn will alter many factors already known to adversely affect aquatic biodiversity; water resource management will likely become progressively more challenging in many parts of the world.

Question 2: If pharmaceuticals are a significant threat to aquatic biodiversity, which of the very many pharmaceuticals are of greatest concern?

Approximately 3000 structurally distinct pharmaceuticals are in routine use across the world. Many are present in most of the world's rivers (Wilkinson et al., 2022; Figure 2). If "Environmental exposure to active pharmaceutical ingredients (APIs) can have negative effects on the health of ecosystems and humans" (Wilkinson et al., 2022), then one would assume that there were well-documented, widely accepted examples of pharmaceuticals causing major adverse effects to the environment, but is this the case? With the exception of the devastating effects of diclofenac on old-world vultures (Oaks et al., 2004) which, sadly, represents possibly the worst-ever example of a chemical affecting biodiversity, the evidence for pharmaceuticals harming aquatic biodiversity is not strong (Johnson & Sumpter, 2014). Probably all scientists investigating the potential effects of pharmaceuticals on aquatic organisms would agree that the first step in any logical approach to this issue would be to identify those pharmaceuticals most likely to be causing adverse effects. Yet, surprisingly, there is very little evidence in the literature demonstrating that such an approach has been undertaken. A few attempts have been made to risk-rank pharmaceuticals, of which the most informative has probably been that of Roos et al. (2012) because it compared many different ways of ranking the risks posed by pharmaceuticals. However, even that thoughtful ranking exercise was severely compromised by lack of information, especially ecotoxicological information; the majority of pharmaceuticals have little, or no, ecotoxicological data associated with them. Without that information, it is difficult currently to rank pharmaceuticals with any degree of confidence. A consequence of this difficulty is that many, and perhaps most, scientists who have investigated the effect of a pharmaceutical on an aquatic species may well have chosen a pharmaceutical that is of very little, or no, threat to freshwater biodiversity.

FIGURE 2: A simple illustration to demonstrate that aquatic organisms are simultaneously exposed to many different pharmaceuticals.

Surprisingly, few scientists state why they chose to do their research on a particular pharmaceutical when they publish their results. At most they are likely to write something like "It was shown that pharmaceutical X affects the behavior of aquatic species A" as their justification for conducting their research with pharmaceutical X. They very rarely question whether or not the previously reported effects appear robust, that is, are likely to be reliable and hence repeatable, and occur at environmentally relevant concentrations (see Sumpter et al. [2014] for a discussion of this issue). The folly of not thinking carefully about which pharmaceutical on which to base your research can be found in the study by Sumpter et al. (2021), which reviewed all published research on the beta-blocker propranolol. These authors found over 600 research papers covering all aspects of the presence, fate, and effects of propranolol in the freshwater environment. They showed that propranolol posed an insignificant, even nonexistent, threat to aquatic biodiversity. That conclusion leads one to question why so much research was devoted to this pharmaceutical (even some conducted by the first author of the present study). We accept that there are strong reasons for being concerned about the presence in the aquatic environment of some pharmaceuticals–diclofenac and some of the steroid hormones are examples–but for the vast majority of pharmaceuticals we currently have no idea whether or not they represent a threat to the aquatic environment. Ways to find out are required before even more time and resources are devoted to research on pharmaceuticals in the environment.

It is unlikely that ranking pharmaceuticals by the amount (weight) prescribed annually will lead to the most worrying pharmaceuticals being identified. This is easily demonstrated by the fact that very little EE2 is used (~20 kg per year in the UK, for example), yet that synthetic estrogen is, understandably, a pharmaceutical of environmental concern (Runnalls et al., 2010). Of the various possible approaches to attempting to identify the pharmaceuticals of greatest concern to the environment (Roos et al., 2012), application of the read-across hypothesis, based on the fish plasma model, appears to be the most useful in identifying pharmaceuticals likely to be of concern (Rand-Weaver et al., 2013). The hypothesis can also be used in reverse to predict environmental concentrations of pharmaceuticals likely to be of concern (Fick et al., 2010). However, the read-across approach may not be useful for all groups of pharmaceuticals. It probably cannot be applied to antibiotics, and therefore antimicrobial resistance, and it may prove difficult to apply it to cytostatic drugs. Both groups are, of course, relevant when trying to rank pharmaceuticals by the degree of risk they pose. Although no single approach is likely to provide a completely accurate ranking list, the application of the read-across hypothesis could be used routinely to determine if a particular pharmaceutical in use had a reasonable chance of posing a threat to aquatic biodiversity – especially fish – or alternatively if it was very unlikely to pose a threat. It would probably be most useful to focus on sublethal responses to pharmaceuticals that result from molecular initiation events.

It is also important to realize that some pharmaceuticals released into the environment may cause effects there that could ultimately adversely affect human health. This possibility is well illustrated by antibiotics. Many different antibiotics have been reported to be present in the aquatic environment (see the recent editorial by Calero-Cáceres et al. [2022] and the articles they refer to). This example demonstrates the need for a one-health approach to managing chemicals and waste. The one-health perspective is a collaborative, interdisciplinary approach that considers the risks posed by chemicals and waste on both ecosystems and human health, and the connections between the two (Brack et al., 2022).

Whatever approach is used to select pharmaceuticals for study, it is very clear that considerably more thought needs to be devoted to identifying those pharmaceuticals that could pose a threat to freshwater biodiversity. Equally important is identifying those pharmaceuticals—quite possibly the vast majority—that are very unlikely to pose even a minimal threat to freshwater biodiversity. After over 20 years of intensive research on pharmaceuticals in the environment, it ought to have been possible to identify those pharmaceuticals posing a risk to the environment, yet that has not been achieved. Nor has much effort been devoted to this key issue.

SUMMARY

It has recently been shown (Maack et al., 2022) that nearly 18 000 documents—most being scientific papers—have, to date, been published on the topic of "pharmaceuticals in the environment". This is a very high number and one that continues to increase rapidly, hence most scientists would probably assume two things: (1) that pharmaceuticals were causing serious adverse effects to the environment, and (2) that the majority of those documents were concerned with the most toxic pharmaceuticals. Yet it is not possible presently to know if either of these two assumptions is correct. If the two most important questions about pharmaceuticals in the environment were those ranked 1 and 2 by Boxall et al. (2012), as we consider they were, then surely one would have expected that a reasonable proportion of those 18 000 documents identified by Maack et al. (2022) would have been explicitly focused on those two questions. We have not read all 18 000 articles, but we have read a significant proportion of them. Having done so, we are not aware of even a single article that has attempted to address the question ranked 1 and extremely few articles that addressed the question ranked 2 (e.g., Gunnarsson et al., 2019; Malev et al., 2020; Runnalls et al., 2010; Sumpter & Margiotta-Casaluci, 2022). This situation needs to change if environmental scientists are to provide the information required to best protect the environment from pharmaceuticals; a general suggestion on how to proceed is provided at the very end of the present study.

It is also worth keeping in mind that when Johnson et al. (2017) ranked a variety of diverse chemicals based on the risks that they posed to aquatic organisms, they concluded that the few pharmaceuticals for which there were enough data did not rank particularly highly: a number of metals were considered to present much greater threats. Thus, before another 18 000 articles on pharmaceuticals in the environment are published in the next decade or two, we implore research scientists trying to protect the environment from the effects of chemicals to think very carefully about which chemical(s) they will focus their research on. Only by doing so will the limited resources and expertise available be used most effectively.

It can be strongly argued that more analytical chemistry will not take us forward much more, if at all. This is because it is now very well established and accepted that many pharmaceuticals are present in the aquatic environment across the entire world (e.g., Wilkinson et al., 2022). It is robust, reliable ecotoxicity data that are lacking. Only in the case of EE2 and a few natural oestrogens is there agreement on concentrations that pose a threat to at least one group of aquatic organisms, namely fish (Caldwell et al., 2012). Hence, the focus of future research needs to be on the ecotoxicity of pharmaceuticals: which ones can cause adverse effects, to what organisms, and at what concentrations? As it will probably be impossible to test all 3000 pharmaceuticals on a range of aquatic species, as well as being unethical to do so, a consensus needs to be agreed by all stakeholders on how best to proceed (Sumpter & Margiotta-Casaluci, 2022).

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