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Neuroactive Pharmaceuticals In Aquatic Ecosystems: Are We Doing Enough To Protect Environmental Health?

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KEY MESSAGE

Healthy rivers are vital for biodiversity as well as human health and wellbeing; however, contamination of surface waters by pharmaceuticals is an emerging problem globally. Of increasing concern is the release of neuroactive pharmaceuticals into the environment, some of which can bioaccumulate in fish and reach blood concentrations high enough to exert pharmacological effects, leading to the potential perturbation of wildlife behaviour. Work at King's College London led by Dr Margiotta-Casaluci, Institute of Pharmaceutical Science, aims to integrate complex multidimensional data to better understand the environmental and toxicological dimensions of the problem. Most of the studies investigating the potential environmental effects of neuroactive substances consider one compound at the time; however, tens of neuroactive pharmaceuticals are simultaneously present in our rivers, increasing the risk of possible mixture effects. A scientifically-sound and pharmacology-informed prioritization approach is essential to systemically identify the compounds that drive the overall risk. Novel inter-disciplinary strategies are urgently needed to predict and interpret the wider ecological implications of chemical-induced disruption of wildlife behaviour.

HIDDEN THREATS, EMERGING CHEMICAL CONTAMINANTS

Emerging contaminants in rivers are becoming increasingly commonplace, affecting local environments; in England for example, 0% of rivers are currently at 'good' chemical status,[1] and only 14% qualify as having 'good' ecological status.[2] Such statistics can be partly explained by poor practice: Thames Water, for example, dumped raw sewage aced with pharmaceuticals into local waters 5,028 times in 2021 alone.[3] Pollution doesn't just affect the water itself: within the last two decades a rapidly growing number of studies have reported the impact of human activities on wildlife health as well as behaviour in both aquatic and terrestrial ecosystems,[4] sparking a renewed interest in behavioural ecotoxicology.

Chemical pollution has been classified as one of the greatest global threats to both humans[5] and wildlife.[6] Further, there is growing concern that the release of such chemicals into the environment has already modified the behaviour of wild organisms.[7,8] Some of these chemicals are neuroactive and psychoactive pharmaceuticals specifically designed to interact with molecular targets in the central nervous system (CNS) and modify human behaviour.[9] Many of their pharmacological targets are evolutionarily conserved in fish and other species; these drugs may therefore cause behavioural alterations of aquatic wildlife as they do in humans.[10]

Considering that appropriate behavioural responses are critical for individual survival and population sustainability, drug-induced behavioural alterations may potentially, then, lead to profound ecological effects.[11] With prescription rates of neuroactive pharmaceuticals globally – including England[12] – on the rise, how we determine whether observed levels of pharmaceuticals in aquatic environments are safe for both human and wildlife health demands further investigation.

MAPPING ENVIRONMENTAL OCCURRENCE AND PREDICTING RISKS

Existing laboratory studies[10] have demonstrated that some neuroactive pharmaceuticals can affect various behavioural aspects of a range of aquatic organisms (Figure 1); however, these investigations have typically focused on a very small species set, and often consider one compound at a time. Working on the hypothesis that exposure to a cocktail of neuroactive compounds has a high probability of perturbing animal behaviour, Dr Luigi Margiotta-Casaluci and colleagues' recent work focusses on mapping environmental occurrence and predicting risks of *all* marketed neuroactive pharmaceuticals in the UK to delineate underlying toxicological threats and offer new solutions.[9] To establish whether observed levels of pharmaceuticals in aquatic environments represent a risk to wildlife health, Sumpter & Margiotta-Casaluci[9] have used a combination of predictive models to translate existing clinical and human pharmacology data into environmentally-relevant predictions (for example, tailored specifically to fish).

Figure 1: *The zebrafish (Danio rerio) is one of the most common fish species used to investigate the behavioural effects of pharmaceuticals in the laboratory setting (Photo by Lynn Ketchum, courtesy of Oregon State University).*

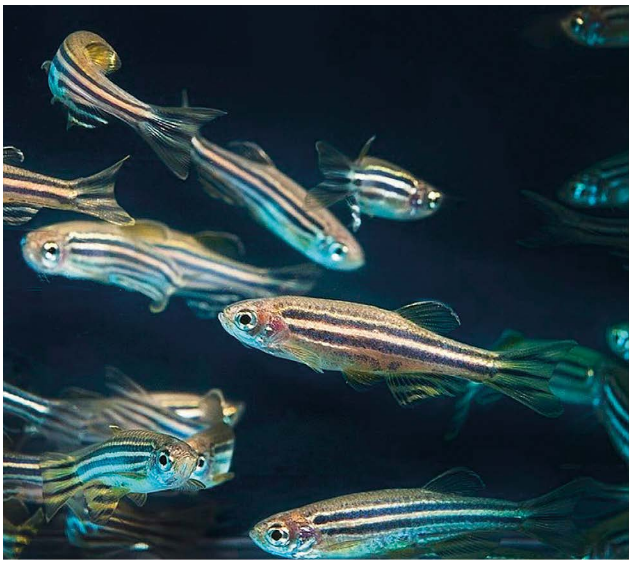
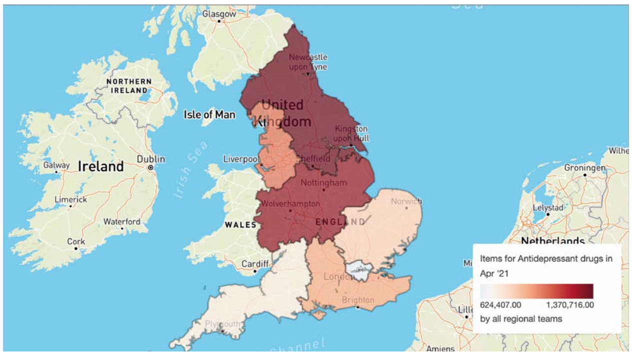
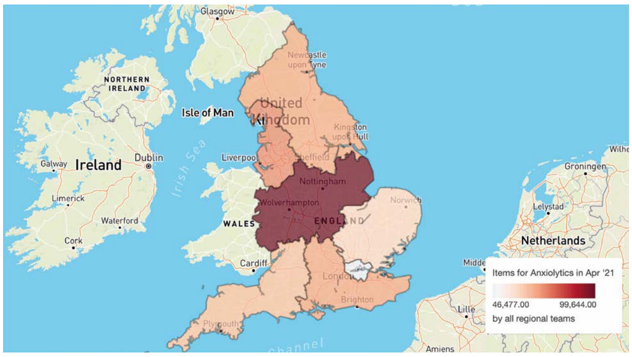


Figure 2: *Regional differences in the prescription volumes of two selected classes of neuroactive pharmaceuticals (antidepressants, anxiolytics, opioid analgesics) in England in April 2021. Reprinted with permission from "Sumpter, J.P.; Margiotta-Casaluci, L. Environmental Occurrence and Predicted Pharmacological Risk to Freshwater Fish of over 200 Neuroactive Pharmaceuticals in Widespread Use. Toxics 2022, 10, 233. https://doi.org/10.3390/toxics10050233".*

Antidepressants



Anxiolytics

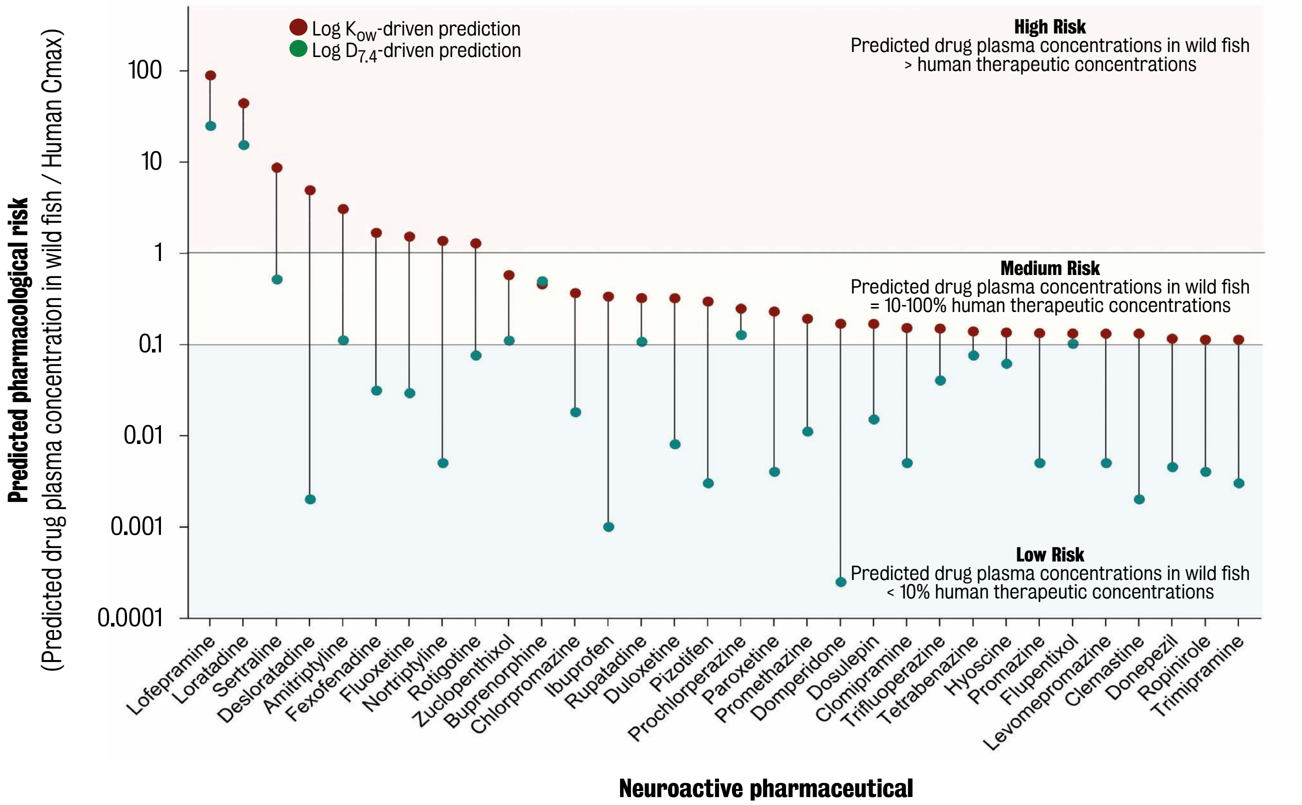


PHARMACOLOGICAL RISK OF NEUROACTIVE PHARMACEUTICALS IN ENGLISH RIVERS

Taking England's pharmaceutical market as a case study, Sumpter & Margiotta-Casaluci[9] mapped the environmental occurrence and predictive risks of all neuroactive pharmaceuticals dispensed in England by the National Health Service. To do so, they identified 210 different CNS-acting pharmaceuticals prescribed to treat a variety of CNS-related conditions (e.g. Figure 2); further analysis of existing databases revealed 84 of these compounds have already been detected in surface waters worldwide. This data was then used to predict the concentrations of select pharmaceuticals in England's rivers as well as in the bloodstreams of resident wild fish, which were then compared against established concentrations known to elicit therapeutic effects in humans.

Then, using a biological read-across approach based on clinical data extrapolation, the authors predicted that the

Figure 3: *Predicted pharmacological risk to freshwater fish of neuroactive pharmaceuticals. The pharmacological risk of 210 neuroactive pharmaceuticals was estimated by comparing the predicted concentrations of pharmaceuticals in fish plasma and the human therapeutic plasma concentrations. The figure displays all neuroactive pharmaceuticals predicted to have medium and high risk, based on the use of LogKOW for the prediction of drug uptake (red dots). To understand the impact of the use of different partitioning factors on the overall pharmacological risk, the same prediction was also performed using Log D7.4 (green dots). Reprinted with permission from "Sumpter, J.P.; Margiotta-Casaluci, L. Environmental Occurrence and Predicted Pharmacological Risk to Freshwater Fish of over 200 Neuroactive Pharmaceuticals in Widespread Use. Toxics 2022, 10, 233. https://doi.org/10.3390/toxics10050233.*



concentration of 32 said compounds in surface waters in England may be high enough to elicit pharmacological effects in wild fish (Figure 3). These results strongly suggest that the many neuroactive pharmaceuticals currently detectable in the environment may act additively as a mixture, increasing overall risk of adverse behavioural alterations. Such an approach, Sumpter & Margiotta-Casaluci[9] propose, represents a model that can effectively introduce pharmacological concepts into environmental risk assessments.

LOOKING FORWARD

At King's College London, Dr Margiotta-Casaluci and colleagues are leading research in this field that tackles global issues and adds value to the UK economy. It helps local and international communities lead healthier and happier lives; makes the planet safer, fairer, and cleaner by influencing policy and practice. Chemical pollution poses a threat to environmental and human health at global level, and it represents an obstacle for the delivery of the United Nations Sustainable Development Goals.[13]

Moving forward, the translation of biological complexity into science-based decision-making contexts represents a major challenge to future research. Laboratory-based fish in vivo testing represents the gold standard to detect chemical-induced behavioural effects (Figure 1). However, the experimental reproducibility of such effects is sometimes limited due to numerous factors, including the intrinsic complexity and variability of animal behaviour. Consequently, the interpretation of behavioural data in a regulatory and decision-making context remains difficult.[9] Despite the growing attention on the issue of neuroactive pharmaceuticals in the environment, the majority of these compounds have not been studied for their fish ecotoxicity. Filling this data gap with further *in vivo* laboratory experiments involving protected animals would likely have unsustainable financial and ethical costs, and it would rapidly become incompatible with the growing global ambition to phase out animal testing for chemical safety assessment in the next decade or so. These considerations highlight the urgency of supporting research initiatives aimed at understanding the mechanistic basis of chemical-induced behavioural perturbation in fish (and other relevant vertebrate species potentially exposed to pharmaceuticals in the environment).

There is a need to support the identification of a suitable set of new approach methodologies (NAMs) that could be deployed to predict the risk of chemical-induced behavioural alterations without the need to perform animal testing. Dr Margiotta-Casaluci and colleagues are currently working to develop novel methods to assess the safety of these compounds for ecotoxicology (in the absence of animal testing) by using cell cultures, organoids, organs on chip, or, ideally, computer models leveraging artificial intelligence. These novel approaches are intended to generate novel mechanistic understanding able to support regulatory risk assessment. NAMs can be applied for the assessment of individual chemicals, but they can also be useful to assess the effects of pharmaceutical mixtures, either directly (for example, experimentally) or indirectly (for example, generating mechanistic data able to support mathematical modelling of mixture effects).

Currently, assessing the risk posed by neuroactive chemical mixtures throughout life courses represents a great challenge. In addition to the advancement of novel scientific methods, interdisciplinary training is critically important to generate the expertise we need to support toxicology education at a global level, and transfer data into policy outcomes. To make a real difference, we need to increase the real-world relevance of toxicology evidence and foreground solutions by exploring ethically difficult questions, such as: "would you potentially give up using x drug that has potentially adverse effects within the environment, and would you instead ask your GP for a greener alternative?"

A NOTE TO READERS

At King's College London we carry out pioneering high-impact research aimed at advancing our ability to assess the safety of drugs and other chemical products across species, including humans and wildlife. We integrate advanced experimental technologies with big data analysis and artificial intelligence to unravel the complex network of biological processes underlying chemical-induced toxicity. With greater mechanistic understanding and highly precise predictions, we contribute to maximising the impact of our research in the real world by collaborating closely with a wide set of global stakeholders, including governmental and public health agencies, regulators, pharmaceutical and consumer products industries.

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ABOUT KING'S WATER CENTRE

King's Water Centre works to incubate, elevate, and empower the best science and innovation to tackle the world's water problems. We are curiosity-driven, interdisciplinary, and solutions-focused. Based in the heart of London, King's Water Centre brings together scholars and practitioners for a just and sustainable water future.

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