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# A review of the pharmaceutical exposome in aquatic fauna☆

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ABSTRACT

Pharmaceuticals have been considered 'contaminants of emerging concern' for more than 20 years. In that time, many laboratory studies have sought to identify hazard and assess risk in the aquatic environment, whilst field studies have searched for targeted candidates and occurrence trends using advanced analytical techniques. However, a lack of a systematic approach to the detection and quantification of pharmaceuticals has provided a fragmented literature of serendipitous approaches. Evaluation of the extent of the risk for the plethora of human and veterinary pharmaceuticals available requires the reliable measurement of trace levels of contaminants across different environmental compartments (water, sediment, biota - of which biota has been largely neglected). The focus on pharmaceutical concentrations in surface waters and other exposure media have therefore limited both the characterisation of the exposome in aquatic wildlife and the understanding of cause and effect relationships. Here, we compile the current analytical approaches and available occurrence and accumulation data in biota to review the current state of research in the field. Our analysis provides evidence in support of the 'Matthew Effect' and raises critical questions about the use of targeted analyte lists for biomonitoring. We provide six recommendations to stimulate and improve future research avenues.



## 1. Pharmaceuticals as a cause for concern in the aquatic environment

Chemical contaminants entering the environment are a consistent cause for concern. In particular, pharmaceutical and personal care products (PPCPs) have been identified as emerging contaminants (Daughton and Ternes, 1999; Ellis, 2006), i.e. compounds which are not routinely monitored and are suspected to cause adverse effects in the environment. In 2015, at the International Conference on Chemicals Management (ICCM), the pharmaceutical industry and non-governmental bodies agreed that the environment now requires protection from "pharmaceutical pollution" (Time to get clean. Nature, 2015). The combination of total compounds exposed to, and their effects on, an organism over an entire life cycle is termed the 'exposome' (Rappaport, 2011; Escher and Hermens, 2004). Global occurrence and fate in abiotic aqueous (Balakrishna et al., 2017; Bu et al., 2013; Heberer, 2002) and solid matrices (Díaz-Cruz et al., 2003; Halling-Sørensen et al., 1998; Pan et al., 2009; Tadeo et al., 2012) have formed the focus of several in-depth reviews. In the context of the exposome - especially pharmaceutical residues - it is arguably the internalised compound concentrations that will determine biological effects in an organism. To date, biomonitoring of pharmaceuticals in aquatic biota (as potentially the most at risk group) have not been reviewed in great depth as studies have only relatively recently begun to emerge more frequently in the literature. However, we direct the reader to earlier literature from 2011, that covers a wide range of contaminants in aquatic wildlife including the very first studies

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associated with the measurement of pharmaceuticals (Beyer and Meador, 2011).

The EU Water Framework Directive has included pharmaceuticals on a dynamic 'watch-list' based on potential for adverse effects in the aquatic environment. This list includes insecticides, herbicides, a sunscreen, several antibiotics, some natural hormones and two pharmaceuticals (17-alpha-Ethinylestradiol (EE2) from the birth control pill and diclofenac, a non-steroidal inflammatory drug) under the Environmental Quality Standards Directive and are subject to European monitoring (Carvalhoet al, 2015). The Convention for the Protection of the Marine Environment of the North-East Atlantic (OSPAR) was the first body to formally recognise pharmaceutical contamination, where the compound clotrimazole was included on their priority action list (OSPAR, 2002). OSPAR now lists 28 substances or groups of substances, with a further 264 compounds (including 25 pharmaceuticals) as contaminants of possible concern under four separate categories (OSPAR). Several non-regulatory groups, such as the Network of reference laboratories, research centres and related organisations for monitoring of emerging environmental substances (NORMAN), share knowledge on environmental contaminants gathered from monitoring campaigns and aim to harmonise analytical approaches for contaminant identification and determination in a range of environmental compartments (Brack et al., 2012). Other groups include those such as the United Nations Educational, Scientific, and Cultural Organization (UNESCO) which have recently released a series on 'emerging pollutants in water' (UNESCO and HELCOM, 2017). Whilst, the collation and dissemination of information from these groups is valuable, it is also essential that reported information is consistent and accurate otherwise it can lead to reduced data value. Therefore, it may be prudent to standardise units when reporting occurrence data (e.g. $\mu g\ L^{-1}$) to avoid this type of error. As observed in other fields, reporting to accepted quality standards in research articles is critical if they are used to help inform policy, scientific practice and knowledge (Munafò et al., 2017). However, research articles can omit critical information relevant to the study and this potentially decrease their value. Appropriate chemical analysis method validation guidelines should be used, ideally integrated within the wider umbrella of acceptable reporting guidelines, and this would help ensure the reliability of any reported contaminant concentrations in biota. A range of guidelines are available that have been developed to improve reporting standards across health research (Simera et al., 2010) and this should ideally be no different for ecotoxicology. For example, guidelines such as Animals in Research: Reporting In Vivo Experiments (ARRIVE) (Kilkenny et al., 2010) could be adapted to improve the reporting standards for monitoring campaigns and effect-based studies (especially those using bespoke behavioural endpoints). However, guidelines for both method validation and reporting standards still require consensus within the scientific community in this particular field.

Pharmaceutical concentrations in environmental waters are generally considered non-toxic to humans directly (ng-$\mu g\ L^{-1}$), but this may not be the case for wildlife. Unlike other traditional persistent organic pollutants, PPCPs are not so easily classified as they are not always persistent. They are, however, pseudo-persistent due to continual influx to the environment from several sources, including waste water treatment plants (WWTPs), manufacturing, agriculture and aquaculture, amongst other routes (Boxall et al., 2012). Furthermore, pharmaceuticals are generally designed not to be bioaccumulative (Lipinski et al., 1997), as demonstrated during *in vivo* laboratory exposures (Miller et al, 2016, 2017; Meredith-Williams et al., 2012; Nichols et al., 2015; Nallani et al., 2011). Effects are often studied and observed at non-environmentally relevant concentrations of single compounds (i.e. acute toxicity) under defined laboratory conditions (Carlsson et al., 2006). Any effects observed are generally not explicitly linked to the cause (i.e. the internalised drug is not determined) (Rand-Weaver et al., 2013). Pharmaceutical residues are rarely monitored within wild biota, leading to a knowledge gap in the extent and route of exposure these organisms encounter over their lifetime within their respective habitats. Thus, measurement of pharmaceutical tissue concentrations in aquatic wildlife is increasingly important. The challenges in understanding potential environmental risks are exacerbated by a large disparity between laboratory and the field-derived bioconcentration data. Surface water drug concentration measurements are a useful alternative, and have been the focus to date, but represent only one single compartment. For example, partitioning to sediments also needs to be considered, especially for benthic-dwelling organisms (Gilroy et al., 2012). Significant spatial and temporal fluctuations also exist (Miller et al., 2015; Luo et al., 2014). For pharmaceuticals, further complexity is added by their ionisation state in comparison to typical non-polar compounds, and this is important because it makes comparisons difficult across scenarios where water chemistry can impact ionisation and therefore uptake into biota (Karlsson et al., 2017).

Pharmaceuticals are often designed to cross biological membranes and therefore rate of uptake and internal concentrations are critically important. Therefore, to fully understand the potential for pharmaceuticals to cause harm in the aquatic environment, it is essential to assess wider occurrence in biota (including fish, invertebrates, plants and algae). The limited number of reports detailing occurrence in biota is potentially caused by two factors. The first of these is biological variation (there are estimated to be ~31,000 fish species and ~176,000 aquatic invertebrates described to date). The second is the analytical capabilities required for broad scope, multi-residue determination of thousands of human and veterinary pharmaceuticals and their metabolites in so many complex matrices at very high sensitivity.

The aim of this work is to review the occurrence of pharmaceutical residues in aquatic fauna. As part of this, a critical discussion will be presented focussing on (a) the range and reliability of analytical approaches for trace pharmaceutical and metabolite determination in aquatic fauna; (b) the reported occurrence of pharmaceuticals across a range of species, including fish and invertebrates, up to 2016; and (c) the bioaccumulation potential of pharmaceuticals and comparisons of field- and laboratory-based measurements. The use and collation of biomonitoring data to characterise pharmaceutical contamination is critical to understanding the extent of exposure and potential impact on aquatic fauna.

## 2. Systematic literature searching and statistical tests

A systematic search of published reports in the literature was performed using Scopus® (Elsevier, Netherlands). Several keywords were included to identify published works for pharmaceutical occurrence in fish and invertebrates. These included "occurrence", "PPCPs" or "pharmaceuticals", and "fish" or "invertebrates". The terms were searched across document titles, types, abstracts and keyword lists across all years up to 2016. The same keywords were also included in searches using Google Scholar up to 2016, to improve coverage of the available literature. Using this structured search strategy and to the best of our ability, all papers on pharmaceutical occurrence in aquatic fauna (fish or invertebrates) have been included, see Supplementary Information (SI) for full occurrence data tables. All statistical tests were performed in Minitab 18 (Minitab Inc., US) or Sigma Plot (Systat Software Inc., US) with a significance level set to alpha = 0.05.