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Assessing the exposure risk and impacts of pharmaceuticals in the environment on individuals and ecosystems


1. Introduction

The continued expansion of the human population is leading to escalating demand for resources, including human and veterinary pharmaceuticals. Pressures are exerted by increasingly intensive agriculture and exacerbated by rising human longevity and obesity, leading to more health problems [1]. With this comes a proliferation in the quantity and diversity of pharmaceuticals consumed and...
excretion of un-metabolized ‘parent compounds’ or bioactive metabolites, persistence in the environment and potential to bioaccumulate in food chains. Such an approach has been used by Chris Metcalfe (Trent University) to predict environmental concentrations of antidepressants. Long-term monitoring of pharmaceuticals in rivers and lakes confirmed the presence of antidepressants and other pharmaceuticals in plumes around STW outflows [9]. Wild fish gaged within these plumes exhibited significant changes in a range of biomarkers, but consequences for individual fitness and population persistence are unknown.

Monitoring exposure to pharmaceuticals in terrestrial ecosystems is less well developed than in freshwater, but transferable techniques have been used to assess exposure risk to plant protection products on farmland [10]. Via radio-tracking, Helen Thompson (FERA) has mapped how wild birds and mammals disperse around contaminated resources at the landscape scale, which could also be used to record the movements of terrestrial vertebrates on STWs or sewage sludge fertilized fields, for example. At the national level, Richard Shore (CEH) suggested that current wildlife monitoring schemes, for example, the Predatory Bird Monitoring Scheme (http://pbms.ceh.ac.uk/), could be adapted to include surveillance for pharmaceutical exposure in addition to other contaminants [11]. Temporal and spatial trends in pharmaceutical exposure could therefore potentially be traced.

As with terrestrial habitats, there is a lack of data on pharmaceutical exposures for the marine environment, highlighted by Sally Gaw (University of Canterbury), despite it being a major receptor for wastewater due to increasing human habitation of coastal areas and more intensive use of pharmaceuticals in aquaculture.

4. Uptake and fate of pharmaceuticals in food webs

In contaminated environments, uptake of pharmaceuticals by invertebrates was shown by Alistair Boxall (University of York) to vary depending on the chemistry of the environmental matrix and species’ mode of feeding, thus effects can be difficult to predict [12]. Similarly, in terrestrial vertebrates, understanding consequences of group versus solitary feeding, or responses to novel food types, is important when designing captive experiments to calculate a realistic uptake rate [10]. Extending his work on the uptake and fate of NSAIDs in Asian vultures [6,13], Mark Taggart (University of the Highlands and Islands) is also analysing vulture and livestock samples with the aim of assessing the true risk of veterinary antibiotics to scavenging birds in Spain, a stronghold for vultures in Europe. Understanding the ecology of susceptible, exposed animals is vital.

5. Behaviour of pharmaceuticals

Risk assessment in the twenty-first century faces many challenges, including the growing numbers of compounds in circulation, while avoiding excessive use of animal testing. Thomas Hutchinson (CEFAS) described recent work on developing the OECD’s Adverse Outcome Pathway (AOP) approach to prioritize species selection for laboratory research and field monitoring; it uses six levels of information ranging from the chemical properties of a toxicant through to population impacts [14]. While there are data gaps for
pharmaceuticals, this AOP approach can facilitate read-across between chemicals with similar modes of action across diverse taxa. This can increase the power of such models to predict pharmaceutical effects on wildlife [4].

Judith Madden (LJMU) demonstrated the use and limitations of in silico tools for predicting ecotoxicity of pharmaceuticals, including predictions based on simple physico-chemical properties, as well as tools for grouping compounds into categories to allow for read-across. Categories can be formed using profilers for relevant interactions such as DNA or oestrogen receptor binding [15]. While models are also available for uptake and metabolism, understanding inter- and intraspecies variation is fundamental to predicting toxicity. Experiments by Vinny Naidoo (University of Pretoria) have shown that Gyps and other vulture species have an unusual metabolism with respect to NSAIDs [16]; they are suggested to be CYP 2C9 deficient or diminished, as are cats, which are also highly sensitive to NSAIDs and so may provide a pharmacokinetic model for vultures.

6. Effects of pharmaceuticals on wildlife

The paucity of studies on the effects of pharmaceuticals on non-model, particularly terrestrial, species was further highlighted by Judit Smits (University of Calgary). Essentially, we now need further development of non-lethal assays or biomarkers of subclinical toxicity following exposure to contaminants, for example, biotransformation enzymes and hormones [17]. Key features of an ideal sentinel for pharmaceutical risk in the wild include natural risk of exposure, toleration of human disturbance and relevance to the food web of interest. One such species is the European starling *Sturnus vulgaris*, which commonly feeds on pharmaceutical-contaminated invertebrates living on STWs. The species is robust to capture and captivity and forages on invertebrates, a potentially important but unstudied exposure route. Kathryn Arnold (University of York) found that long-term exposure to an environmentally relevant dosage of fluoxetine (Prozac), a commonly used antidepressant, altered physiology, behaviour and mass balance in starlings. While behaviours are non-lethal and ecologically relevant endpoints to measure in such studies, they can be challenging to analyse and interpret because of the high degree of individual variability [18].

Standardized laboratory tests and endpoints are required in order to ensure the reliability and repeatability of ecotoxicological studies. Exposure conditions and test organisms need careful consideration, as, for example, there may be significant inter- and intraspecies variation in sensitivity, requiring the use of additional safety factors. Although many studies claim to use outbred strains, which are considered more representative of wild populations, these claims are rarely supported by pedigree or genetic evaluation. Ross Brown (AstraZeneca and University of Exeter) has shown that inbred family lines of zebrafish can differ significantly in their physiological and developmental responses to pharmaceuticals, compared with outbred wild-type family lines [19].

7. Grand challenges for research, regulation and policy development

We identified several grand challenges for researchers in this field including, firstly, realistic assessments of exposure risks to pharmaceuticals, which are missing for most species, should account for the diversity and abundance of pharmaceuticals in environmental matrices, dispersal data for animals in contaminated landscapes and processes affecting uptake via diet or other routes. Assessments need to be future-proofed against increasing water scarcity and recycling of raw sewage, wastewater and application of sewage sludge in agriculture.

Secondly, current prospective risk assessments are based on individuals exposed to a single pharmaceutical under relatively benign laboratory conditions. In reality, animals are exposed to cocktails of chemicals, including pharmaceuticals and multiple environmental stressors, which can interact synergistically, additively or antagonistically [3]. Pharmaceutical impacts, where they occur, need to be distinguished from variation in fitness-related traits due to natural or anthropogenically mediated fluctuations in food availability, parasitism, etc.

Thirdly, for assessing pharmaceutical risks to wildlife globally, we need to focus on the developing world, where pharmaceutical production and consumption is rapidly increasing. With little or no treatment of some manufacturing discharges or municipal and agricultural waste streams containing human and veterinary pharmaceuticals, risks to wildlife and humans are predicted to be high, but remain virtually unassessed [20,21]. Such scientific research could support future international development policies.

Populations of many species living in human-altered landscapes are declining for reasons that often cannot be fully explained. Therefore, we believe that diverse approaches used by academic researchers, industry risk assessors and regulators need to be better integrated to assess current and future risks from pharmaceuticals in the environment.

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