Moving Beyond Model Organisms – Next Generation Species Extrapolation

567 Use of the Adverse Outcome Pathway Framework to Represent Cross-species Consequences of Specific Pathway Perturbations

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The adverse outcome pathway (AOP) framework has been developed as a means for assembling scientifically defensible descriptions of how particular molecular perturbations, termed molecular initiating events (MIEs), can evoke a set of predictable responses at different levels of biological organization (key events, KEs) culminating in an adverse outcome (AO) of regulatory significance. It is however recognized that the consequences of chemical-induced pathway perturbations can vary significantly among species. Therefore, for the framework to be useful in an ecological risk assessment context, it is important that both cross-species similarities and differences can be represented. Recent case studies with thyroperoxidase and deiodinase inhibition leading to adverse developmental outcomes in fish, frogs, and mammals, and aryl hydrocarbon receptor activation leading to adverse effects in fish, birds, and mammals, provide examples of how the AOP framework, and AOP networks, can be applied to capture knowledge concerning the range of AOs that may manifest across species. The examples provide insight into how the AOP framework can serve as a foundation and justification for using high throughput toxicology data from a limited range of model species to predict apical outcomes in a broader range of taxa. Additionally, they demonstrate how a systematic evaluation framework can be applied to consider the relevant taxonomic applicability domain of any given AOP. Overall, the case studies demonstrate how the AOP framework can be effectively applied to support and inform cross-species extrapolation as part of a pathway-based to risk-based ecological decision-making. The contents of this abstract neither constitute nor necessarily reflect official USEPA policy.

568 Species extrapolation between humans and fish: A two-way street

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Fish are an important translational model for the pharmacological and toxicological characterization of human pharmaceuticals in both environmental and biomedical applications. However, do fish respond to pharmaceuticals as humans do? To address this question, we applied a novel quantitative cross-species extrapolation approach based on the hypothesis that similar plasma concentrations of pharmaceuticals cause comparable target-mediated effects in both humans and fish at similar level of biological organization (Read-Across Hypothesis). This approach was developed with the aim of taking species extrapolation beyond the horizon of qualitative applications and to fully exploit its translational power in a quantitative decision-making scenario. Here, we will provide an overview of the predictive power of the Read-Across approach using a set of pharmaceuticals acting via different mechanisms of action. Anchoring the interpretation of pharmacological and toxicological effects to drug internal concentrations resulted in a significant improvement of the predictive power of species extrapolation. This suggests that a deeper understanding of uptake as well as absorption, distribution, metabolism, and excretion processes in different species can represent a major driving factor to enhance the reliability of the extrapolation of risk assessment of pharmaceuticals across species. The theoretical implications of the Read-Across approach will be discussed in the context of the Adverse Outcome Pathway concept and we will propose possible future steps for large-scale application of cross-species extrapolation approaches to the risk assessment of pharmaceuticals.

569 Leveraging a large scale mammalian pharmacological dataset to prioritize potential environmental hazard of pharmaceuticals

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The potential for pharmaceuticals in the environment to cause adverse ecological effects is of increasing concern. Given the thousands of active pharmaceutical ingredients (APIs) which can enter the aquatic environment through various means, a current challenge in aquatic toxicology is identifying those that pose the greatest risk. Because empirical toxicity information for aquatic species is generally lacking for pharmaceuticals, an important data source for prioritization is that generated during the mammalian drug development process. Applying concepts of species read-across, mammalian pharmacokinetic data were used to systematically prioritize APIs by estimating their potential to cause adverse biological consequences to aquatic organisms, using fish as an example. Mammalian ADME (absorption, distribution, metabolism, excretion) data (e.g., peak plasma concentration, apparent volume of distribution, clearance rate and half life) were collected and curated, creating the Mammalian Pharmacokinetic Prioritization For Aquatic Species Targeting (MaPPFAST) database representing 1070 APIs. From these data a probabilistic model and scoring system were developed and evaluated. Individual APIs were ranked based on clearly defined read-across assumptions for translating mammalian derived ADME parameters to estimate potential hazard in fish (i.e., greatest predicted hazard associated with lowest mammalian peak plasma concentrations, total clearance and highest volume of distribution, half-life). In addition, the MaPPFAST database can be used to develop data-derived estimates for missing or unknown data, furthering prioritization efforts. It is anticipated that the MaPPFAST database and the associated API prioritization approach will help guide research and/or inform ecological risk assessment.

570 Differences in species sensitivity towards the psychiatric drug oxazepam

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We have previously showed that an anxiolytic drug, the benzodiazepine Oxazepam, alters behavior and feeding rate of wild European perch (*Perca fluviatilis*) at concentrations closely related to those reported in effluent influenced surface waters. Exposed individuals exhibited increased activity, reduced sociality, and higher feeding rate with the implications that anxiolytic drugs in surface waters profoundly alter animal behaviors that are known to have ecological and evolutionary consequences. In our first study only a single species was investigated but inter-species internal levels, following exposure of a pollutant, may vary due to diverse bioaccumulation rates. To make things even more interesting, not all species have the mode-of-action targets for pollutants, which are relevant in the case of pharmaceuticals, since the environmental effects would have to be correlated with conserved targets in exposed biota and not with a general toxic effect. Gunnarsson et al made predictions in 16 species whether or not they had orthologs for 1318 human drug targets and they showed that e.g., zebrafish had orthologs to 86% of the drug targets while only 61% were conserved in *Daphnia*. Benzodiazepines, for examples, act upon the γ-aminobutyric acid (GABA) receptor and several species have orthologs of this receptor, which implies that many, but not all, organisms in aquatic environments could be affected by this pollutant. These inter-specie sensitivity differences will of course have implications in effluent dominated aquatic environments since this will most likely cause asymmetric ecological effects in exposed biota. This study therefore focuses on both the difference in bioconcentrations factors (BCFs) and response, measured as behavioral alterations of the benzodiazepine, oxazepam, in both vertebrates and invertebrates.