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Session: Adverse outcome pathway concept in research and risk assessment

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Title:
Quantitative AOP Linking Aromatase Inhibition to Impaired Reproduction: A Case Study in Predictive Ecotoxicology

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Abstract:
The adverse outcome pathway (AOP) framework is intended to help support greater use of mechanistic toxicology data as a basis for risk assessment and/or regulatory decision-making. While there have been clear advances in the ability to rapidly generate mechanistically-oriented data for large libraries of chemicals using in vitro high throughput assays, questions remain about whether the AOP framework can be used to help translate those data into quantitative predictions of the probability or severity of an adverse outcome. This study couples together a series of computational models to yield a quantitative AOP (Q-AOP) construct capable of taking the in vitro relative potency of an aromatase inhibitor as an input and predicting potential effects on fish reproduction, as well as simulating the dose-response time-course behaviors at several key events. As a case study in predictive ecotoxicology, US EPA Toxcast results were used to select eight chemicals that were active in mammalian cell-based and cell-free bioassays designed to detect aromatase inhibition. At test concentrations ranging up to 130 μM, seven of the eight chemicals selected also inhibited fathead minnow ovarian aromatase activity in vitro. Simulations based on the Q-AOP construct predicted that continuous exposure to 2, 10, or 50 μg fadrozole-equivalents/L would lead to 20% to >99% reductions in population size over a 10 year period. However, two independent mechanistically-based models linking aromatase inhibition to predicted plasma vitellogenin concentrations yielded markedly different dose-response time-course behaviors and subsequent population trajectories. These results suggest that model

uncertainty could be reduced considerably through additional iterations of model testing and refinement. Nonetheless, the case study supports the feasibility of using computational representations of generalized biological response motifs in the form of a Q-AOP as a basis for translating mechanistic data generated via high throughput screening into meaningful predictions of ecotoxicologically-relevant outcomes. *The contents of this presentation neither constitute nor necessarily reflect US EPA policy.*

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