

Development of Quantitative Adverse Outcome Pathways Using Health-Protective Assumptions to Fill Data Gaps

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In an adverse outcome pathway (AOP), the target site dose participates in a molecular initiating event (MIE), which in turn triggers a sequence of key events leading to an adverse outcome (AO). Quantitative AOPs (QAOP) are needed if AOP characterization is to address risk as well as hazard. A QAOP is based on data from and, in its mature form, has the ability to predict the dose-response and time-course (DRTC) behaviors linking toxicant dosimetry, the MIE, and the key events with each other and with the AO. Identification of data gaps during QAOP development is common and, typically, some of the gaps cannot be filled given constraints of time and resources. In such situations, alternative assumptions can be identified about how the missing data would affect DRTC behaviors and the more risk-conservative assumptions incorporated until the missing data become available. We are developing a QAOP for fathead minnows. The MIA is inhibition of CYP19A, which converts testosterone to estradiol (E2). Depression of plasma E2, upregulation of CYP19A mRNA, and reduced levels of the glycolipoprotein egg yolk precursor vitellogenin (VTG) are key events. Depression of VTG is associated with decreased fecundity, the AO. Available data include time-course studies with 3 doses of the CYP19A inhibitor fadrozole, plasma E2 and VTG levels, ovarian CYP19A mRNA levels, and fecundity. In this presentation we show how quantitative dose-response relationships between key events, such as expression of CYP19A mRNA as a function of decreased plasma E2 levels, while constrained by data, can be described by alternative functions with different low dose behaviors. These alternative assumptions provide different DRTC behaviors for the overall relationship between the MIA and the AO and can be selected to bias the QAOP to provide risk conservative predictions. *This is an abstract or a proposed presentation and does not necessarily reflect EPA policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.*