ICE Tools for Aligning Assay Endpoints to Adverse Outcome Pathways

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A critical challenge to the implementation of non-animal approaches in chemical safety testing is linking endpoints measured in these approaches to adverse physiological responses in vivo. The adverse outcome pathway (AOP) framework allows these molecular, cellular, and tissue-level endpoints to be placed in a biologically relevant context. The National Toxicology Program's Integrated Chemical Environment (ICE) web resource houses curated data from in vivo, in vitro, and in silico assays and models. Many of these non-animal data sources measuring different key events in an AOP can be integrated to form defined approaches to testing and assessment for particular toxicity endpoints. The ICE ontology maps assay endpoints to key events within AOPs and enables use of ICE data with AOPXplorer, a Cytoscape plugin that allows visualization of data in AOP networks. The ability to map ICE data to AOPs can be used to identify data gaps and build confidence in the mechanistic plausibility and relevance of a proposed defined approach. This work is also relevant to understanding the respective role of active ingredients in mixtures, such as pesticide formulation products. ICE includes data on over 300 active ingredients in over 800 formulations, and provides the ability to highlight key events perturbed by the active ingredients, and compare that to formulation toxicity data. We demonstrate the utility of this workflow using an accepted AOP for skin sensitization and putative AOPs for acute toxicity pathways. This was funded with U.S. federal funds from the NIEHS/NIH/HHS under Contract HHSN273201500010C.

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