Adverse outcome pathways and systems biology as conceptual approaches to support development of 21st century test methods and extrapolation tools.

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The proposed paradigm for "Toxicity Testing in the 21st Century" supports the development of mechanistically-based, high-throughput *in vitro* assays as a potential cost effective and scientifically-sound alternative to some whole animal hazard testing. To accomplish this long-term goal, it is necessary to (1) identify and catalog common adverse outcome pathways (AOPs) and (2) based on these pathways, strategically develop a focused battery of assays with proven predictive value. The concept of AOPs provides an organizing framework for linking cellular-level responses to endpoints conventionally considered in ecological risk assessment (e.g., effects on survival, growth/development, and reproduction). Defining and cataloging AOPs provides a scientific foundation for development of toxicity pathway assays with predictive power. Systems biology is the scientific study of dynamic interactions among elements that comprise biological systems. The goal of systems biology is to understand and predict emergent properties of these complex systems. The approaches of systems biology can be used to understand the intersections and interactions among AOPs, in the context of relevant homeostatic and allostatic functions that modulate outcomes as a function of stressor intensity (e.g., dose), exposure duration, and other toxicologically relevant variables. Thus, systems biology can (1) help optimize an AOP-based *in vitro* testing framework and (2) aid the development of toxicodynamic extrapolation models needed for quantitative risk assessments. This presentation will highlight the utility of these two conceptual approaches, AOPs and systems biology, in evolving strategies for 21st century toxicity testing, using examples and products from recent international expert workshops with participants from academia, industry, government, and non-governmental organizations.