A Systems Biology Approach to Advancing Adverse Outcome Pathways for Risk Assessment

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Editors

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Preface

In 2007, the National Research Council (NRC) released a document titled "Toxicity Testing in the twenty-first Century: A Vision and a Strategy", that called for a paradigm shift in toxicology testing. The NRC report advocated for a testing platform to be based on *in vitro* methods instead of whole animal testing, and that takes a pathway approach by studying perturbations of biological systems and key toxicity pathways. This approach would ideally use a combination of computational biology and a comprehensive array of high-throughput *in vitro* tests, preferably with cells and tissues. The adverse outcome pathway (AOP) framework was born out of this NRC's call for action. The concepts underlying the AOP framework are not necessarily new. Risk assessors and researchers had already adopted mode-of-action based approaches to determine mechanisms underlying adverse toxic effects, and biologists and ecologists had espoused translating stress responses across levels of biological organization for decades. However, what was new was the organizing framework and structure, the common terminology and a convergence of new tools (omics, computational, crowd-sourcing, global connectivity) that helped solidify the framework and propel it forward. Now, almost a decade after its conception, we have made great progress and the momentum is on the side of further development and advances. Currently, there is a worldwide community of scientists that contribute to the online knowledgebase, and there are regularly scheduled workshops and meetings that continue to move the science and framework forward, bringing in an increasingly broader range of expertise. Those that work on AOPs are no longer just biologists, but also include computer scientists, mathematicians, modelers, and social scientists. The framework started as an approach to collect and organize biological information with the original purpose to determine how toxic chemicals can perturb the biological pathways and affect apical endpoints relevant to individual and population risk assessment. However, because the AOP framework is chemically agnostic, it can eventually be used to determine the impacts of any stressor, and as such can potentially unite biologists that work at every level of biological organization. The goal of this book was to explore the current state of the science and regulatory aspects, but also to think a little outside the box and bring in authors that could discuss areas of research that have not been addressed fully but would be

required to move the AOP framework forward. While the title of this book implies the use of systems biology approaches to advance the AOP framework, we also wanted to include chapters focusing on novel technologies or approaches to advance the understanding of potential molecular initiating events, key events or different levels of biological organization. We asked authors to discuss topics such as epigenetics, omics, genetic engineering, cell free assays, life history and adaptation, behavior and social acceptance. We also asked authors to discuss non-model species, invertebrates, plants and the potential of the zebrafish embryo. We wanted to describe novel quantitative and weight of evidence approaches that have the potential to overcome some barriers to prediction and we also wanted to reach scientists that have not been very active in this field yet. We hope that by including these topics and authors in this collection that this helps to advance the AOP framework by connecting to a broader range of scientific expertise and by embracing new areas of research.

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