

TITLE: THE U.S. TOX21 COLLABORATION: ADVANCES MADE AND LESSONS LEARNED

ABSTRACT BODY: Launched in 2007, Tox21 is a multiagency collaborative effort among the National Institutes of Health's National Institute of Environmental Health Sciences/National Toxicology Program and the National Center for Advancing Translational Sciences, the Environmental Protection Agency's National Center for Computational Toxicology, and the Food and Drug Administration. The objective of this partnership is to shift the assessment of chemical hazards from traditional experimental animal toxicology studies to one based on target-specific, mechanism-based, biological observations largely obtained using *in vitro* assays, with the ultimate aim of improving risk assessment for humans and the environment. More specific goals are to identify patterns of compound-induced biological response to characterize toxicity/disease pathways, prioritize compounds for more extensive toxicological evaluation, and develop models predictive of adverse health effects in humans. By 2014, ~1800 compounds have been screened across ~700 assays in the ToxCast program while a 10,000 compound library (which includes all ToxCast chemicals) was screened across a smaller, more focused set of nuclear receptor and stress response pathway assays. Tox21 is committed to full public accessibility and transparency and is releasing data through PubChem and other outlets. This symposium will summarize the progress and lessons learned from these studies; present an example prioritization scheme/prediction model; detail ongoing efforts to increase chemical characterization, biological coverage, and public outreach; and present the perspective of an end-user of the data generated by Tox21 and similar efforts.

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Funding: None

Presentation Title: The U.S. EPA ToxCast Program: Moving from Data Generation to Application

Presentation Description: The U.S. EPA ToxCast program is entering its tenth year. Significant learning and progress have occurred towards collection, analysis, and interpretation of the data. The library of ~1,800 chemicals has been subject to ongoing characterization (e.g., identity, purity, stability) and is unique in its scope, structural diversity, and use scenarios making it ideally suited to investigate the underlying molecular mechanisms of toxicity. The ~700 high-throughput *in vitro* assay endpoints cover 327 genes and 293 pathways as well as other integrated cellular processes and responses. The integrated analysis of high-throughput screening data has shown that most environmental and industrial chemicals are very non-selective in the biological targets they perturb, while a small subset of chemicals are

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relatively selective for specific biological targets. The selectivity of a chemical informs interpretation of the screening results while also guiding future mode-of-action or adverse outcome pathway approaches. Coupling the high-throughput in vitro assays with medium-throughput pharmacokinetic assays and reverse dosimetry allows conversion of the potency estimates to an administered dose. Comparison of the administered dose to human exposure provides a risk-based context. The lessons learned from this effort will be presented and discussed towards application to chemical safety decision making and the future of the computational toxicology program at the U.S. EPA.

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Funding: Registration only
Presentation Title: Tox21 Phase II: Testing the 10K library in Quantitative High Throughput Screening Assays

Presentation Description:
The Tox21 Program has profiled a diverse collection of >10,000 chemicals (i.e., 10K library) across a set of nuclear receptor and stress response pathway assays at 15 concentrations, with each assay run 3 times to improve the robustness of the data. The activity profiles generated have been made public and are being analyzed in terms of structure-activity relationships and biological relevance to assess their potential to serve as predictive signatures for in-depth toxicological testing prioritization, toxicity mechanism interpretation, and extrapolation to in vivo toxicity endpoints. The data generated on the 10K library were used to establish a “crowdsourcing competition” for individual researchers to develop computer models to predict chemical toxicity. The challenge is to use data generated by assays in the Tox21 (Toxicology in the 21st Century) high-throughput screening program to predict how chemicals will interfere with biochemical pathways, using only their structures.

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Funding: None
Presentation Title: Tox21 Phase III: Improving on Biological Coverage, Relevance, and Public Outreach

Presentation Description: Limitations associated with Tox21 Phase II have been identified; these include, for example, the limited pathway coverage (i.e., focus on nuclear receptor and stress response pathways) and the lack of biological complexity (i.e., the use of reporter gene assays using immortal cell

lines with limited capability for xenobiotic metabolism). The purpose of Tox21 Phase III, initiated in 2013, is to overcome these limitations by incorporating into the testing strategy more physiologically-relevant cell types (e.g., HepaRG cells, ES and iPSC-differentiated cell populations) and lower organisms (e.g., zebrafish, *C. elegans*), coupled to high content screening and high throughput transcriptomics platforms to assess chemical toxicity potential. Equally important are continuing efforts to make all data public and to increase stakeholder involvement by establishing formal and informal relationships with investigators and/or organizations interested in contributing to this effort.

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Presentation Title: Prioritization and Predictive Toxicology: Estrogen Receptor Active Compounds

Presentation Description: The cross-partner targeted testing working group evaluates prediction models and prioritization schemes developed from Tox21 data. Multiple Tox21 assays related to estrogen signaling were used to develop prediction models of estrogen receptor agonism or antagonism. Results from 1777 test compounds were used to populate the models and a database of highly curated *in vivo* studies (>400) was developed and used to assess the model predictions. This talk will provide an overview of ER prediction models, a description of the *in vivo* database, and performance of ER models when compared to *in vivo* results.

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Presentation Title: From Data to Decisions – An End User’s Perspective

Presentation Description: As the Tox21 collaboration approaches its decade-long anniversary, its longer term viability and sustainability will rely on moving results of this research effectively into decision and policy arenas. The promised paradigm shift in toxicity testing is but a validation framework away – not just for assay validation, but also validation of the approach to building predictive capacity. Identifying and demonstrating contexts within which these data are ready for application is critical to evolving and realizing this paradigm shift. A near-term goal may be to evaluate methods for the rapid development and validation of “alternatives” to the current regulatory tests, and to demonstrate these new approaches with contextual or fit for purpose case studies. The use of the term “alternative” rather than “replacement” avoids presumption of direct replacement of traditional toxicity tests as “gold-standard”

tests. Instead the alternative approach addresses the overall need defined by the guideline tests by incorporating novel and diverse data streams and models made possible by this successful collaboration. Selection, development, and adoption of these alternative approaches will require continued strategic engagement of research partners in the US and internationally as well as the stakeholder community.

Open Discussion Period

Schedule (165 min total)

10 min = Introductions by Chairs

25 min = Speaker 1 (Thomas)

25 min = Speaker 2 (Simeonov)

25 min = Speaker 3 (Paules)

25 min = Speaker 4 (Casey)

25 min = Speaker 5 (Bahadori)

30 min = open discussion period
