



Toxicology in the 21st Century

A New Tox21 Strategic Plan and the Integration of EPA Science

August 21, 2017

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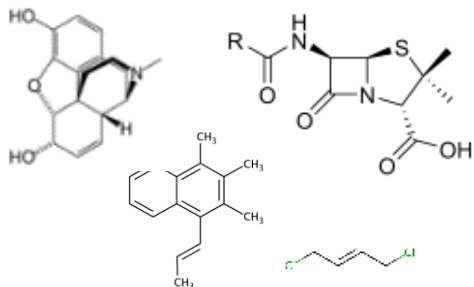
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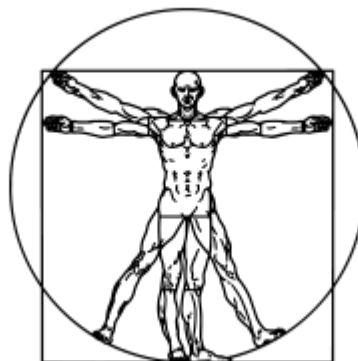
NTP
National Toxicology Program
U.S. Department of Health and Human Services

Underlying Issues Facing Toxicology

Number of Chemicals /Combinations to Test



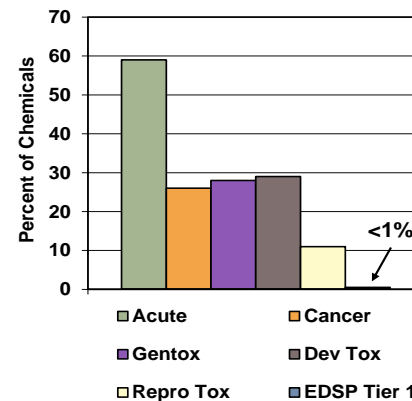
Human Relevance of Existing Tests



Ethics Concerns

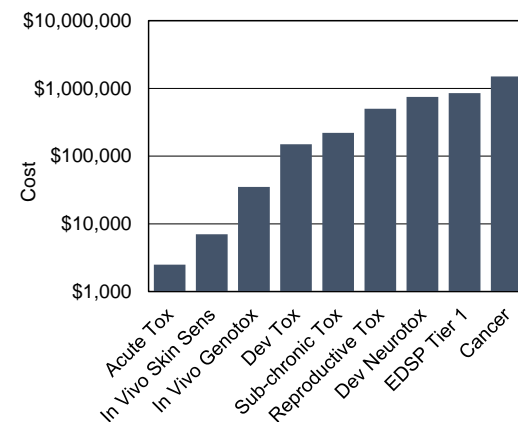


Lack of Data for Environmental Chemicals



Modified from Judson *et al.*, EHP 2010

Economics





Formation and Renewal of U.S. Tox21 Federal Partnership

MEMORANDUM OF UNDERSTANDING

ON

**High Throughput Screening, Toxicity Pathway Profiling,
and Biological Interpretation of Findings**



MOU Signed February, 2008; Revised July, 2010

XI. APPROVAL

National Toxicology Program

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Director

National Institute of Environmental Health Sciences

National Institutes of Health

5-11-15

Date

National Center for Advancing Translational Sciences

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Date

U.S. Environmental Protection Agency

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Lek-G. Kadeli

Acting Assistant Administrator

Office of Research and Development

U.S. Environmental Protection Agency

6/16/15

Date

U.S. Food and Drug Administration

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Susan T. Mayne, Ph.D.

Director

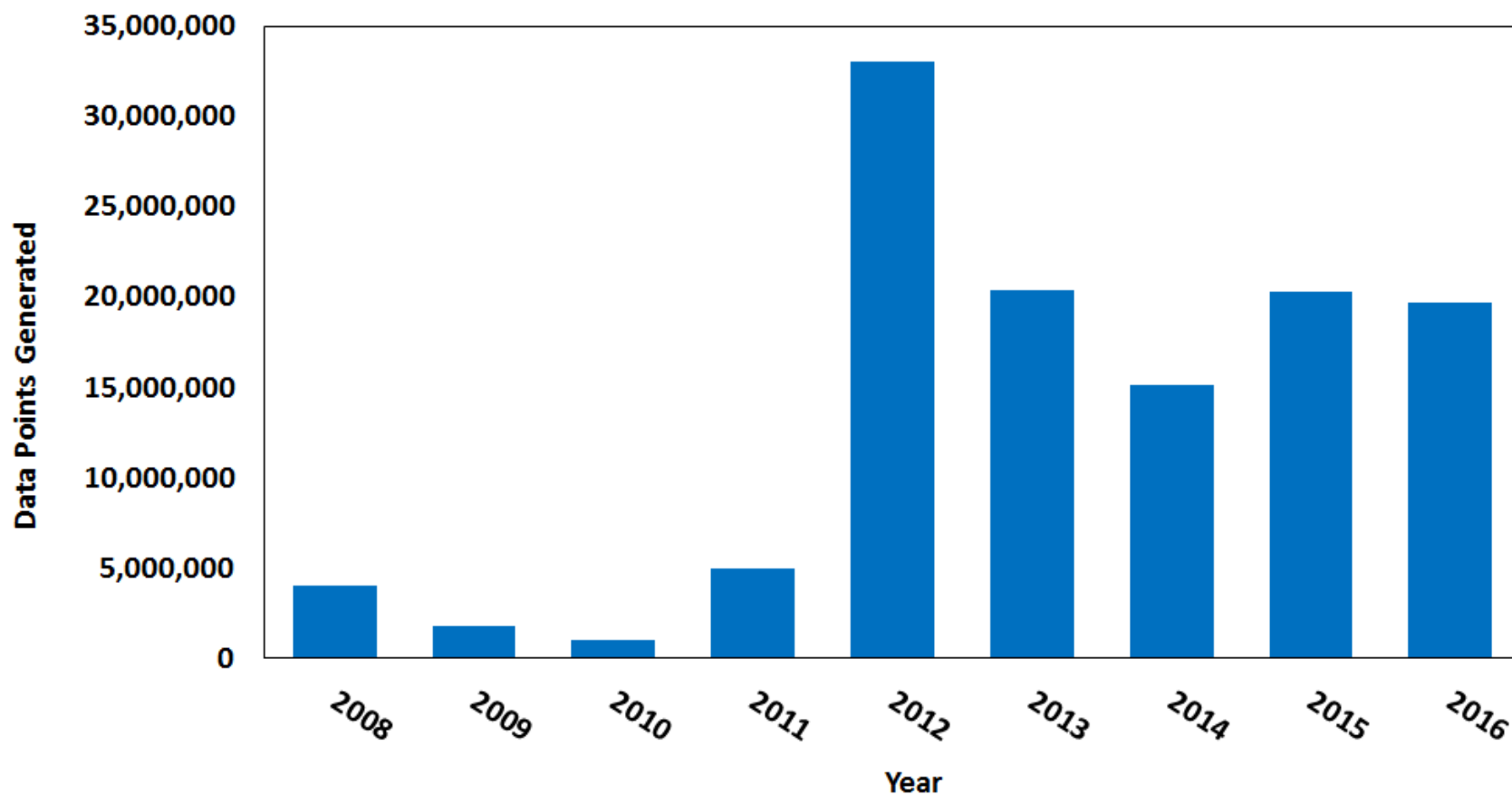
Center for Food Safety and Applied Nutrition

U.S. Food and Drug Administration

5/27/15

Date

Toxicity Testing Data Generated by Tox21

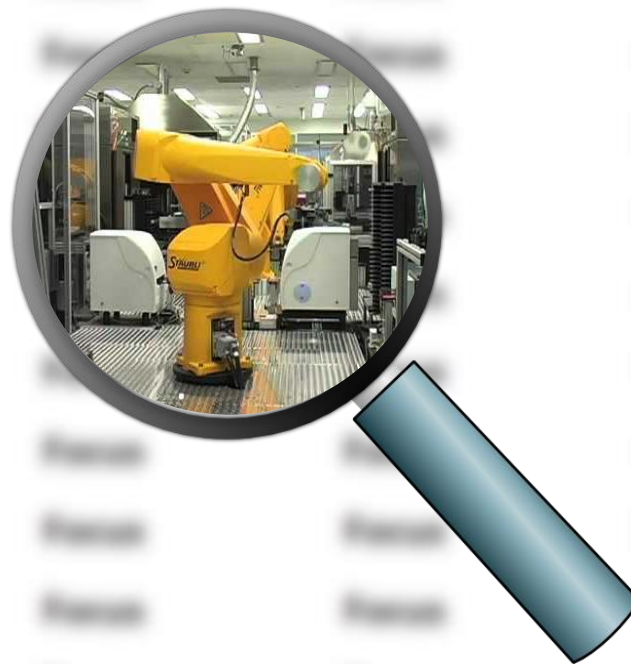


*Total number of assays is ~70

Scientific, Public, and Regulatory Impact of Tox21

- Tox21 collaboration has published over 200 scientific peer-reviewed articles in over 56 journals
- Top 5 Tox21 publications cited an average of over 100 times (Web of Science)
- Tox21 mentioned in over 70 news articles, 13 blogs, 461 Twitter posts, and 8 Wikipedia articles (AltMetric, Aug, 2017)
- Tox21 publications cited in over 140 policy-related and expert panel documents (AltMetric, Aug, 2017).
 - National Academies of Science Reports (~80)
 - Publications Office of the European Union (~15)
 - European Food Safety Authority (~5)
 - World Health Organization (~5)

But, the Focus of Tox21 has been
Predominantly on HTS



Need to Expand Vision to Move Toxicity Testing into 21st Century

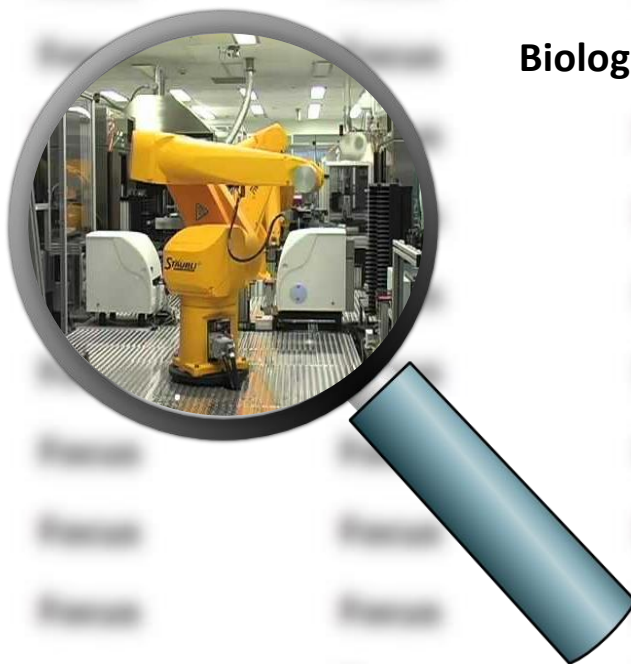
Validation

Biological Coverage

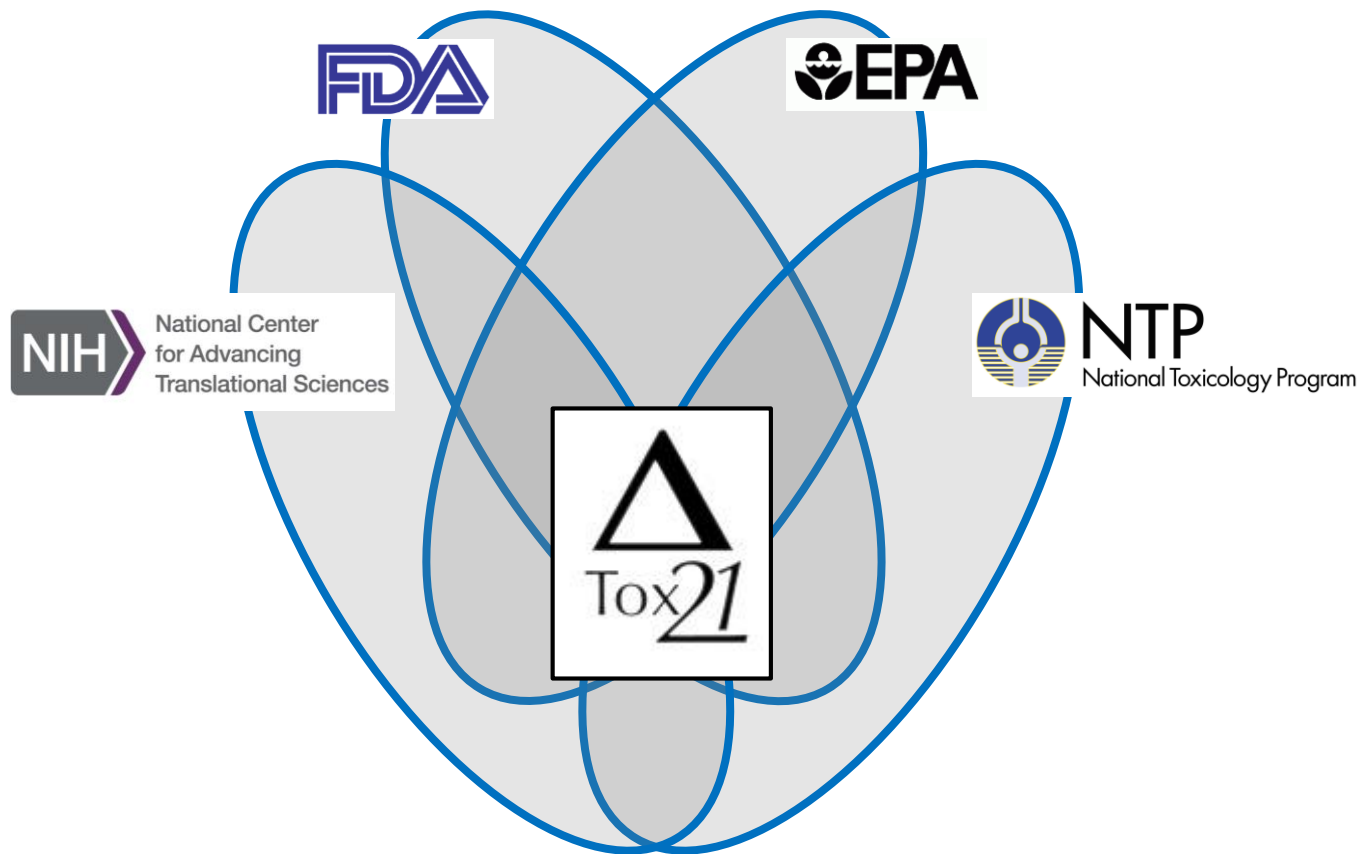
Biokinetics

Organotypic
Assays

Metabolic
Competence



The Challenge

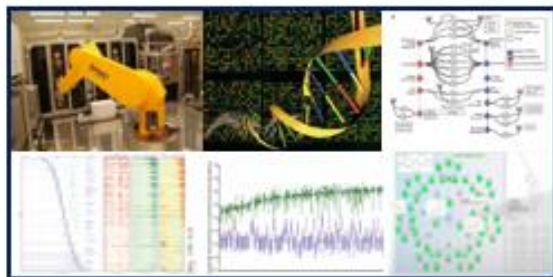


New Tox21 Strategic and Operational Plan

Areas of Focus

Tox21 Collaboration

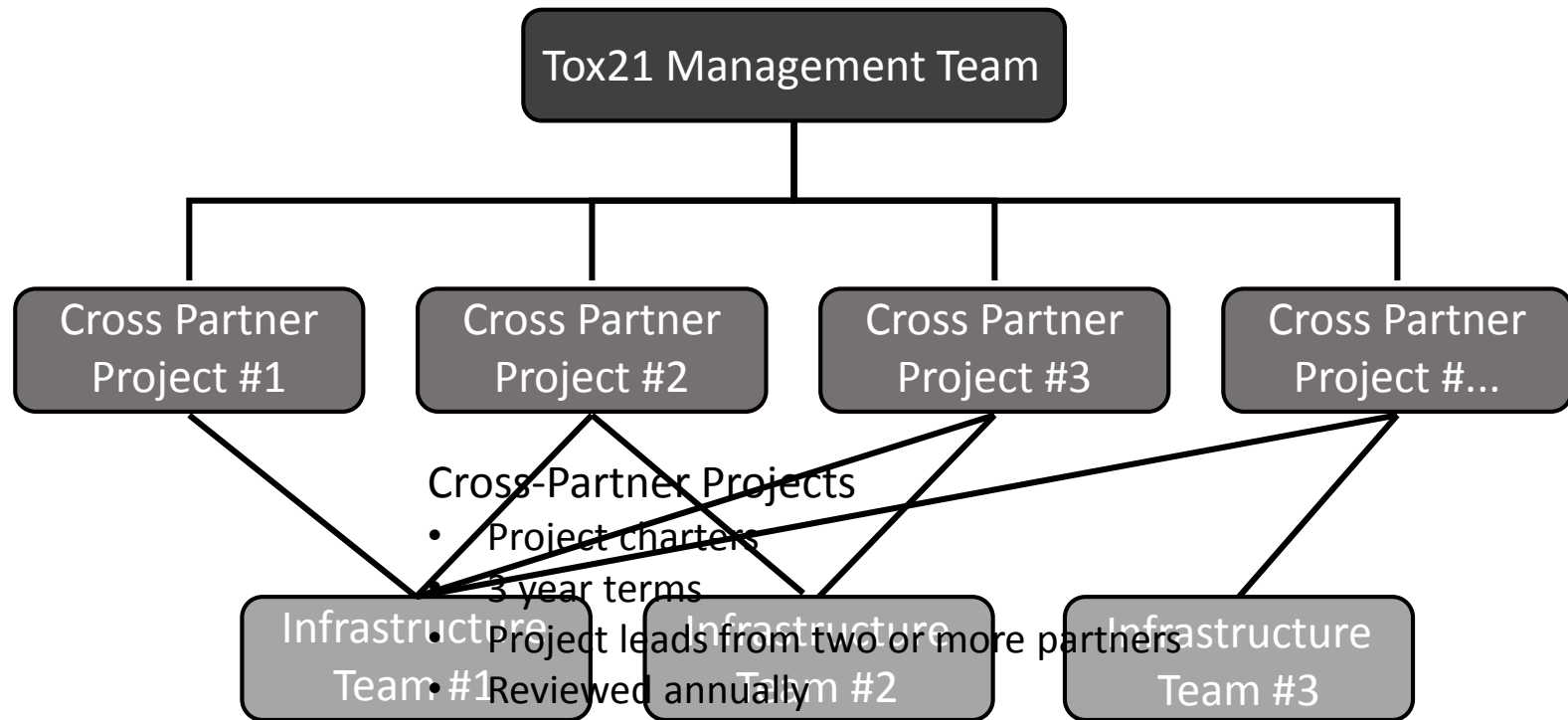
A Strategic Plan for Continued Leadership



Internal Use Only - Do Not Cite or Quote

1. Develop and deploy alternative test systems that are predictive of human toxicity and dose response
2. Address key technical limitations of current *in vitro* test systems
3. Curate and characterize legacy *in vivo* toxicity studies to serve as a resource for interpreting Tox21 data
4. Develop framework for efficient validation of Tox21 approaches
5. Refine and deploy *in vitro* methods for characterizing pharmacokinetics to increase predictivity and reduce uncertainty

New Tox21 Structure



Initial Infrastructure Teams and Example Cross Partner Projects

Infrastructure Teams

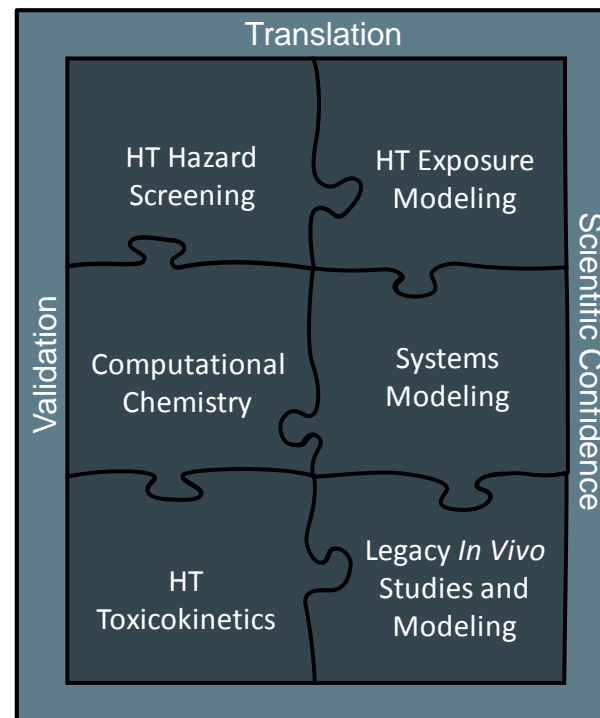
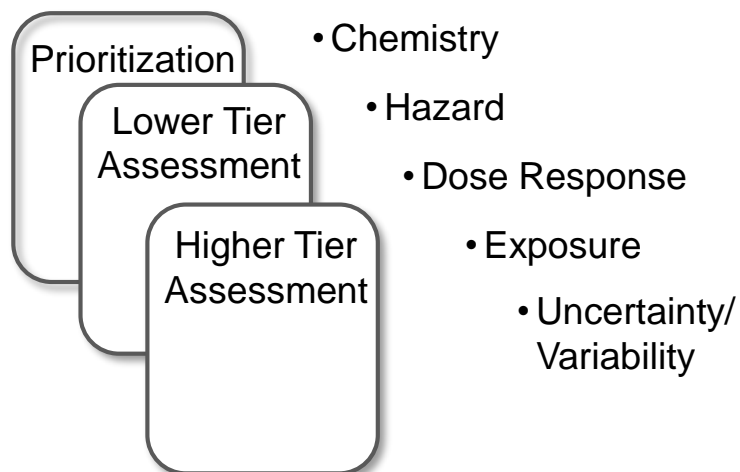
- Chemical Library Management
- Communications
- Assay Evaluation and Screening

Example Cross-Partner Projects

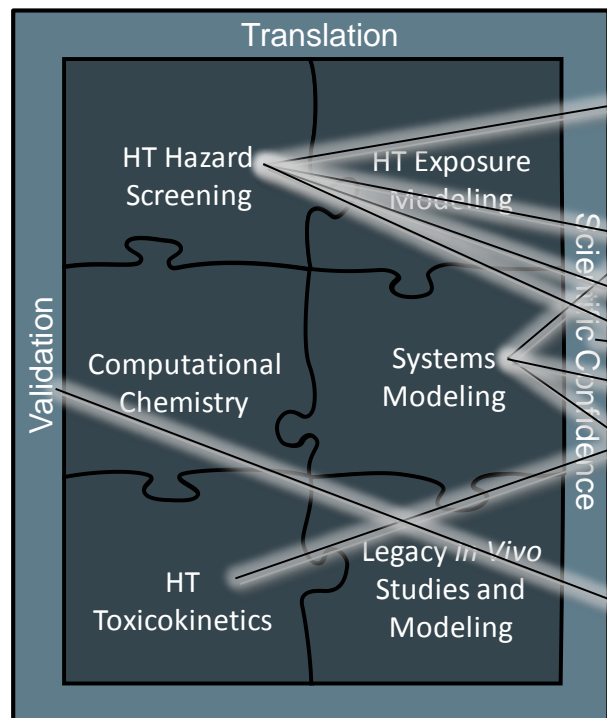
- *In Vitro* Disposition of Tox21 Chemicals
- Performance Based Validation of Tox21 Assays
- Development of a Reference Chemical Dataset for Interpretation of High-Throughput Transcriptomic Screening Data
- Incorporating Genetic Susceptibility into Developmental Neurotoxicity Screening

Integration with EPA Science

Common Components for Chemical Safety Decisions



Integration with EPA Science



Tox21 Projects with EPA Involvement

1. Development of a High-Throughput Assay to Identify 5- α Reductase Inhibitors for Orthogonal Evaluation in an Androgen-dependent Human 3D Prostate Microtissue
2. Cell Line Selection for High-Throughput Transcriptomic Screening
3. In Vitro Disposition of Tox21 Chemicals
4. Development of a Reference Chemical Dataset for Interpretation of High-Throughput Transcriptomic Screening Data
5. Predictive Modeling of Developmental Toxicity with Human Pluripotent Stem Cells
6. Performance Based Validation of Tox21 Assays

Thank You for Your Attention!

EPA's National Center for Computational Toxicology

