Toxicology in the 21st Century

UNITED STATES FEDERAL GOVERNMENT TOX21 COLLABORATION
ADVANCING TOXICOLOGY TO IMPROVE ENVIRONMENTAL HEALTH AND PHARMACEUTICAL SAFETY

Overview

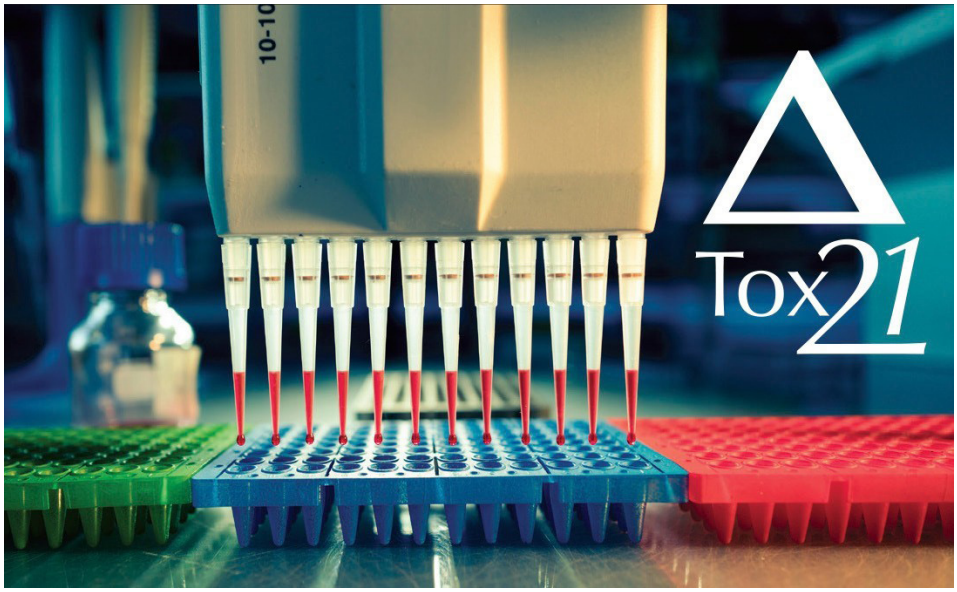
Traditional approaches to toxicity testing have posed multiple challenges for evaluating the safety of industrial and environmental chemicals, pesticides, food additives, food contaminants, and medical products. The challenges include the number of chemicals that need testing, time and resources required for traditional testing, and the unexpected adverse effects that can still occur in clinical trials for drugs despite the extensive toxicological testing.

Over a decade ago, the U.S. Environmental Protection Agency (EPA), National Institute of Environmental Health Sciences (NIEHS), National Center for Advancing Translational Sciences (NCATS), and Food and Drug Administration (FDA) formed the Tox21 Consortium. Tox21 is a U.S. federal research collaboration focused on driving the evolution of toxicology in the 21st Century by developing methods to rapidly and efficiently evaluate the safety of commercial chemicals, pesticides, food additives and contaminants, and medical products. The goals of Tox21 are to (1) identify mechanisms of chemically-induced biological activity; (2) prioritize chemicals for more extensive testing; and (3) develop more relevant and predictive models of *in vivo* toxicological responses.

The Tox21 Consortium has achieved numerous successes over the years, but many challenges remain. To chart a path for addressing these challenges, the Tox21 Consortium strategic and operational plan (Thomas et al, 2018) addresses key challenges in advancing toxicology testing in the 21st century. If successful, it will make substantial progress towards improved evaluation of chemicals for health effects.

Tox21 Consortium Successes

The Tox21 Consortium is successfully generating data on pharmaceuticals and thousands of data poor chemicals, developing a better understanding of the limits and applications of the *in vitro* methods, and enabling the new data generated to be incorporated into regulatory decisions.



Generated data on pharmaceuticals and thousands of data poor chemicals

- Tox21 has screened thousands of chemicals using over 100 high-throughput assays covering over 60 important targets and pathways in the body, generating more than 150 million data points.
- Tox21 data is publicly available through the National Library of Medicine's PubChem, the EPA's Computational Toxicology Dashboard, and the NIEHS Division of Translational Toxicology's Chemical Effects in Biological Systems Database.
- Detailed assay annotations, protocols, and performance statistics are publicly available on EPA's Computational Toxicology website (www.epa.gov/comptox) and the NIH tripod web site (https://tripod.nih.gov/tox21).

Developed a better understanding of new approaches

- Tox21 has published many scientific articles in peer-reviewed journals.
- Tox21 articles are widely cited and frequently referenced in U.S. National Academy of Sciences Reports.

Application to regulatory decisions

- EPA's Endocrine Disruption Screening Program (EDSP) is using Tox21 data to prioritize chemicals for additional testing. Currently, Tox21 data for estrogen receptor activity is used in a computational model to predict potential endocrine activity that has been accepted as alternative tests within the current EDSP Tier 1 testing requirements.
- The World Health Organization's International Agency for Research on Cancer (IARC) has used Tox21 data as supporting mechanistic evidence for chemical carcinogenesis.

Strategic Direction Going Forward

Over the years Tox21 research activities predominantly focused on developing and applying high-throughput screening to toxicity testing. To more broadly address the challenges in toxicology, Tox21's strategic and operational plan expands the focus of its research activities. New focus areas include developing an expanded portfolio of alternative

test systems that are predictive of human toxicity, addressing technical limitations in *in vitro* test systems, curating legacy animal (*in vivo*) toxicity testing data, establishing scientific confidence in the *in vitro* test systems, and refining alternative methods for characterizing pharmacokinetics and disposition in *in vitro* assays. Current research activities under the strategic vision and operational plan include the following cross-partner projects, which may change over time depending on priorities and research outcomes.

- ***In Vitro* Chemical Disposition**
  Goal: Understand the impact of chemical disposition within in vitro test systems across a broad range of chemical categories and develop a computational model to predict differences between the "nominal" concentration of a chemical compared with "true" concentration in the media and cells.
- **High-Throughput Transcriptomic Analysis**
  Goal: Develop a common chemical reference dataset for interpretation of high-throughput transcriptomic screening data.
- **Toxicodynamic Variability in Developmental Neurotoxicity**
  Goal: Incorporate genetic variation into cell-based test systems to better understand potential population differences in response to chemicals that may cause toxic neurological effects.
- **Performance Based Validation of Alternative Test Systems and Models**
  Goal: Develop an evaluation framework for the development of performance standards which can be used to establish confidence in alternative test systems and models.
- **Retrofitting Existing Tox21 High-Throughput Screening Assays with Metabolic Capability**
  Goal: Add xenobiotic metabolism capability to existing Tox21 assays so they provide more accurate and informative data regarding in vivo activity.
- **Expansion of Pathway Coverage by Tox21 High-Throughput Screening Assays for Better Prediction of Adverse Drug Effects**
  Goal: Improve the prediction of adverse drug effects by using additional assays that can probe toxicologically important targets and pathways that are not captured in current Tox21 testing.
- **Predictive Toxicology of the Retinoid Signaling Pathway**
  Goal: Mine bioactivity profiles from the ToxCast/Tox21 portfolio for retinoid transporters, metabolism, receptors, and responsive pathways that can be formally integrated with embryological knowledge to generate data-driven models of the microphysiology of the retinoid system and provide predictive toxicological information.
- **Investigation of Environmental Determinants of Pubertal Timing in Girls**
  Goal: Identify compounds that activate or inhibit the gonadotropin-releasing hormone (GnRH) neurons that control pubertal timing in girls.

History

The Tox21 collaboration was formalized in 2008 through a memorandum of understanding (MOU) between the National Institutes of Health through NIEHS, the National Human Genome Research Institute's National Chemical Genomics Center (NCGC, now a part of NCATS), and EPA's National Center for Computational Toxicology. The Food and Drug Administration joined the Tox21 collaboration in 2010. The Tox21 Consortium recommitted to the collaboration in 2021 by signing a new MOU.

More information available – https://tox21.gov

Tox21 Strategic and Operational Plan Citation

Thomas, R.T., Paules, R.S., Simeonov, A., Fitzpatrick, S., Crofton, K., Casey, W. and Mendrick, D. The US Federal Tox21 Program: A Strategic and Operational Plan for Continued Leadership. ALTEX. (2018). doi:10.14573/altex.1803011