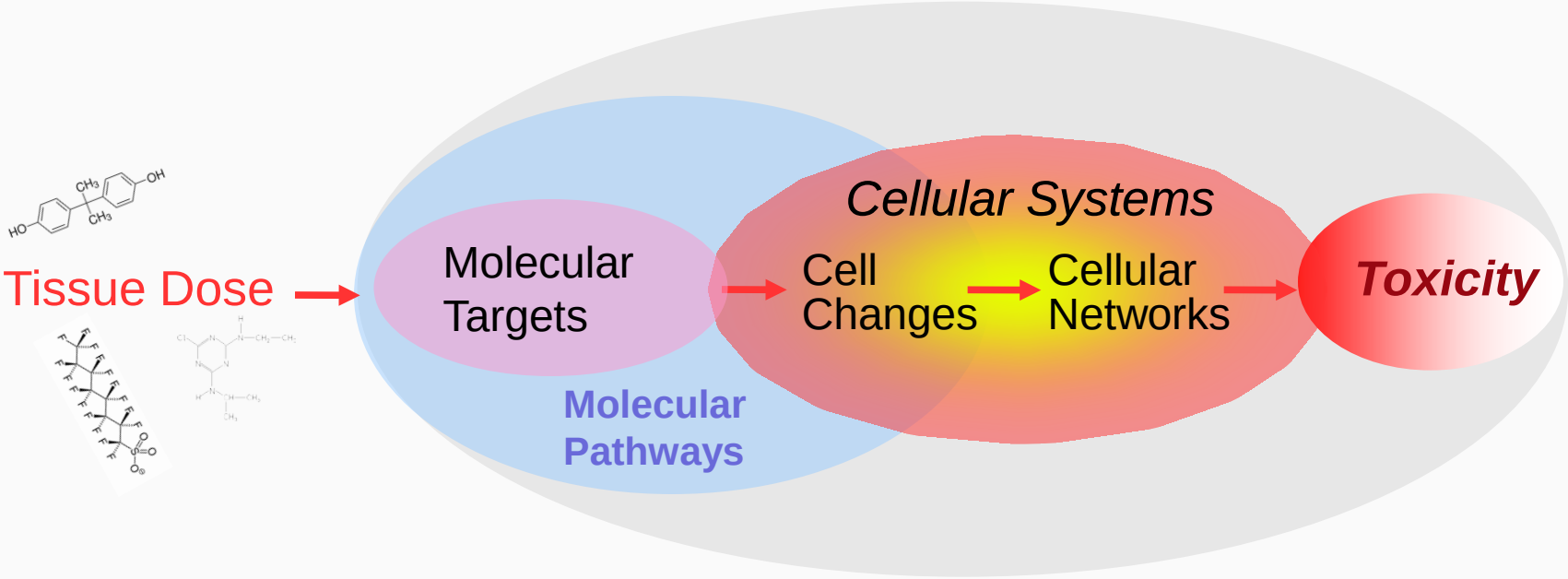
Transforming Toxicology – A US Perspective on the Case for Change

Robert Kavlock
Deputy Assistant Administrator for Science
Office of Research and Development
US Environmental Protection Agency

Systems Toxicology – From Basic Research to Human Risk Assessment
Ascona, Switzerland
28 April. 2013

Predicting Human Toxicity: A Grand Challenge



The Case for Change

- Data poor chemicals with limited recourse under TSCA
  - Chemical category approach

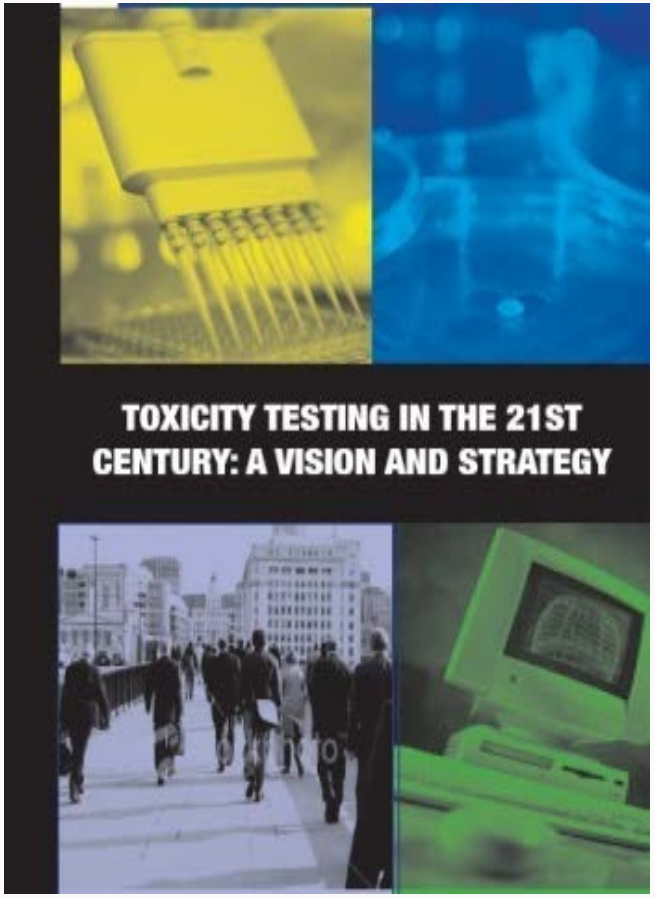
- Thousands of chemicals queued for endocrine disruptor screening
  - 11 tests in current screen, per chemical cost exceeds $750k

- Poor predictive value of rodent toxicology studies
  - High cost of late failures in drug development

- Safer design of chemicals (green chemistry)

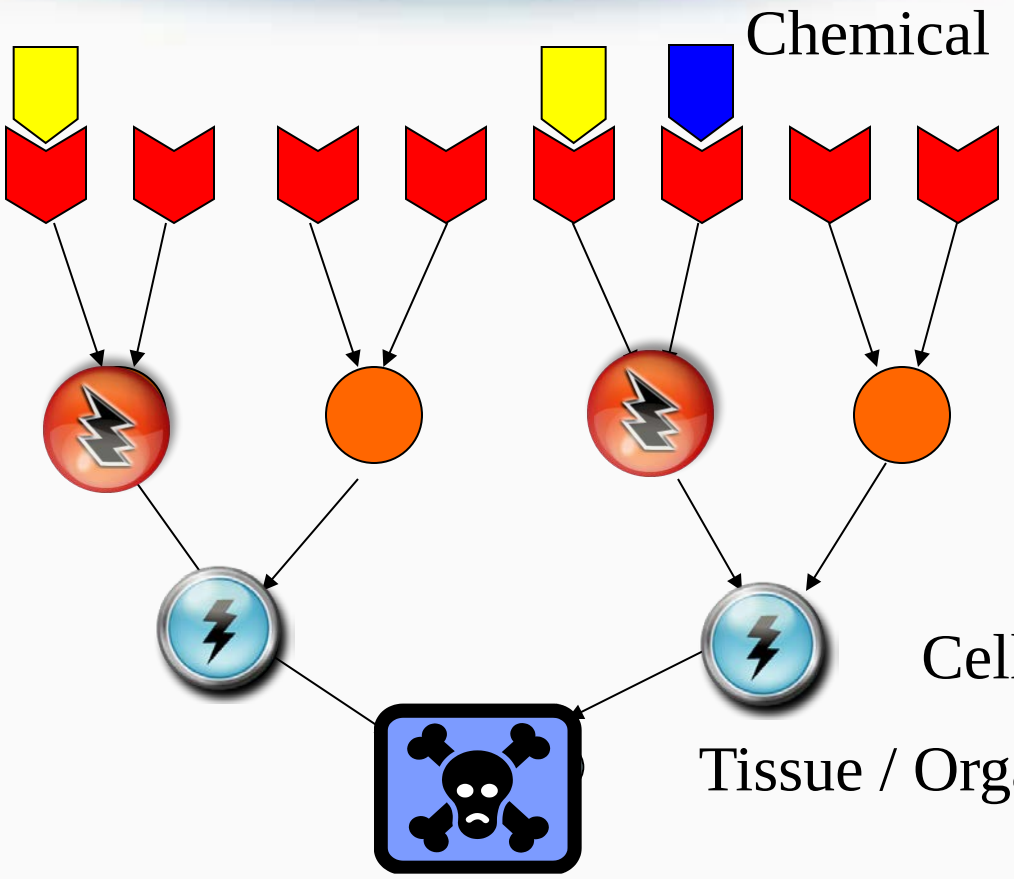
- And most of all, need for improved inclusion of mechanism of action in risk assessment
  - That results in a new system that is as least as protective of human health as current paradigm

National Academy Report (2007)



Design a ‘modern’ toxicity testing program to assess potential human risks posed by exposures to environmental agents over a broad range of doses and compounds and to be in a position to use this information in quantitative human health risk assessment.

Toxicity Pathways



Receptors / Enzymes / etc.
Direct Molecular Interaction

Pathway Regulation /
Genomics

Cellular Processes

Tissue / Organ / Organism Tox Endpoint

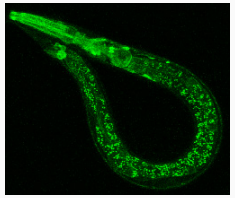
High-Throughput Screening Assays

batch testing of chemicals for biological endpoints using automated liquid handling, detectors, and data acquisition

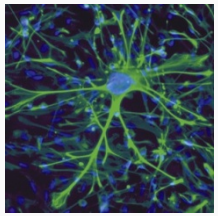
LTS MTS HTS uHTS

10s-100s/yr

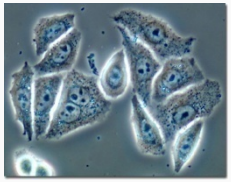
Gene-expression

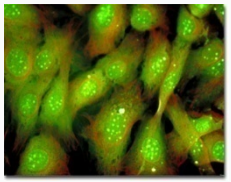


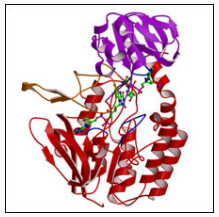
10s-100s/day



1000s/day







10,000s-100,000s/day

Human Relevance/ Cost/Complexity

Throughput/ Simplicity

Some Current US Activities

- NIEHS/NTP (Roadmap, 2003)
- EPAs Computational Toxicology Center (2005)
  - ToxCast, ToxRef, ExpoCast, Virtual Embryo
- USG Tox21 consortium
  - Phase II screening 8193 unique chemicals in qHTS
- The Hamner Institute efforts in pathway modeling
- The Johns Hopkins Humane Toxome project
- DARPA/NIH/FDA microphysiological systems projects
  - Wyss Institute and MIT, $35m each
  - Ten human organs on a chip within 5 years
- OECD Adverse Outcome Pathway codification

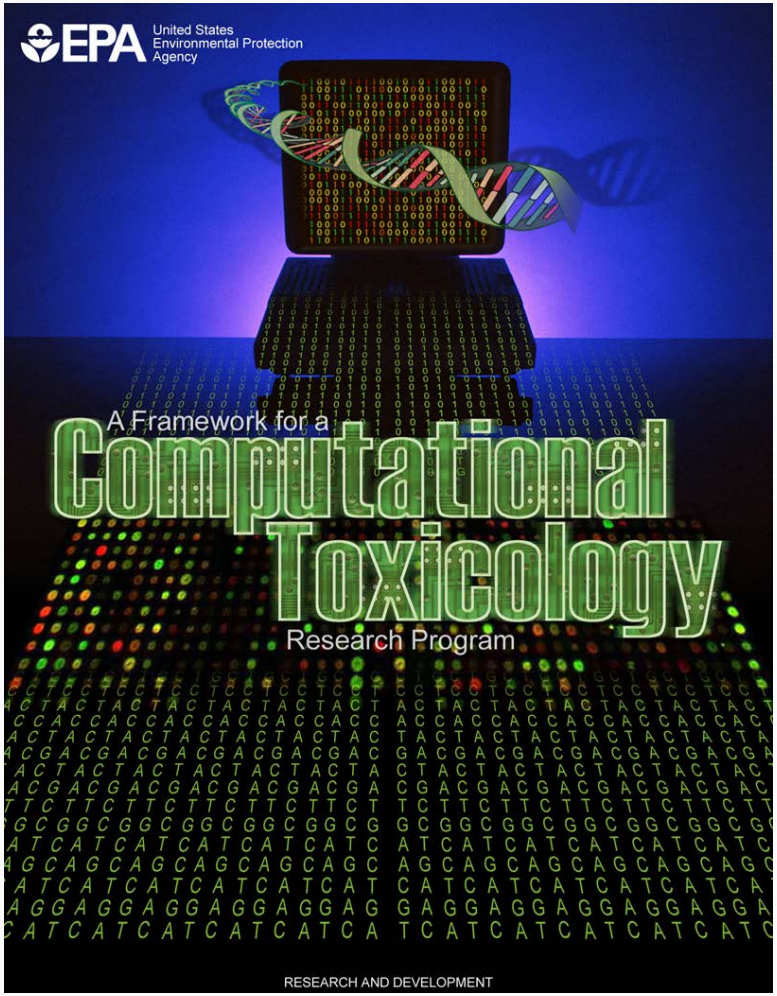
EPA's Computational Toxicology Research Program (2003)

Themes:

- A technology-based, hypothesis-driven effort to increase the soundness of risk assessment decisions within EPA
- Build the capacity to prioritize, screen and evaluate chemicals by enhancing the predictive understanding of toxicity pathways

Success:

- Measured by ability to produce faster and more accurate risk assessments for less cost relative to traditional means and to classify chemicals by their potential to influence molecular and biochemical pathways of concern



www.epa.gov/ncct

Intergovernmental Innovation

MEMORANDUM OF UNDERSTANDING

ON

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

XI. APPROVAL

National Toxicology Program

Linda S. Birnbaum, Ph.D., DABT, ATS — 5·25·10 Date
Director
National Institute of Environmental Health Sciences
National Institutes of Health

NIH Chemical Genomics Center

Eric D. Green, M.D., Ph.D. — 6/3/10 Date
Director
National Human Genome Research Institute
National Institutes of Health

U.S. Environmental Protection Agency

Paul T. Anastas, Ph.D. — 4 June 2010 Date
Assistant Administrator
Office of Research and Development

Food and Drug Administration

Janet Woodcock, MD — Date 5/24/10
Director
Center for Drug Evaluation and Research

Reactions We Get

- Biology is too complicated to addressed by this reductionist approach
- You will miss toxicities expressed due to emergent properties of cells and tissues
- You don’t have feedback loops that could afford resiliency
- We will never know all the toxicity pathways, so this is doomed to failure
- Your approach does not have liver
- Assay (x) in your battery did not get the right answer for my chemical
- My assay disagrees with assay (x), so your approach is flawed
- You can’t test my chemical because of your limitations
- Everything is going to get tagged hazardous because of a positive in vitro response
- You don’t consider dose-response
- How we can we be sure about protectiveness for human health

- Finally someone is tackling the problem, let’s give them a chance

Validation/Qualification

- Definition
  - A process to determine the relevance, reliability and fitness for purpose of a test
- Relevance
  - Assay must test an aspect of biology that will help assess the safety of a chemical. A positive result in the assay should be indicative of perturbations to or interactions with the target or pathway the assay is designed to test. (Evaluate with reference compounds)
- Reliability
  - Assay must produce similar results over time, across reagent batches, etc. (Evaluate with reference compounds)
- Fitness for Purpose
  - For prioritization application, an HTS assay should provide sufficient positive and negative predictive power so that the prioritized chemicals are significantly enriched in positives when run in the guideline test.

Critical Tox21 Issues

- Cells don’t get disease
- Not all compounds can be screened in HTS
- Incorporation of metabolic capabilities
- Interactions between different cell types
- Range of human variability
- Extrapolation from acute to chronic exposure conditions
- Interpretation of effective *in vitro* concentrations

Future needs

- More chemicals, more pathways, more informatics
  - IVIVE, metabolic competency

- Fit for purpose acceptance
  - Transparency and training

- Tools of high throughput exposure estimates
  - More use based than volume based

- Translation into Applications
  - Prioritization
  - Animal Refinement (Integrated Test Strategies)
  - High throughput risk assessment methodologies
  - National Emergencies

Future Needs (cont'd)

- Better linkage with international activities
  - Research
    - US and EU activities (Suerat, eTOX, etc.)
  - Regulatory
    - Canadian DSL List 3 evaluation (1700 chemicals, 2016-2020)
    - Australian NICNAS evaluation of ~20,000 chemicals
    - REACH
    - TSCA Reform (if it occurs)
    - Endocrine activity

- Systems models for integrating diverse data streams and knowledge
  - Virtual tissue experiments
  - Impact of co-exposures through systems level models+

Predicting Human Toxicity: A Grand Challenge