

# Computational Toxicology: New Approaches for the 21st Century

May 28, 2009 Session 1: **Computational Toxicology: An Introduction to Key Concepts and Approaches**

Dr. Kim Boekelheide, Professor of Pathology and Laboratory Medicine,  
SBRP-Brown University

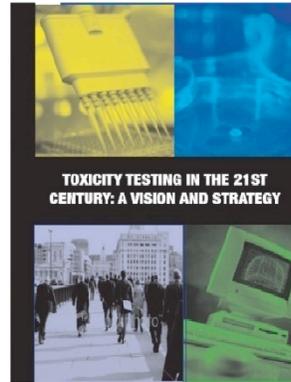
Dr. Robert Kavlock, Director of the National Center for Computational  
Toxicology (NCCT/ORD/USEPA)



# Toxicity Testing in the 21st Century

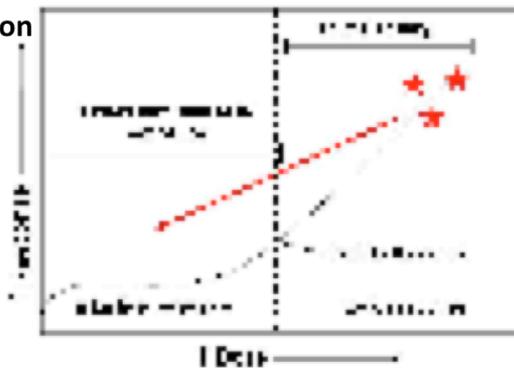
**Computational Toxicology: An  
Introduction to Key Concepts and  
Approaches**

**Kim Boekelheide, MD, PhD  
Brown University**



## Increasing frustration with current approaches to toxicity testing from many sectors...

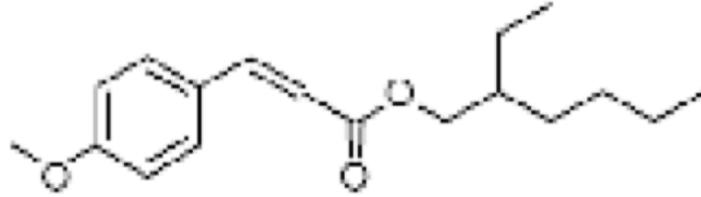
- Low throughput; expensive
- Questionable relevance to actual human risks
- Conservative extrapolation defaults
- Traditional approaches dating to 1930's
- Little use of modern biology, mode of action
- Reliance on animals



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## An Example — Toxicity Testing in Practice



Ethylhexyl methoxycinnamate (EHMC)

A very common UV filter in sunscreen

Reviewed by the NTP as a “proposed research project.”

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## The Concern

- **Widespread use**
- **Lifelong exposure**
- **Potential for endocrine disruption**
- **Potential for increased absorption in children**
- **Lack of information on the effects of *in utero* exposure**

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## The Limited Information Generates Questions

- Industry says it has a study that clears EHMC of concerns as an endocrine disruptor, but the data are not public
- Reasonably strong evidence that absorption through the skin is most often very limited (~1%)
- Sunlight causes a large amount of EHMC isomerization
- Metabolism generates 2-ethylhexanol and 2-ethylhexanoic acid, known developmental toxicants
- Nanoparticles now widely used in sunscreens have unknown effects on transdermal transport
- Young age and some common skin conditions (eczema) may enhance transdermal absorption

## The NTP Testing Proposal

- Evaluate toxicokinetics and absorption, distribution, metabolism, and excretion (ADME), comparing dermal and oral routes of exposure
- Conduct a large **ORAL** multigenerational study

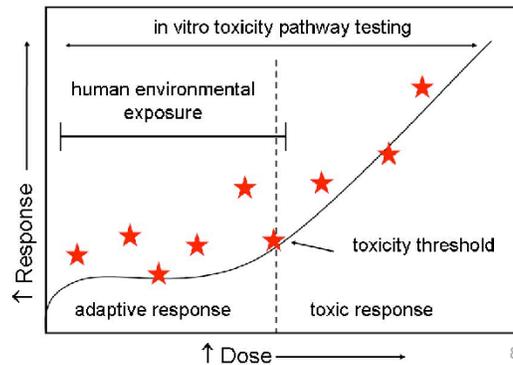
The proposed high dose is the maximally tolerated dose (MTD), and the low dose is many orders of magnitude above anticipated exposure levels

With our current approach, this is what we do, but does it make sense?

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## Vision of a future of toxicity testing based on a very different paradigm.....

- Multiple doses in vitro
- Defined number of toxicity pathways
- High throughput
- Expensive to develop, cheap to do
- Fast
- Mechanistic endpoints
- In vitro-to-in vivo extrapolations of dose response
- Based on human biology



## A National Research Council Committee

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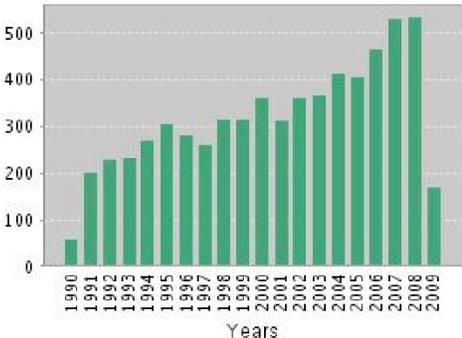
- Sponsored by the US EPA with support from NIEHS
- Advance the practice of toxicity testing and human health assessment of environmental agents

Is the focus on environmental agents important for the design criteria?

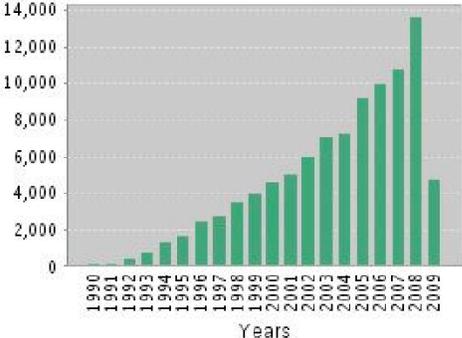
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# “toxicity testing”

**Published Items in Each Year**



**Citations in Each Year**

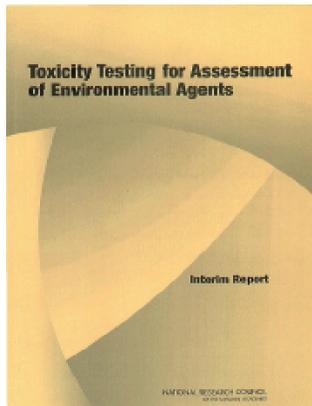


## Committee Roster

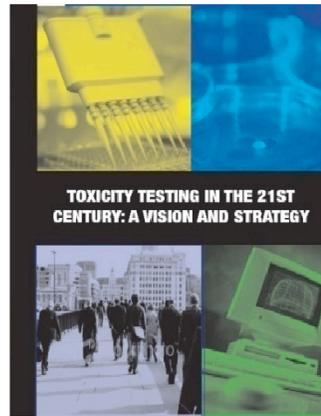
**Daniel Krewski** (*Chair*), University of Ottawa, Ottawa, ON  
**Daniel Acosta, Jr.**, University of Cincinnati, Cincinnati, OH  
**Melvin Andersen**, CIIT Centers for Health Research, Research Triangle Park, NC  
**Henry Anderson**, Wisconsin Division of Public Health, Madison, WI  
**John Bailar III**, University of Chicago, Chicago, IL  
**Kim Boekelheide**, Brown University, Providence, RI  
**Robert Brent**, Thomas Jefferson University, Wilmington, DE  
**Gail Charnley**, HealthRisk Strategies, Washington, DC  
**Vivian Cheung**, University of Pennsylvania, Philadelphia, PA  
**Sidney Green**, Howard University, Washington, DC  
**Karl Kelsey**, Harvard University, Boston, MA  
**Nancy Kerkvliet**, Oregon State University, Corvallis, OR  
**Abby Li**, Exponent, Inc., San Francisco, CA  
**Lawrence McCray**, Massachusetts Institute of Technology, Cambridge MA  
**Otto Meyer**, Danish Institute for Food and Veterinary Research, Søborg, Denmark  
**D. Reid Patterson**, Reid Patterson Consulting, Inc., Grayslake, IL  
**William Pennie**, Pfizer, Inc., Groton, CT  
**Robert Scala**, Exxon Biomedical Sciences (Ret.), Tucson, AZ  
**Gina Solomon**, Natural Resources Defense Council, San Francisco, CA  
**Martin Stephens**, The Humane Society of the United States, Washington, DC  
**James Yager, Jr.**, Johns Hopkins University, Baltimore, MD  
**Lauren Zeise**, California Environmental Protection Agency, Oakland, CA

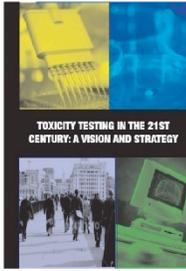
**With particular thanks to Mel Andersen for permission to use his slides**

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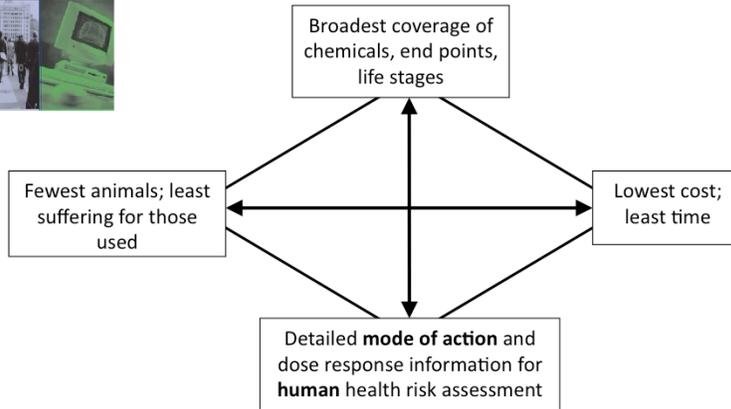


- A transformative redefinition of toxicity testing is required to meet key design criteria.



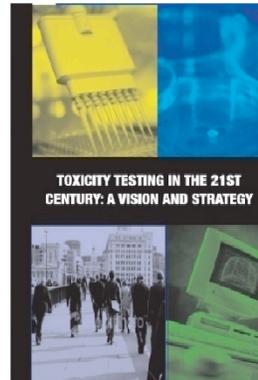


## Design Criteria: Toxicity Testing of Environmental Agents



## **Contents**

1. Introduction
2. Vision
3. Components of Vision
4. Tools and Technologies
5. Developing the Science Base and Assays to Implement the Vision
6. Prerequisites for Implementing the Vision in Regulatory Contexts



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The quote is from Simon Manchester's – A Crack in the Edge of the World.

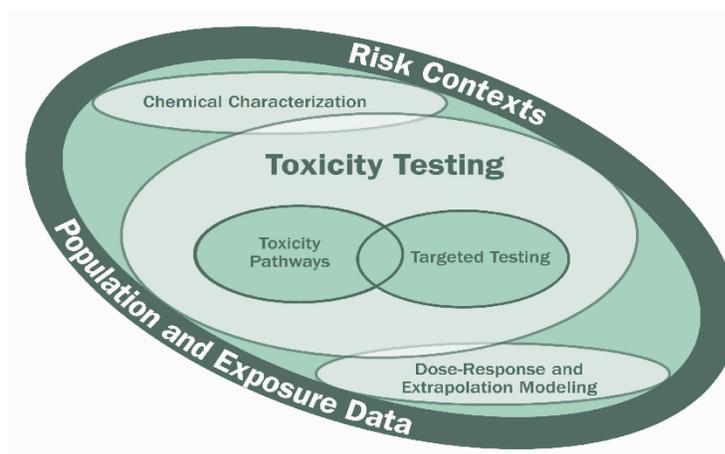
## Options for Future Toxicity Testing Strategies Table 2-1

Option I In Vivo	Option II Tiered In Vivo	Option III In Vitro/In Vivo	Option IV In vitro
Animal biology	Animal biology	Primarily human biology	Primarily human biology
High doses	High doses	Broad range of doses	Broad range of doses
Low throughput	Improved throughput	High and medium throughput	High throughput
Expensive	Less expensive	Less expensive	Less expensive
Time consuming	Less time consuming	Less time consuming	Less time consuming
Relative large number of animals	Fewer animals	Substantially fewer animals	Virtually no animals
Apical endpoints	Apical endpoints	Perturbations of toxicity pathways	Perturbations of toxicity pathways
	Some <i>in silico</i> and <i>in vitro</i> screens	<i>In silico</i> screens possible	<i>In silico</i> screens

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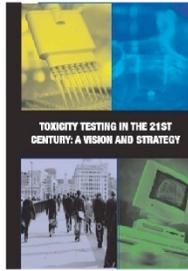
## Components of the Vision

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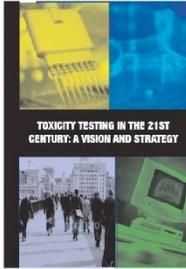
## Toxicity Testing

... a not-so-distant future where all routine toxicity testing will be conducted in human cells or cell lines *in vitro* by evaluating perturbations of cellular responses in a suite of toxicity pathway assays.

Andersen and Krewski (2009). Toxicity Testing in the 21<sup>st</sup> Century: Bringing the Vision to Life. *Tox. Sci.*, 107, 324-330.

How long will it take to implement this new toxicity testing paradigm?

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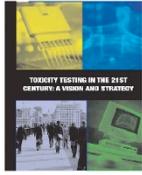
## Toxicity Pathways

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- A cellular response pathway that, when sufficiently perturbed, is expected to result in an adverse health effect.
- Just a normal biological signaling pathway and its components

Is the focus on "toxicity pathways" useful or distracting?

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# What are the toxicity pathways? How many are there?

Endogenous hormones

DNA damage

PXR, CAR, PPAR and AhR receptors

Nrf2 oxidative stress

Hypo-osmolarity

Heat-shock proteins

p38 MAPK

## Designing Toxicity Pathway Assays

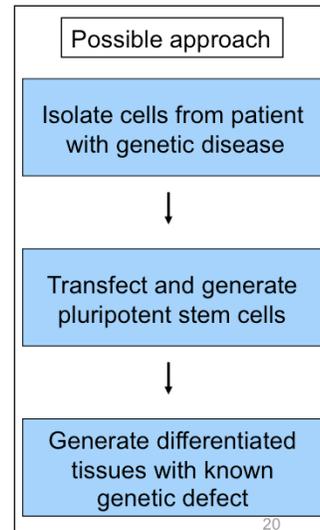
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In vitro, rapidly performed toxicity pathway tests in primary human cells, cell lines, or tissue aggregates

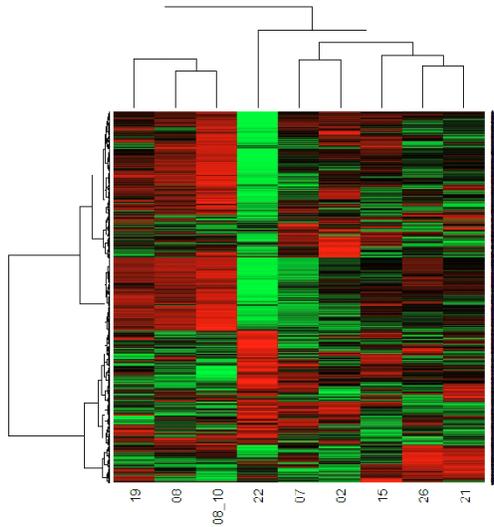
**Rapid progress since completing the report:**

- Human stem cell biology
- Better access to human cells
- Bioengineered tissues

Does a test for neurodevelopmental effects have to look at neurons?



## Targeted Testing – toxicogenomics, etc.



**Assess pathways,  
integrate tissue  
responses, and in  
some cases evaluate  
metabolites**

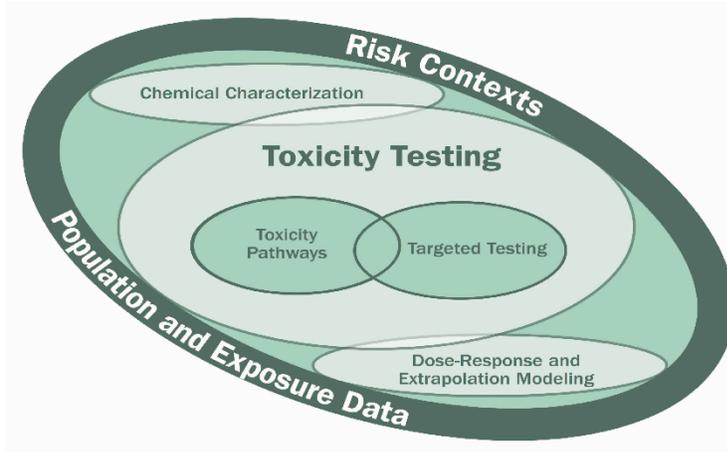
**Discuss use of new  
technologies in  
targeted testing  
strategies**

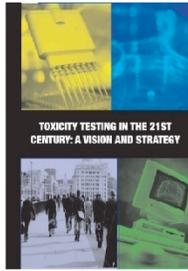
## In the new approach,

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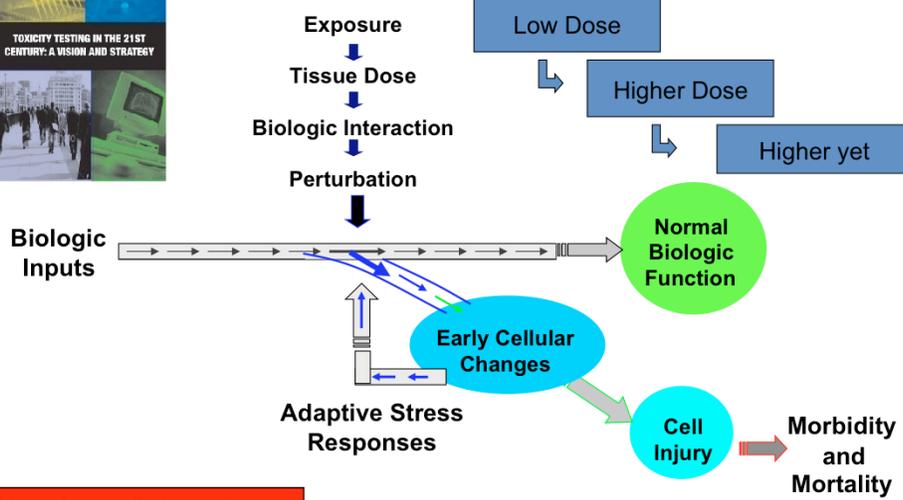
- Toxicity pathways assays, better reflecting biological targets and modes of action
- Increased speed and throughput for chemicals and decreased costs and animal usage
- Move away from extrapolating from high dose animal results to low doses in humans and focus on results of perturbations of toxicity pathways in humans
- **Now extrapolations include *in vitro* - *in vivo* and across levels of biological organization**

## Dose-Response and Extrapolation Modeling

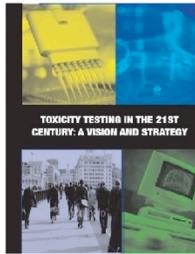




## Perturbation of Toxicity Pathways



How do we distinguish adaptive versus adverse (toxic) responses?



## Dose Response and *in vitro* to *in vivo* extrapolations

Dose response modeling of perturbations of pathway function would be organized around *computational systems biology models of the circuitry underlying each toxicity pathway*. *In vitro to in vivo extrapolations would rely on pharmacokinetic models* – ideally physiologically based pharmacokinetic models - that would predict human blood and tissue concentrations under specific exposure conditions.

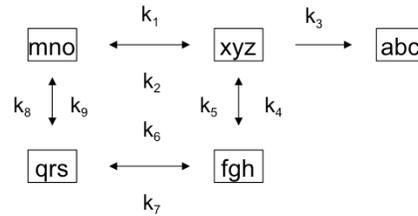
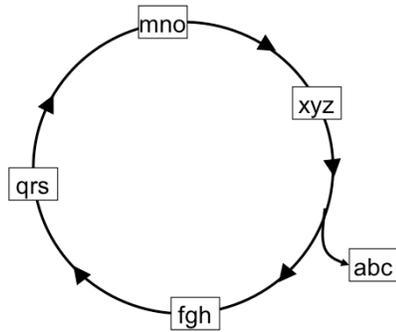
Andersen and Krewski (2009). Toxicity Testing in the 21<sup>st</sup> Century: Bringing the Vision to Life. *Tox. Sci.*, 107, 324-330.

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# Systems Modeling of Toxicity Pathways

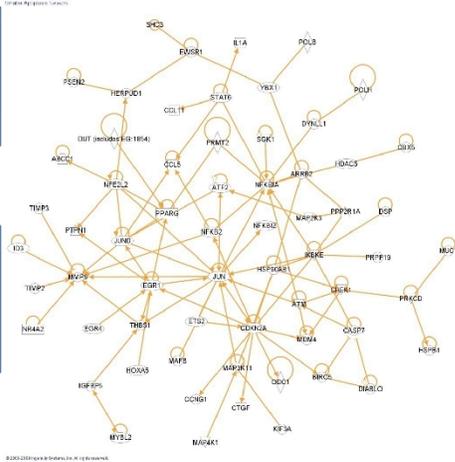
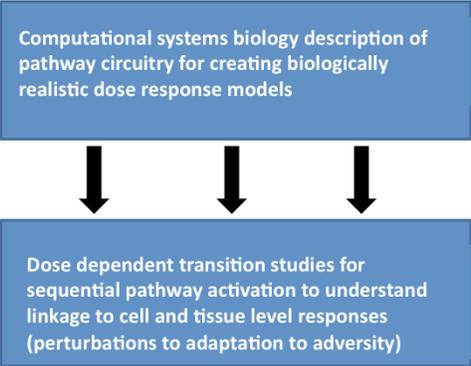
Computational systems biology description of pathway circuitry to support dose response modeling of pathway perturbations

Virtually all biology is controlled by non-linear feedback (positive and negative)



Map and model circuitry of the toxicity pathway assay for dose response assessment and to assess susceptibility factors

# Dose Response Models Linking Perturbations to more Integrated Responses



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## ***in vitro* – *in vivo* extrapolations with biokinetic/PBPK modeling**

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PBPK Modules – Compound specific or QSAR-based models for *in vitro*- *in vivo* extrapolation, interpreting biomonitoring studies and inferring human population exposures for specific use patterns

## Toxicity Pathway Results and Quantitative Risk Assessments – A Possible Scenario

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Order hits in dose response context

i. *in vitro* rapidly performed toxicity pathway test battery for *n*-assays in human cells, cell lines, or tissue aggregates

Select key pathway(s) for dose response

ii. Computational systems biology description of pathway circuitry for creating biologically realistic dose response models

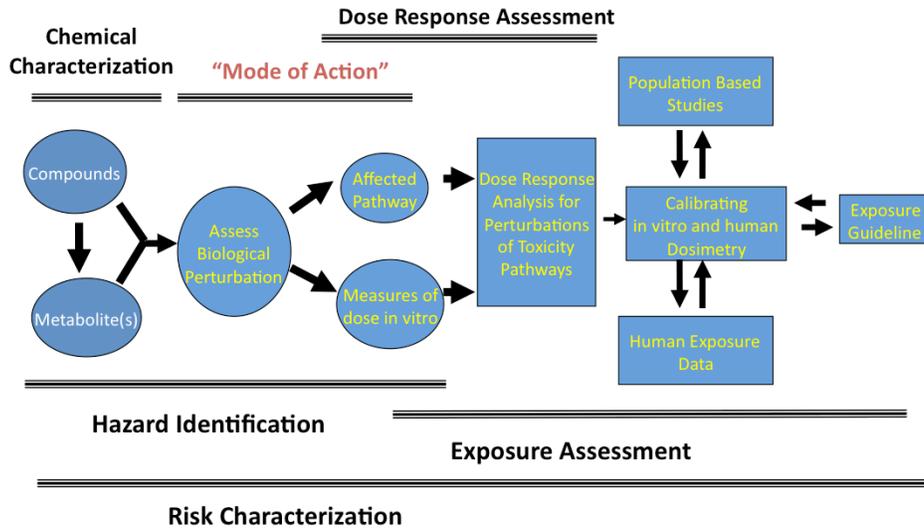
Evaluate regions of safe exposures based on pathways affected by the chemical, the circuitry of the response, linkage from perturbation to integrated cell response, and knowledge of pharmacokinetics and exposure

iii. Dose dependent transition studies for sequential pathway activation to understand linkage to cell and tissue level responses (perturbations to adversity)

iv. PBPK Modules – Compound specific or QSAR-based models for *in vitro*- *in vivo* extrapolation, interpreting biomonitoring studies and inferring human population exposures for specific use patterns

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## How does the new 'risk' paradigm compared to the 1983 Red Book for environmental agents?



## Some advantages

Testing in vivo  Research in vitro

- Toxicity testing more focused on human biology; not an uncertain reflection of high dose animal studies for what is expected at low doses in humans
- Creates detailed understanding of pathway targets, functional design of pathway circuitry, more diverse dose response models for target and integrated cellular responses for ties to possible outcomes

## And promises

Testing in vitro  Research in vivo

Human relevance  
 Dose relevance  
 Chemical coverage  
 Mixtures effects on toxicity pathways  
 Mechanistic focus: mode of action based  
 Cost effective  
 Fast  
 The 3 Rs: replacement, reduction, refinement

## Challenges.....

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- Assay Design/Development for Toxicity Pathways
- Improved methods to identify (predict) and **test metabolites** – targeted testing
- Co-ordinate development of ‘functional genomic tools’ to map and model pathways and use results to establish safe levels of exposures
- Train toxicologists and regulators about need for new approach and then in the tools and methods that will be involved in the transformation

## And conundrums.....

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What about epigenetics and other new biology?

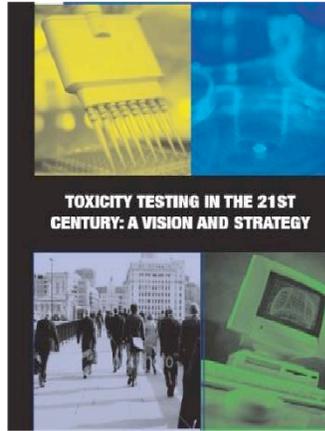
Is this a screening tool or a stand-alone system?

How is the new paradigm validated?

How do regulators handle the transition in testing?

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This change in direction for testing “environmental” agents is inevitable; how can we speed up implementation.

## Questions.....

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- Is the focus on environmental agents important for the design criteria?
- How long will it take to implement this new toxicity testing paradigm?
- Is the focus on “toxicity pathways” useful or distracting?
- Does a test for neurodevelopmental effects have to look at neurons?
- How do we distinguish adaptive versus adverse (toxic) responses?
- Is this a screening tool or a stand-alone system?
- How is the new paradigm validated?
- What about epigenetics and other new biology?
- How do regulators handle the transition in testing?

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# Computational Toxicology

*Robert Kavlock*

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY



Office of Research and Development  
National Center for Computational Toxicology



**“...to integrate modern computing and information technology with molecular biology to improve Agency prioritization of data requirements and risk assessment of chemicals”**

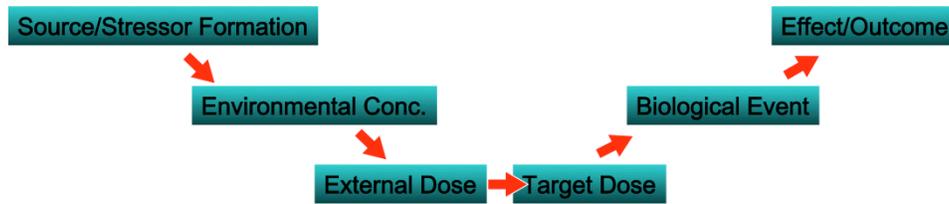
[www.epa.gov/ncct](http://www.epa.gov/ncct)

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National Center for Computational Toxicology

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## The Source to Outcome Continuum





## The Source to Outcome Continuum

Historically the problem has been approached one chemical at a time, one stage at a time, with little progress in predicting across the stages and across chemicals. Current demands on the EPA are making this an untenable approach. Computational Toxicology was initiated to provide new thinking to overcoming the bottlenecks.





## What's It All About

- Digitization
  - Legacy data (e.g., pesticide registration studies)
  - Dispersed data
- Scale
  - Chemicals
  - Biological space
  - Levels of biological organization
- Quantifying
  - Physiology, biochemical pathways and networks, biology
- Data mining and management







# Toxicological Information Gaps

The screenshot shows the EPA website page for the Drinking Water Contaminant Candidate List (CCL). The page title is "Drinking Water Contaminant Candidate List (CCL)". Below the title, there is a "Frequent Questions" section with a list of questions and answers. The questions are:

1. What is the Drinking Water CCL?  
The Drinking Water CCL is the primary screen or priority control strategy to assess the potential hazard of chemicals to public drinking water systems. The control strategy is not intended to address the safety of drinking water for individual consumers. However, the CCL will help to identify chemicals that may be of concern to public drinking water regulators.
2. How often is the CCL published?  
The Drinking Water CCL is published biennially. The first CCL was published in March 2009 and the second CCL is "Target 2015" and is published in March 2015.
3. What contaminants are included in the CCL?  
The CCL includes 191 chemicals. The chemicals are listed in the CCL by their CAS number, chemical name, and chemical structure. The CCL also includes information on the chemical's physical and chemical properties, its use, and its potential for environmental release. The CCL also includes information on the chemical's potential for adverse effects on human health and the environment.
4. Does the CCL impose any restrictions on public water systems?  
No. The CCL is a screening tool and does not impose any restrictions on public water systems. However, the CCL may be used by public water regulators to identify chemicals that may be of concern to public drinking water regulators.
5. What happens to chemicals on the CCL?  
The CCL is a screening tool and does not impose any restrictions on public water systems. However, the CCL may be used by public water regulators to identify chemicals that may be of concern to public drinking water regulators.
6. What is a regulatory determination?  
A regulatory determination is a decision by the EPA regarding whether a chemical is on the CCL. The EPA may determine that a chemical is on the CCL if it is a synthetic chemical, it is a pesticide, it is a pharmaceutical, it is a chemical that is used in consumer products, or it is a chemical that is used in industrial processes.
7. Why are some chemicals on the CCL and others are not?  
The EPA uses a screening process to determine which chemicals are on the CCL. The screening process is based on the chemical's physical and chemical properties, its use, and its potential for environmental release. The EPA also considers the chemical's potential for adverse effects on human health and the environment.
8. How can I find out more about the CCL?  
For more information about the CCL, please visit the EPA website at [www.epa.gov/dwcccl](http://www.epa.gov/dwcccl).

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# Toxicological Information Gaps

The screenshot shows the EPA website's 'Pesticides: Regulating Pesticides' page. The left sidebar contains navigation links: 'Regulating Pesticides', 'Pesticides: Pesticides Enforcement', 'Registration', 'Laws', 'International Issues', 'Research & Monitoring', 'Storage & Disposal', 'Pesticides & Land Use', 'Pesticide Tolerances', 'Registration', and 'International Issues'. The main content area is titled 'Inert (other) Pesticide Ingredients in Pesticide Products' and includes a paragraph explaining that these ingredients are not active ingredients but are necessary for the pesticide to work. It also lists 'Outlook Resources' with links to 'Pesticide Registration System (PRS)', 'Pesticide Registration System (PRS) - Inert Ingredients', 'Pesticide Registration System (PRS) - Inert Ingredients', and 'Pesticide Registration System (PRS) - Inert Ingredients'. Below this, there is a section for 'Name Change from Inert to Other Ingredients' with a paragraph explaining that in 1992, the EPA issued a rule that required the registration of inert ingredients. It also includes a 'Submit Feedback' link and a 'Customer Support' link.

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# Toxicological Information Gaps

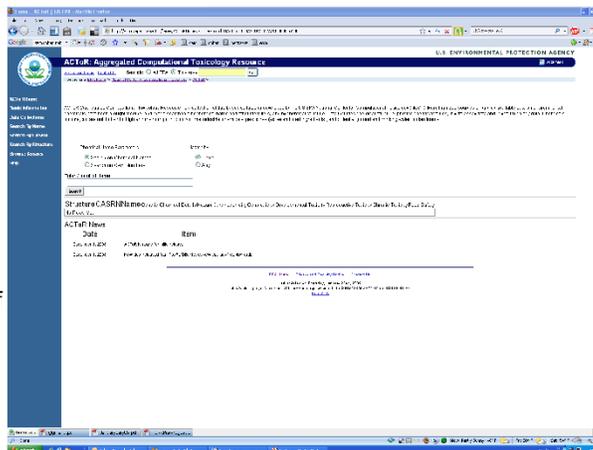
The screenshot displays the REACH (Registration, Evaluation, and Authorization of Chemicals) website. The main heading is "THE NEW EU CHEMICALS LEGISLATION - REACH". The text below discusses the European Commission's proposal for a new regulatory framework for chemicals, effective from 2008. It mentions that the proposal aims to improve the safety of chemicals and to ensure that the most dangerous substances are properly managed. The text also notes that the proposal is subject to a public consultation process, which is currently underway. The website interface includes a navigation menu on the left with options like "Overview", "Activities", "REACH Process", "Registration", "Evaluation", and "Information". On the right side, there is a "News & Updates" section with a list of recent news items, each with a date and a brief description.

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# ACToR

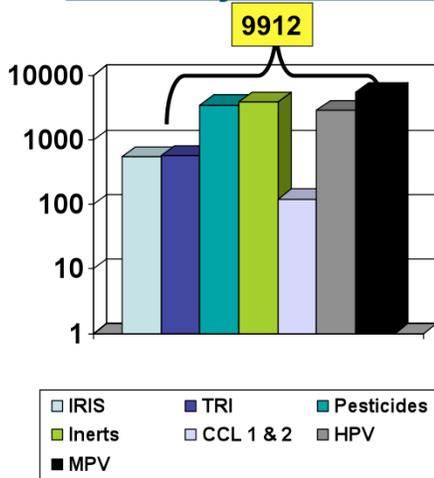
- Aggregated Computational Toxicology Resource
- Internet portal of information of chemicals
- +200 public sources
- +500,000 chemicals
- Searchable by
  - Name, CASRN, substructure
- Tool for identifying chemicals of concern and their data gaps
- Modeled on NCBI databases:
  - <http://www.ncbi.nlm.nih.gov/>
  - <http://actor.epa.gov>





# EPA's Need for Prioritization

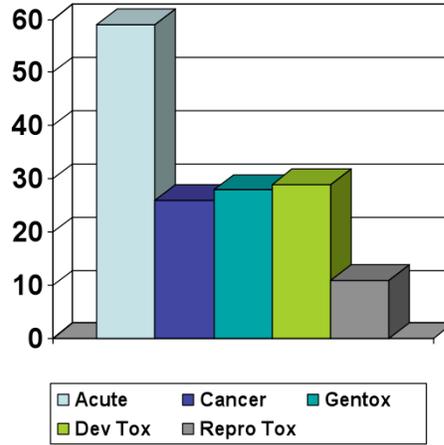
## Too Many Chemicals



- IRIS
- TRI
- Pesticides
- Inerts
- CCL 1 & 2
- HPV
- MPV

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## Too Little Data (%)



- Acute
- Cancer
- Gentox
- Dev Tox
- Repro Tox

Judson, et al *EHP* (2009)



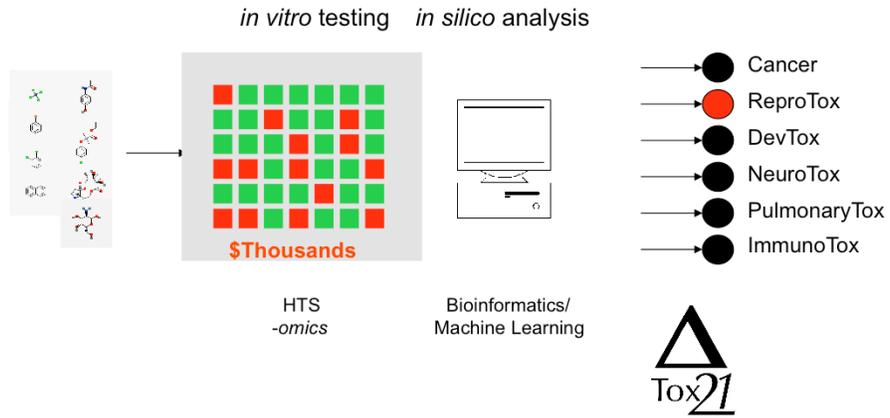
## How Can We Prioritize?

- Animal studies
  - cost, time, ethical considerations
- Exposure
  - lacks hazard information
- QSAR
  - domain of applicability issues
  - lack of availability of sufficient models
- Bioactivity Profiling
  - biologically relevant chemical characterization
  - high-throughput capacity
  - needs development and validation

➔ **ToxCast**



# Future of Toxicity Testing



EPA's Contribution: The ToxCast Research Program

Office of Research and Development  
National Center for Computational Toxicology

[www.epa.gov/ncct/toxcast](http://www.epa.gov/ncct/toxcast)

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# Future of Toxicity Testing

**THE NATIONAL ACADEMIES**  
REPORT IN BRIEF  
July 2007

## Toxicity Testing in the 21st Century: A Vision and a Strategy

Advances in molecular biology, bioinformatics, and other fields are paving the way for major improvements in how scientists evaluate the health risks posed by potentially toxic chemicals found at low levels in the environment. These advances would make toxicity testing quicker, less expensive, and more directly relevant to human exposure. They would also reduce the need for animal testing by substituting more laboratory tests for use as human cells. This National Research Council report reviews the existing system for the testing of toxicity testing.

The report calls for a culture change in the way that scientists, regulators, and the public think about toxicity testing. It calls for a more integrated approach to testing, one that combines the strengths of different disciplines and methods. It also calls for a more systematic approach to testing, one that is based on a clear understanding of the biological processes that are affected by chemicals and on a clear understanding of the ways in which these processes are affected by chemicals. The report also calls for a more systematic approach to testing, one that is based on a clear understanding of the biological processes that are affected by chemicals and on a clear understanding of the ways in which these processes are affected by chemicals.

**THE NATIONAL ACADEMIES**  
National Academy of Sciences • National Academy of Engineering • Institute of Medicine • National Research Council

## EPAs Contribution: The ToxCast Research Program

Office of Research and Development  
National Center for Computational Toxicology

[www.epa.gov/ncct/toxcast](http://www.epa.gov/ncct/toxcast)

# Future of Toxicity Testing

## POLICYFORUM

### TECHNOLOGY

#### Transforming Environmental Health Protection

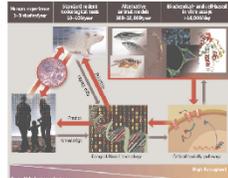
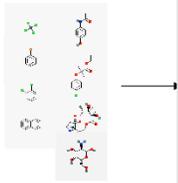
By David S. Bonner, Director, National Center for Computational Toxicology

The National Center for Computational Toxicology (NCCT) was created by the U.S. Environmental Protection Agency (EPA) in 2003, as part of the National Research Council's (NRC) report, "Toxicology in the 21st Century." The NRC report called for a new paradigm in toxicology, one that is more predictive, more efficient, and more cost-effective. The NRC report also called for a new paradigm in toxicology, one that is more predictive, more efficient, and more cost-effective. The NRC report also called for a new paradigm in toxicology, one that is more predictive, more efficient, and more cost-effective.

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- Cancer
- ReproTox
- DevTox
- NeuroTox
- PulmonaryTox
- ImmunoTox



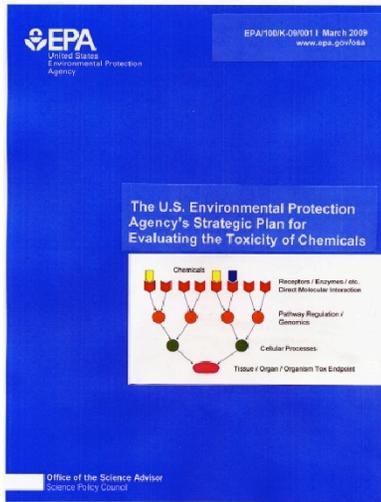
## EPAs Contribution: The ToxCast Research Program

Office of Research and Development  
National Center for Computational Toxicology

[www.epa.gov/ncct/toxcast](http://www.epa.gov/ncct/toxcast)



## EPA Reacts to Challenge of the NRC on the Future of Toxicity Testing



Office of Research and Development  
National Center for Computational Toxicology

### Strategic Goals

- Toxicity Pathway ID and Screening
- Toxicity Based Risk Assessment
- Institutional Transition

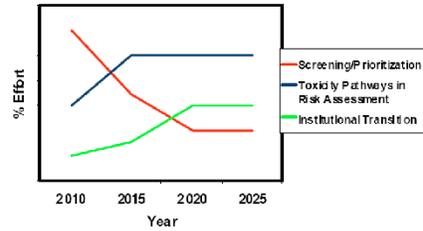
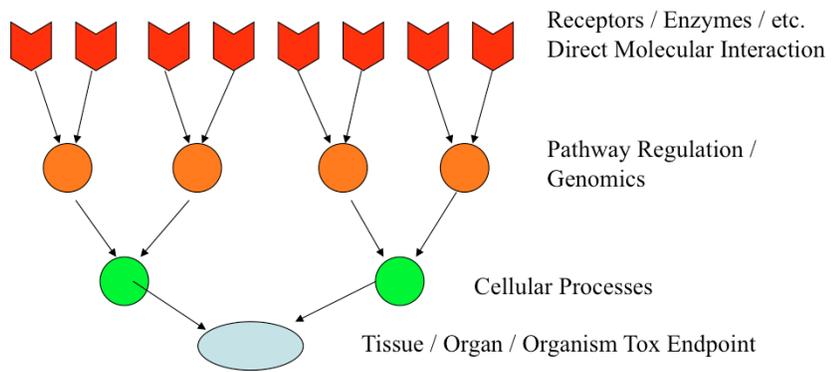


Figure 6. Relative (%) Emphasis of the Three Main Components of this Strategic Plan over its Expected 20-year Duration.

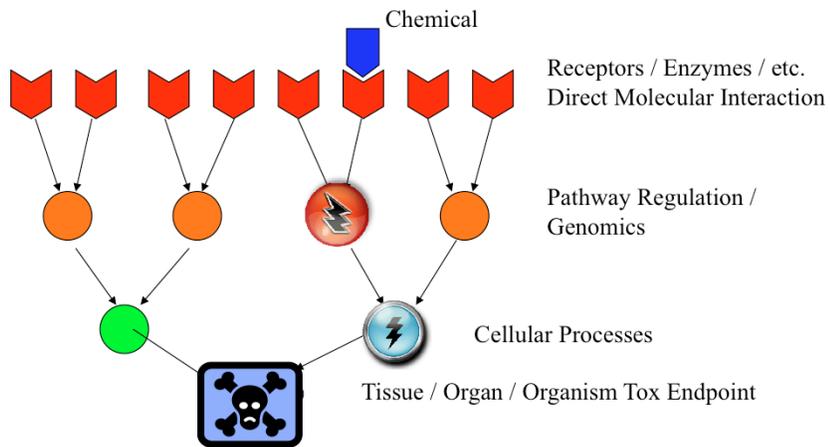
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<http://www.epa.gov/osa/spc/toxicitytesting/index.htm>

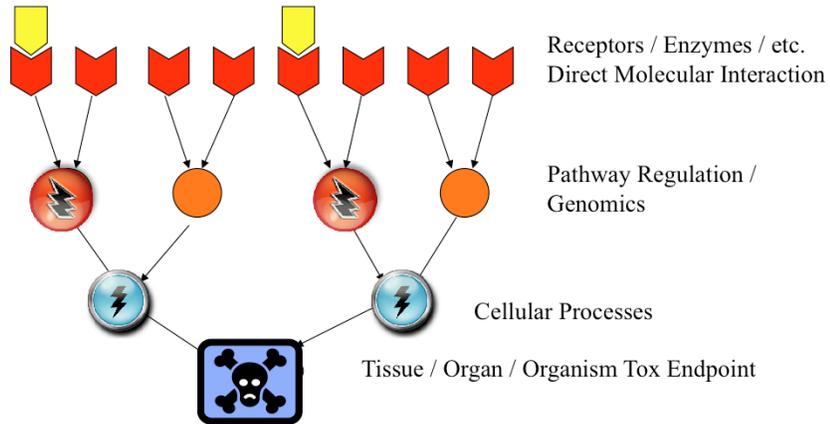
## Toxicity Pathways



## Toxicity Pathways



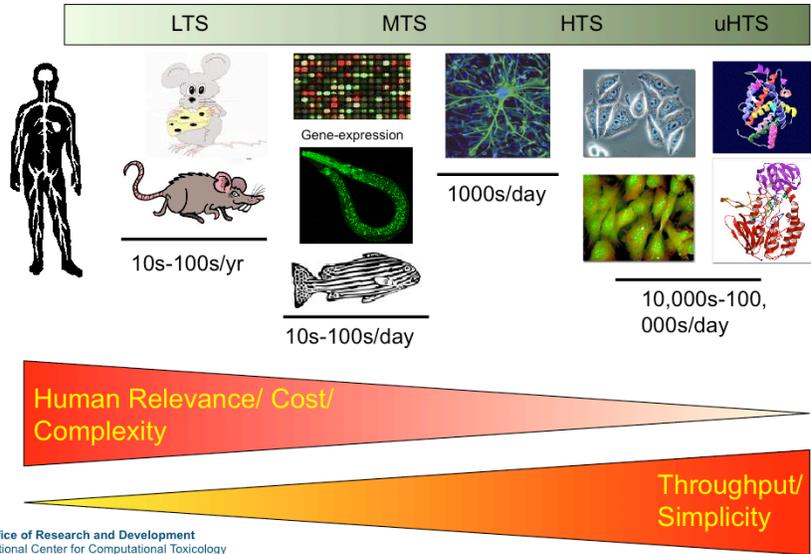
## Toxicity Pathways





# High-Throughput Screening Assays

*batch testing of chemicals for pharmacological/toxicological endpoints using automated liquid handling, detectors, and data acquisition*





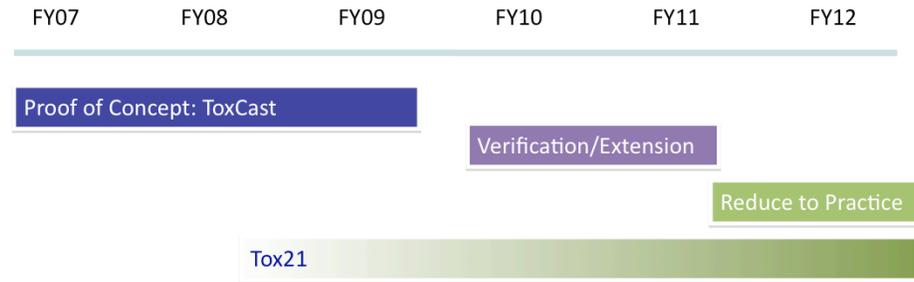
## ToxCast™ Background

- Research program of EPA's National Center for Computational Toxicology
- Addresses chemical screening and prioritization needs for pesticidal inerts, anti-microbials, CCLs, HPVs and MPVs
- Comprehensive use of HTS technologies to generate biological fingerprints and predictive signatures
- Coordinated with NTP and NHGRI/NCGC via Tox21
- Committed to stakeholder involvement and public release of data
  - Communities of Practice- Chemical Prioritization; Exposure
  - NCCT website- <http://www.epa.gov/ncct/toxcast>
  - ACToR- Aggregated Computational Toxicology Resource  
<http://www.epa.gov/actor/>





## Prioritization Product Timeline





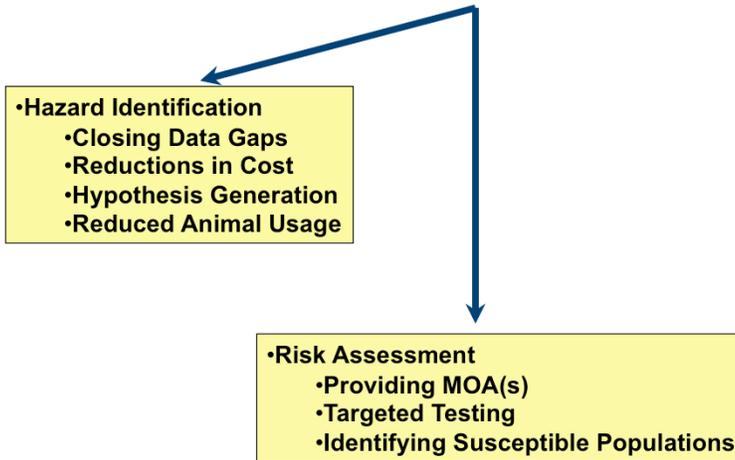
## Implications for Success



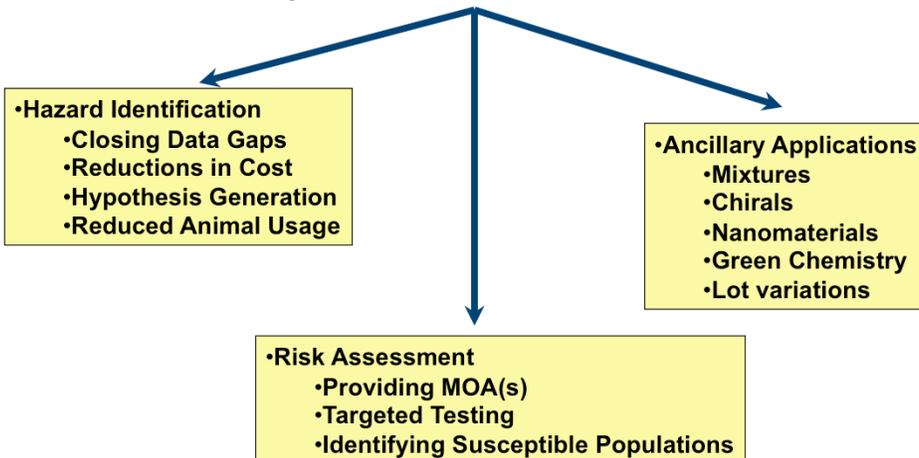
- **Hazard Identification**
  - Closing Data Gaps
  - Reductions in Cost
  - Hypothesis Generation
  - Reduced Animal Usage



## Implications for Success

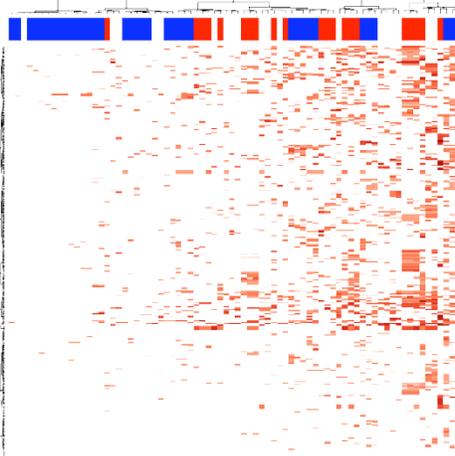


## Implications for Success



## ToxCast In Vivo Data from ToxRefDB

Chemicals

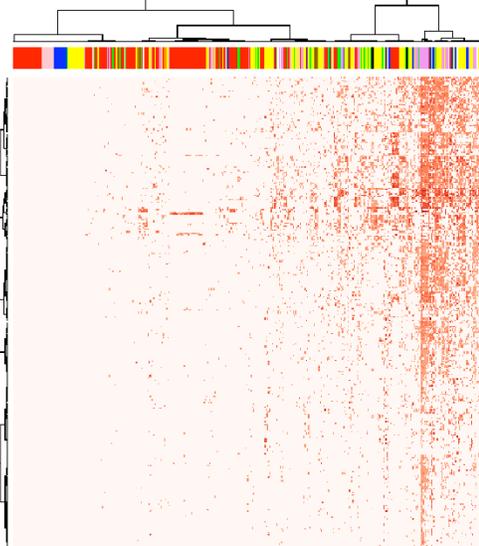


■ Chronic/Cancer  
■ Multigeneration  
■ Developmental

## ToxCast In vitro data (467 assays)

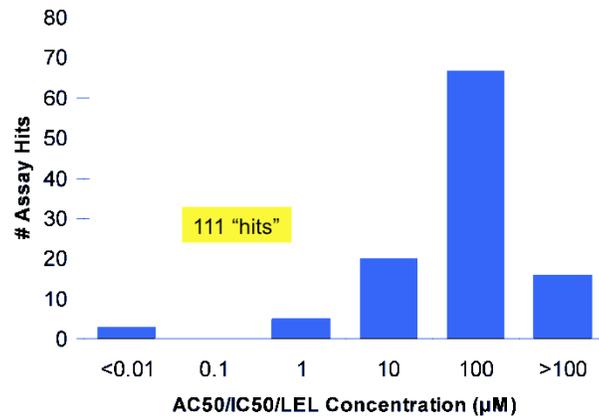
- Cell Free HTS
- Multiplexed TF
- Human BioMap
- HCS
- qNPAs
- XMEs
- Impedance
- Genotoxicity

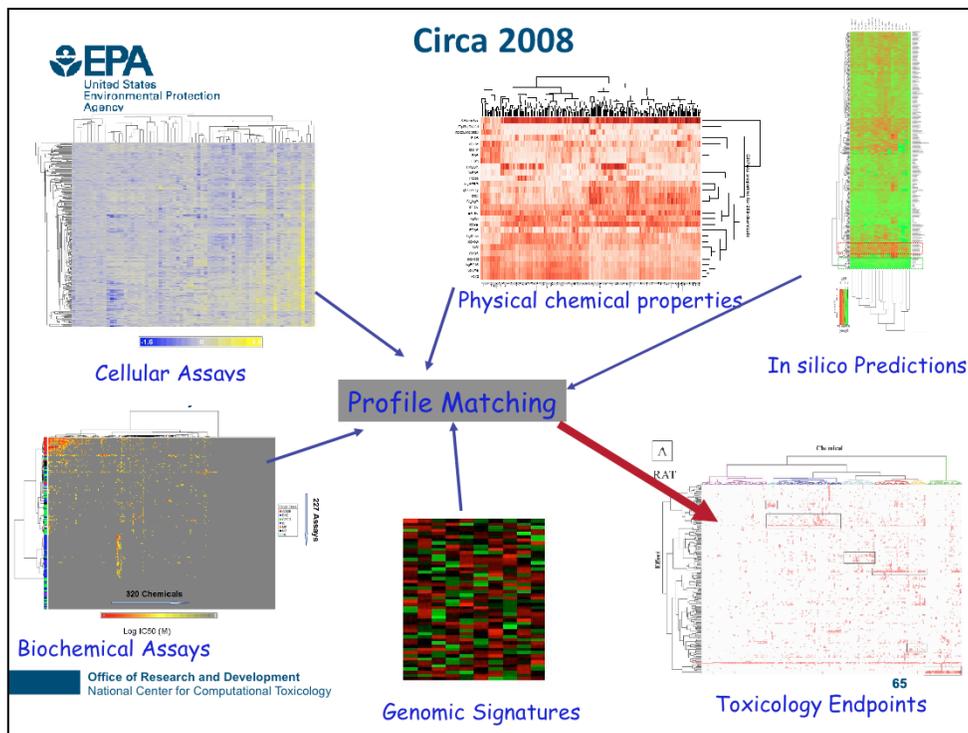
Chemicals



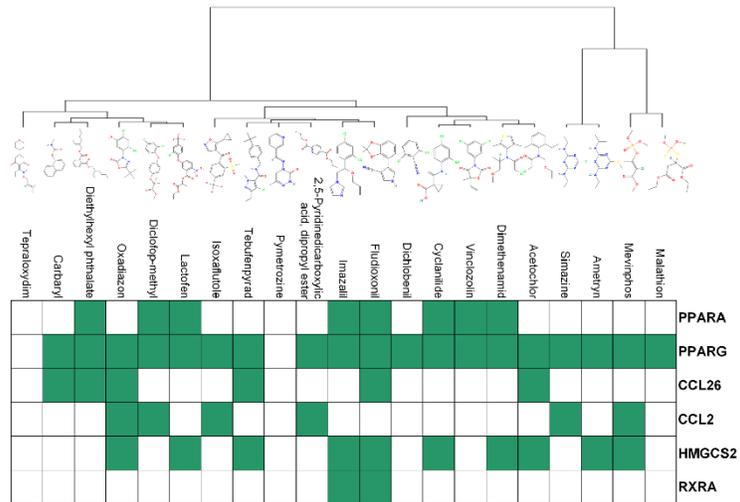
## ToxCast In vitro data (467 assays)

### Bisphenol A

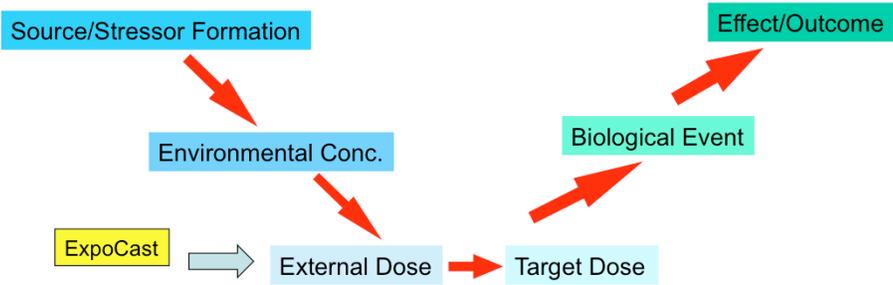




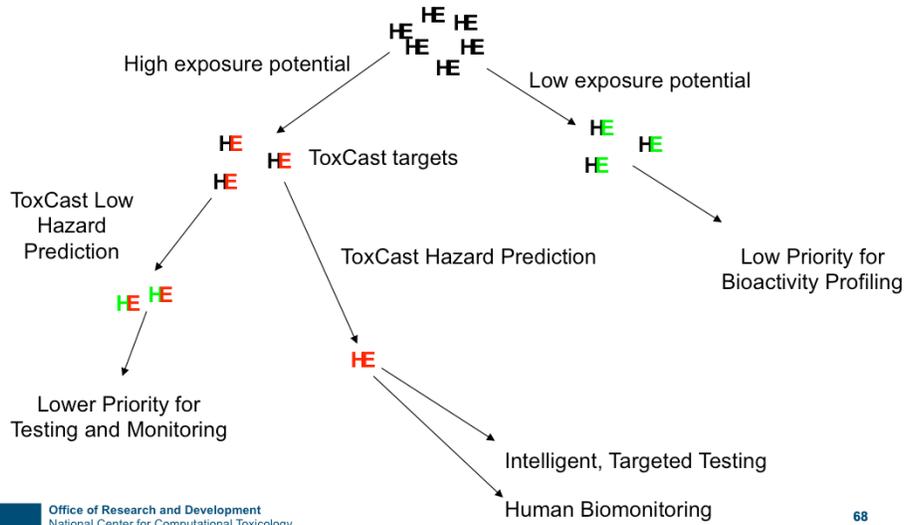
## Rat Liver Tumor Correlations



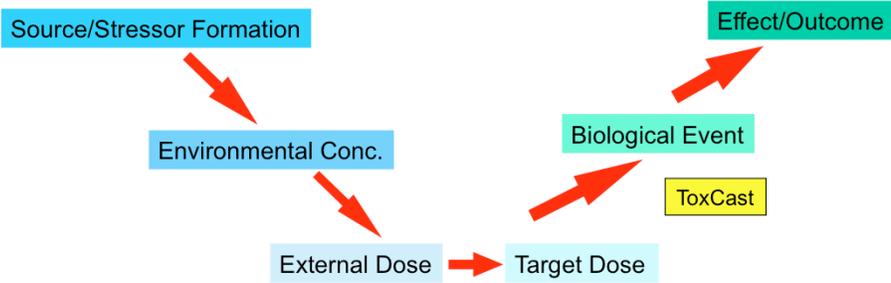
## Applying Computational Toxicology Along the Source to Outcome Continuum



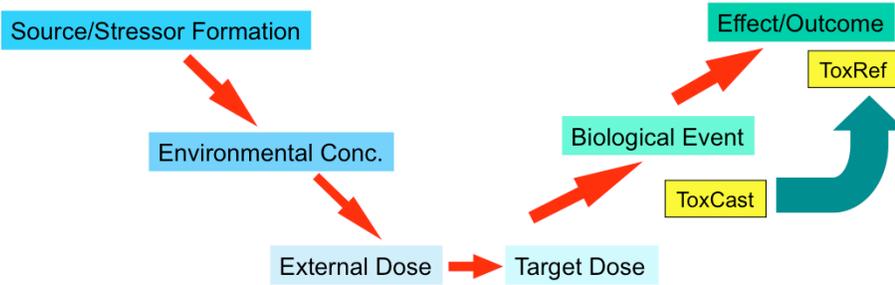
## The Future State: Using Hazard and Exposure Information for Prioritizing Testing and Monitoring



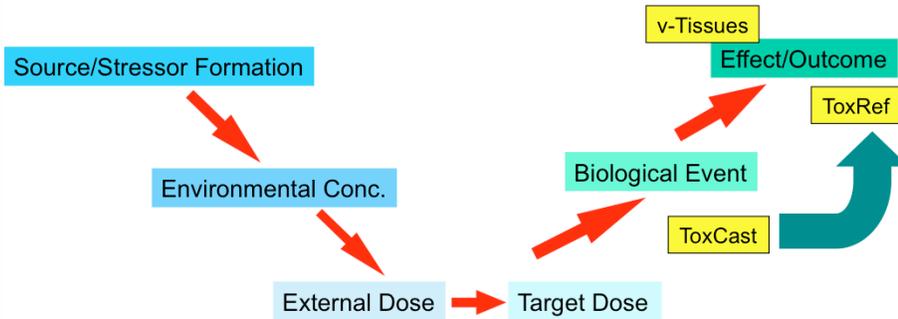
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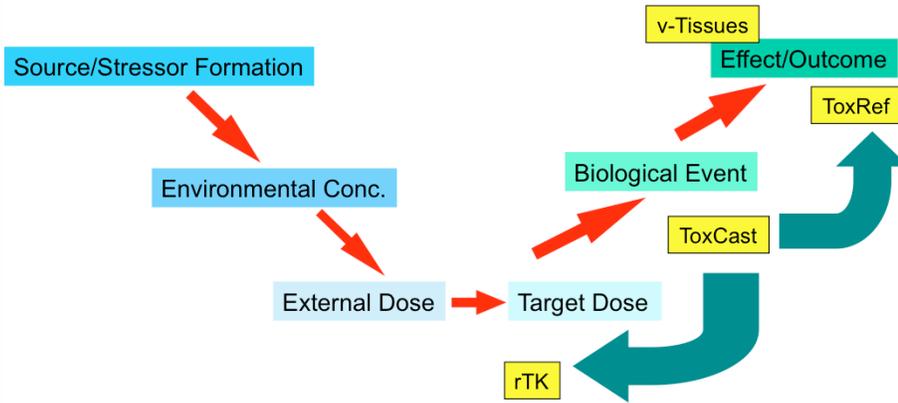
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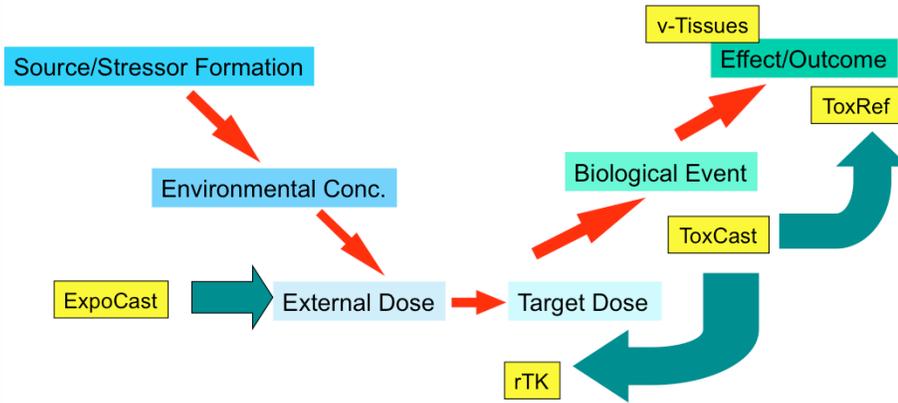
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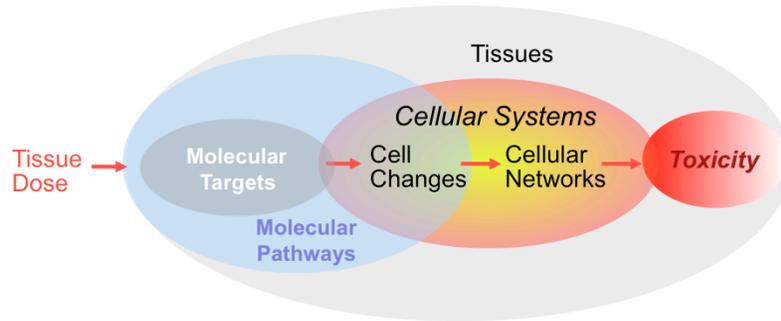
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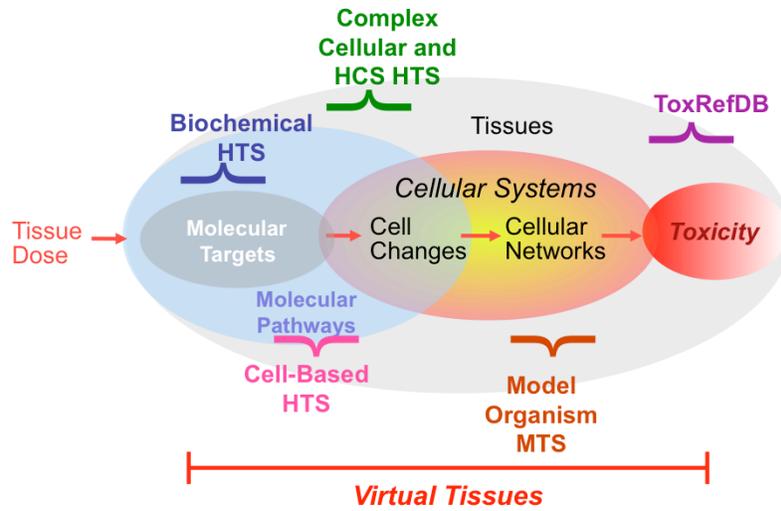
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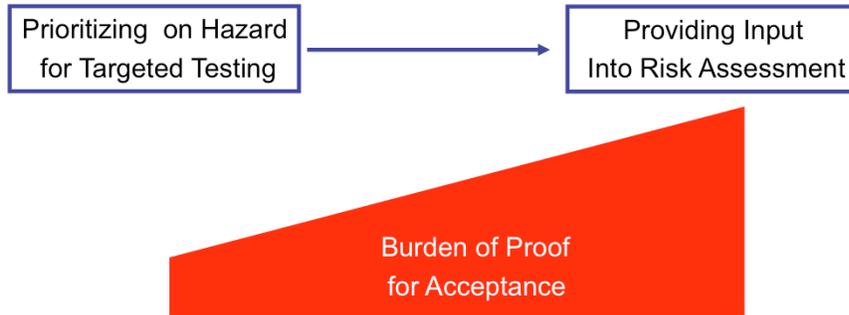
## Predicting Human Toxicity: The Grand Challenge in Toxicology



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## Applications of HTS in Health Assessment





Register now for the second presentation of the Computational Toxicology series:

## “Computational Toxicology: Dose Response Modeling” June 24th, 2009

by following the registration link on the [Computational Toxicology](#) web page.

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[http://tools.niehs.nih.gov/sbrp/risk\\_elearning/](http://tools.niehs.nih.gov/sbrp/risk_elearning/)



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