

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

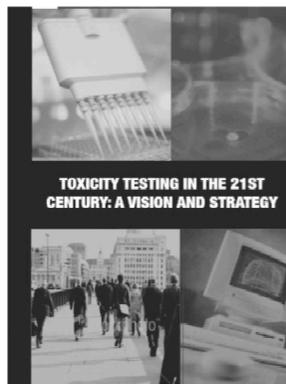
Dr. Robert Kavlock, Director of the National Center for Computational
Toxicology (NCCT/ORD/USEPA)



Toxicity Testing in the 21st Century

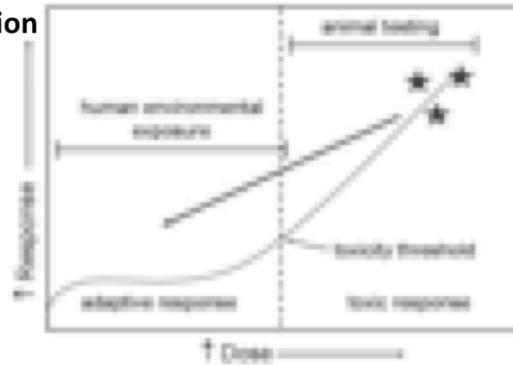
**Computational Toxicology: An
Introduction to Key Concepts and
Approaches**

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



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

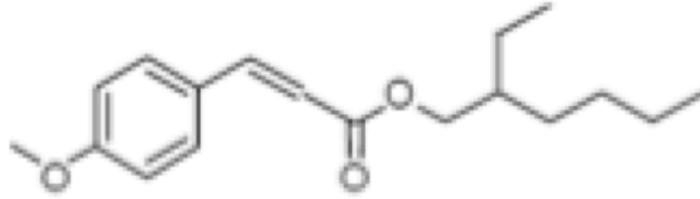
- Low throughput; expensive
- Questionable relevance to actual human risks
- Conservative extrapolation defaults
- Traditional approaches dating to 1930's
- Little use of modern biology, mode of action
- Reliance on animals



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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

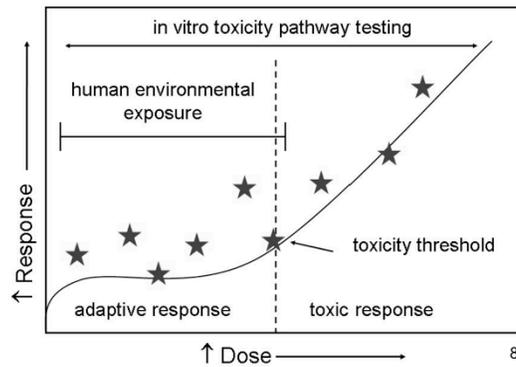
The proposed high dose is the maximally tolerated dose (MTD), and the low dose is many orders of magnitude above anticipated exposure levels

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



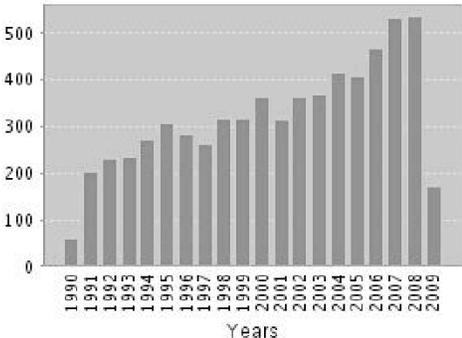
A National Research Council Committee

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

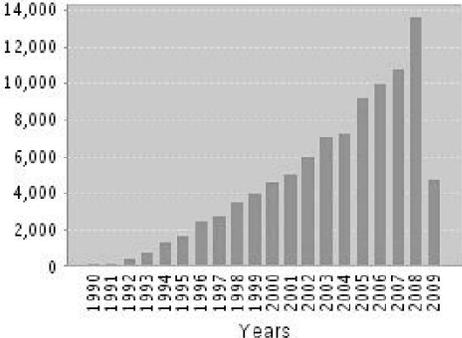
Is the focus on environmental agents important for the design criteria?

“toxicity testing”

Published Items in Each Year



Citations in Each Year

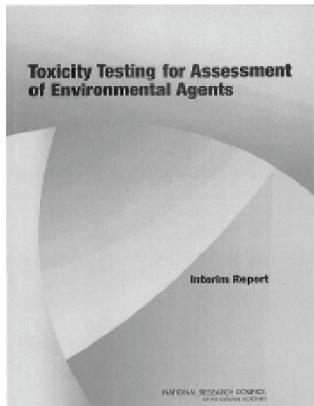


Committee Roster

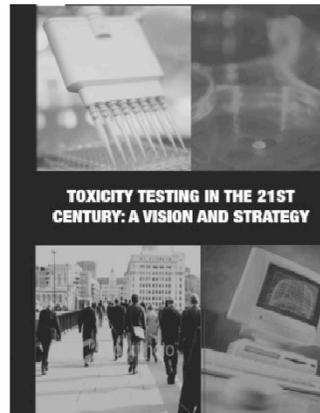
Daniel Krewski (*Chair*), University of Ottawa, Ottawa, ON
Daniel Acosta, Jr., University of Cincinnati, Cincinnati, OH
Melvin Andersen, CIIT Centers for Health Research, Research Triangle Park, NC
Henry Anderson, Wisconsin Division of Public Health, Madison, WI
John Bailar III, University of Chicago, 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

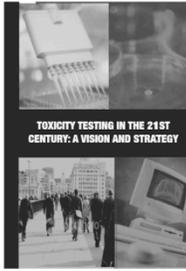
With particular thanks to Mel Andersen for permission to use his slides

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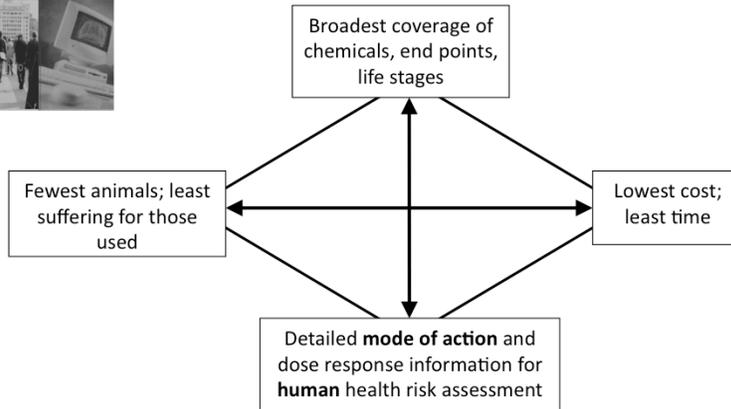


- A transformative redefinition of toxicity testing is required to meet key design criteria.



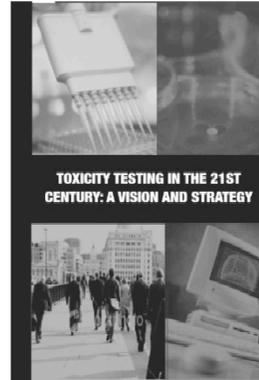


Design Criteria: Toxicity Testing of Environmental Agents



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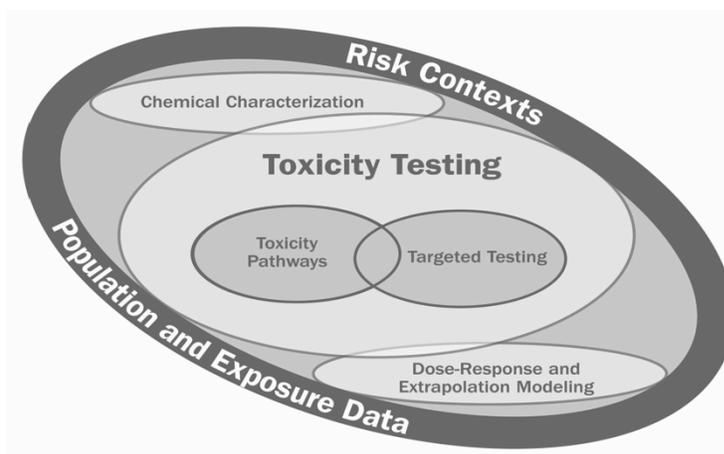
The quote is from Simon Manchester's – A Crack in the Edge of the World.

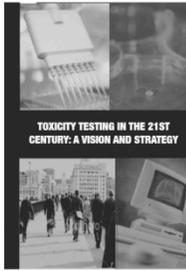
Options for Future Toxicity Testing Strategies Table 2-1

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





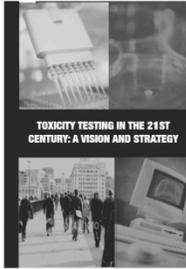
Toxicity Testing

... 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 21st 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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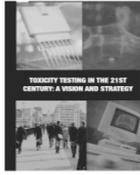


Toxicity Pathways

- 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

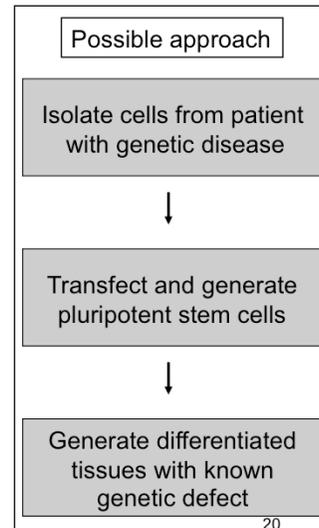
Designing Toxicity Pathway Assays

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

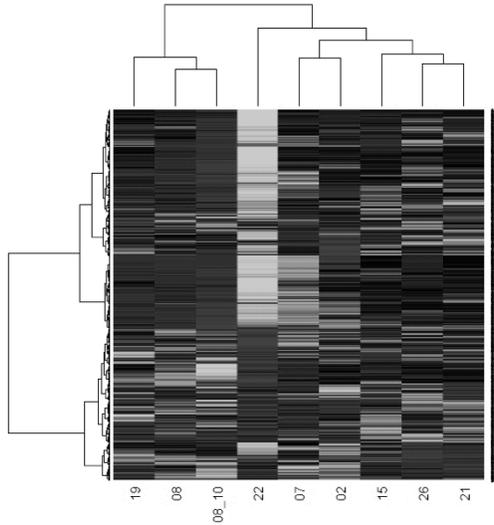
Rapid progress since completing the report:

- 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.



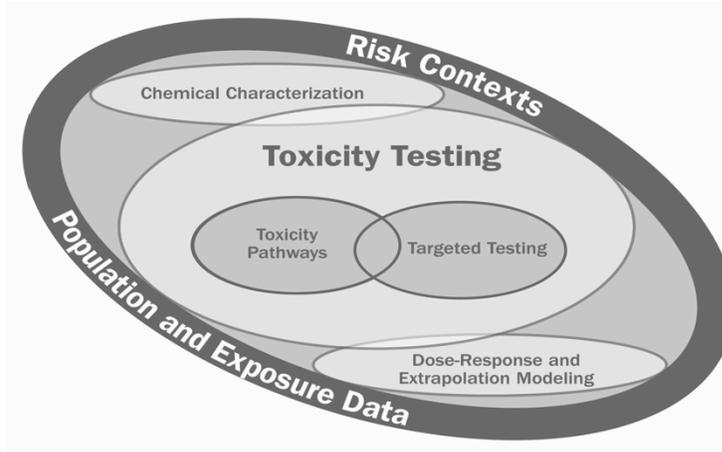
**Assess pathways,
integrate tissue
responses, and in
some cases evaluate
metabolites**

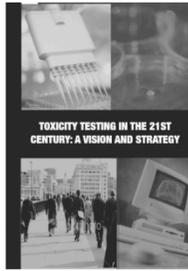
**Discuss use of new
technologies in
targeted testing
strategies**

In the new approach,

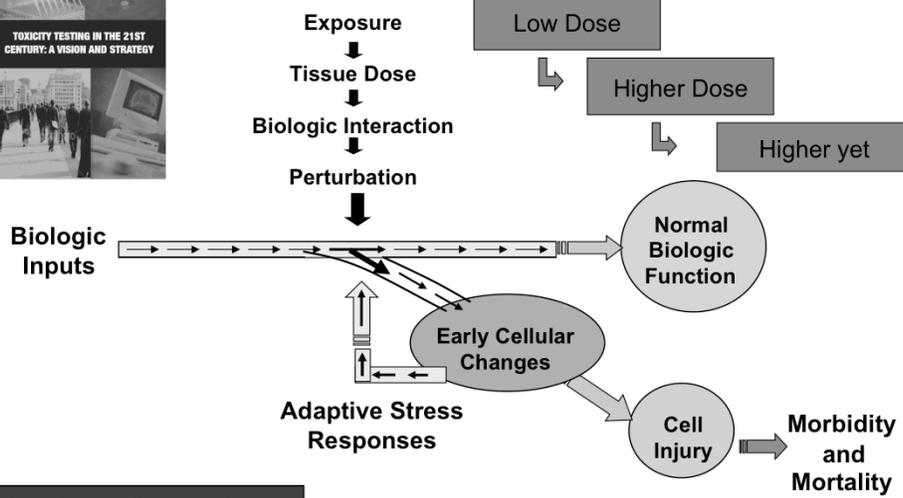
- Toxicity pathways assays, better reflecting biological targets and modes of action
- Increased speed and throughput for chemicals and decreased costs and animal usage
- Move away from extrapolating from high dose animal results to low doses in humans and focus on results of perturbations of toxicity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

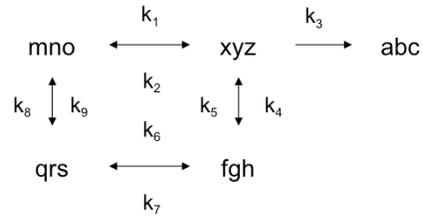
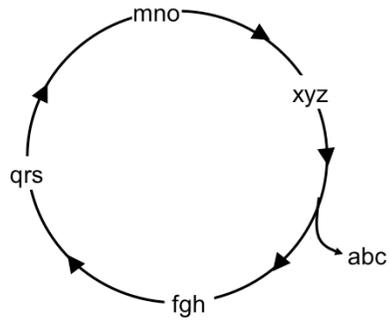
Dose response modeling of perturbations of pathway function would be organized around ***computational systems biology models of the circuitry underlying each toxicity pathway***. ***In vitro to in vivo extrapolations would rely on pharmacokinetic models*** – ideally physiologically based pharmacokinetic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

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

Systems Modeling of Toxicity Pathways

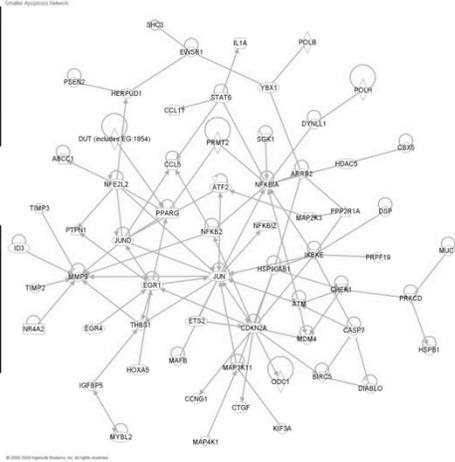
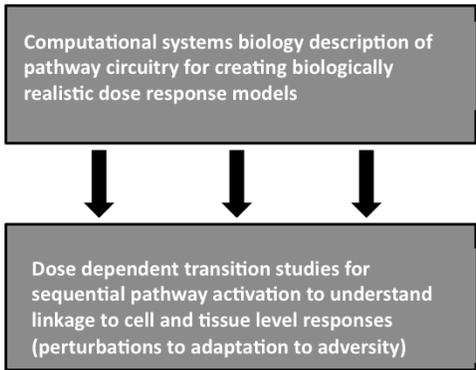
Computational systems biology description of pathway circuitry to support dose response modeling of pathway perturbations

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



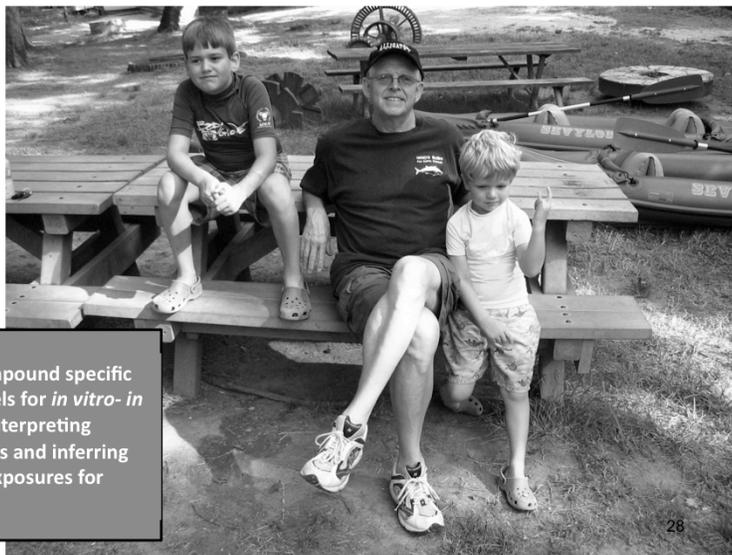
Map and model circuitry of the toxicity pathway assay for dose response assessment and to assess susceptibility factors 26

Dose Response Models Linking Perturbations to more Integrated Responses



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



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

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

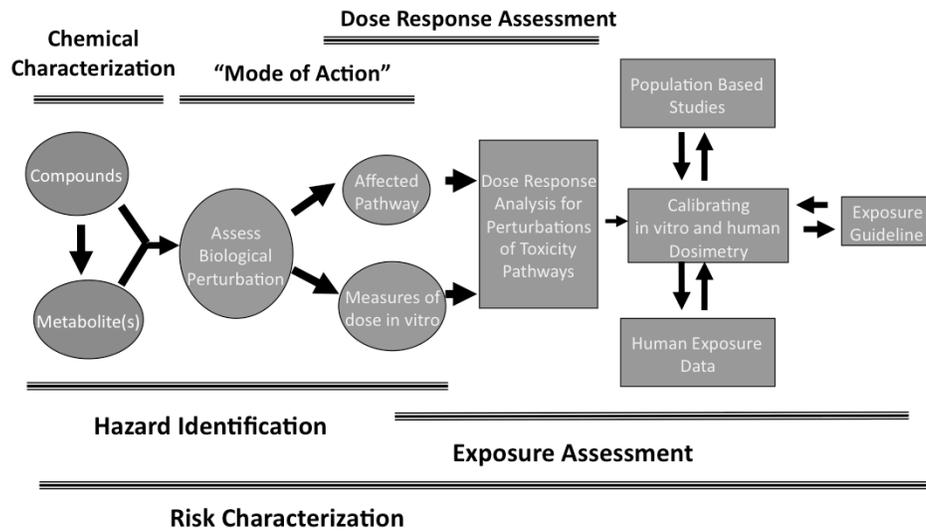
Evaluate regions of safe exposures based on pathways affected by the chemical, the circuitry of the response, linkage from perturbation to integrated cell response, and knowledge of pharmacokinetics and exposure

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.....

- 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.....

What about epigenetics and other new biology?

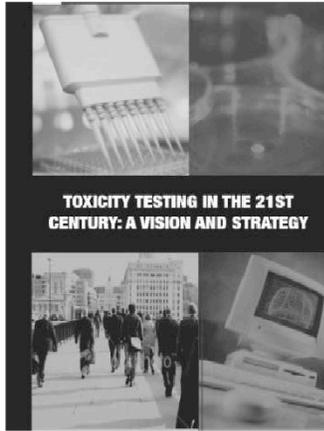
Is this a screening tool or a stand-alone system?

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.....

- 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



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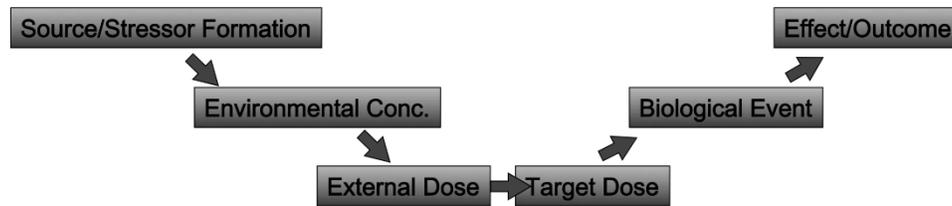
“...to integrate modern computing and information technology with molecular biology to improve Agency prioritization of data requirements and risk assessment of chemicals”

www.epa.gov/ncct

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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

High Production Volume (HPV) Challenge Program

The HPV Voluntary Challenge Chemical List

The U.S. high production volume (HPV) chemicals are those which are manufactured in or imported into the United States in amounts equal to or greater than one million pounds per year. The U.S. HPV chemicals were identified through information collected under the Toxic Substances Control Act (TSCA) Inventory Update Rule (IUR). Organic chemicals that are manufactured in, or imported into, the United States in amounts equal to or exceeding 10,000 pounds per year are subject to reporting under the TSCA IUR. Reporting is required every four years.

The HPV Challenge Program Chemical List consists of all the HPV chemicals reported during the 1990 IUR reporting year. Inorganic chemicals and polymers, except in special circumstances, were not subject to the IUR reporting requirements, although a number were reported in error. The HPV Challenge Program Chemical List contains about 2,800 chemicals.

The 1990 IUR list was selected as the starting point for this program. As subsequent reporting years identify additional chemicals (including inorganics), once the corresponding reporting requirements have been added under the IUR, they will be posted here for information purposes. EPA expects that, over time, the testing of new HPV chemicals will become routine, and companies may wish to test new HPV chemicals as they appear.

In keeping with that eventual goal, EPA posted the 1994 List of HPV Additions, which contains about 500 organic HPV chemicals which were newly reported as HPV in the 1994 IUR and are thus not part of the HPV Challenge Program at this time. This list is being provided particularly for use by companies who desire to propose categories of chemicals for testing and wish to include chemicals from the 1994 list in their category definitions. In some cases, companies or consortia have sponsored chemicals that are not on either the HPV Challenge Program Chemical List or the 1994 List of HPV Additions. A list of these chemicals, called "Additional Chemicals Sponsored Under the HPV Challenge Program" is also available.

Each list contains the Chemical Abstract Services (CAS) registry number, which is a unique identification number assigned to a chemical; an indicator variable signifying whether the chemical falls outside the scope of the HPV Challenge Program, the chemical sponsorship status, and the sponsor commitment information. The explanations of the various values used in the indicator and status columns can be viewed under the "Title to Use the List" button. Searches for CAS numbers, chemical names, indicators, chemical sponsorship status, and sponsor commitment status may be conducted using the "Search" function. Lists may be downloaded in either Portable Data Format (PDF) or database format (ODP).

These lists have been annotated periodically since they were first posted on October 9, 1998. Only the most recent description of updates to the lists is shown below. To view a chronology of amendments to the lists, please consult the "Chemical List History" button.

January 31, 2005

In order to standardize the chemical names of the HPV Challenge Program chemical lists, with this update, EPA is changing the chemical names to reflect the Chemical Abstracts (CAS) Full Collective Index (FCI) names. Full Collective Index names are those used for the TSCA Inventory. Changes have been made to the following lists only: the HPV Challenge Program Chemical List, the 1994 List of HPV Additions, the Additional Chemicals Sponsored Under the HPV Challenge Program, and the Sponsored Chemicals List. Please note that chemical name changes are not highlighted on these lists. Chemical names on the HPV Challenge Summary Report have not been changed. Additional changes to chemical names will occur with future website updates as the Agency continues to review and modify its lists to reflect the appropriate chemical names.

Indicator - 1 (Not Considered a Candidate for Testing)

A chemical that is not considered a candidate for testing under the HPV Challenge Program, based on preliminary EPA review indicating that testing using the SDS base set would not further our understanding of the chemical's properties has been assigned an indicator of "1". This chemical may be sponsored, however.

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Toxicological Information Gaps

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Drinking Water Contaminant Candidate List (CCL)

U.S. Environmental Protection Agency

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EPA Home > Water > Groundwater & Drinking Water > Drinking Water Contaminant Candidate List Home > Frequent Questions

Frequent Questions

- 1. What is the drinking water CCL?**
The drinking water CCL is the primary source of priority contaminants for which we conduct research to make decisions about whether regulations are needed. The contaminants on the list are known or anticipated to occur in public water systems. However, they are currently unregulated by existing national primary drinking water regulations.
- 2. How often is the CCL published?**
The Safe Drinking Water Act directs that we periodically publish a CCL. We published the first CCL of 60 contaminants in March 1998 and the second CCL in February 2006 after deciding to continue research on the list of contaminants on the first CCL. [See the related activities and dates page for these notices.](#)
- 3. What contaminants are included in CCL 2?**
The CCL publishes a 2006 cycle forward 51 of the original 60 unregulated contaminants from the first CCL, including nine microbiological contaminants and 42 chemical contaminants or contaminant groups (see table). In July 2005, EPA announced its final determination for a subset of nine contaminants from the first CCL, which concluded that sufficient data and information was available to make the determination not to regulate Acanthamoeba, aldrin, dieldrin, hexachlorobutadiene, manganese, methionin, naphthalene, radon, and sulfite. These nine contaminants were not carried forward to the 2006 CCL.
- 4. Does the CCL impose any requirements on public water systems?**
No. The CCL alone does not impose any requirements on public water systems. However, we may regulate contaminants on the list in the future. Public water systems would have to follow specific requirements to comply with a regulation.
- 5. What happens to contaminants on the CCL?**
We carry out studies to develop analytic methods for detecting the contaminants, determine whether they occur in drinking water, and evaluate treatment technologies to remove them from drinking water. We also investigate potential health effects from the contaminants. These efforts help us to determine if actions such as drinking water guidance, health advisories or regulations need to be developed for contaminants on the CCL, or if no action is necessary at this time.
- 6. What is a regulatory determination?**
A regulatory determination is a formal decision on whether we should issue a national primary drinking water regulation for a specific contaminant. The law requires that we make regulatory determinations for few or more contaminants from the most recent CCL.
In 2003, we made regulatory determinations for nine contaminants from the first CCL (see the [first CCL determinations](#)). We plan to propose the second cycle of preliminary regulatory determinations from the second CCL in the summer of 2006 and make final regulatory determinations in August of 2006.
It is important to note that we are not limited to making regulatory determinations for only those contaminants on the CCL. We can also decide to regulate other unregulated

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Toxicological Information Gaps

The screenshot shows a web browser window displaying the EPA website. The page title is "Inert (other) Pesticide Ingredients in Pesticide Products". The main content area includes a search bar, a navigation menu on the left, and a main text block. The text block contains a definition of inert ingredients, a list of examples, and a "Name Change: From Inert to Other Ingredients" section. The "Name Change" section states that in September 1997, the EPA issued Pesticide Regulation Notice 97-6, which encourages manufacturers, formulators, producers, and registrants of pesticide products to voluntarily substitute the term "other ingredients" as a heading for the "inert" ingredients in the ingredient statement on the label of the pesticide product. EPA made this change after learning the results of a consumer survey on the use of household pesticides. Many comments from the public, and the consumer interviews prompted EPA to discontinue the use of the term "inert." Many consumers are misled by the term "inert ingredient," believing it to mean "harmless." Since neither federal law nor the regulations define the term "inert" on the basis of toxicity, hazard or risk to humans, non-target species, or the environment, it should not be assumed that all inert ingredients are non-toxic.

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Toxicological Information Gaps

The screenshot shows the REACH website with the following content:

THE NEW EU CHEMICALS LEGISLATION - REACH

Overview

Activities:

- REACH Proposal
- Proposed
- Impact Assessment
- Trials from

The White Paper

Information:

- Call
- Links
- Contact

On 29 October 2003, the European Commission adopted a proposal for a new EU regulatory framework for chemicals, COM (2003) 644. Under the proposed new system called REACH (Registration, Evaluation and Authorisation of Chemicals), enterprises that manufacture or import more than one tonne of a chemical substance per year would be required to register in a central database.

The aims of the proposed new Regulation are to improve the protection of human health and the environment while maintaining the competitiveness and enhancing the innovative capability of the EU chemicals industry. REACH would furthermore give greater responsibility to industry to manage the risks from chemicals and to provide safety information on the substances. This information would be passed down the chain of production.

The proposal has been drafted in close consultation with all interested parties, including an [Internet consultation](#). This has allowed the Commission to propose a streamlined and cost-effective system. The proposal is now being considered by the European Parliament and the Council of the EU for adoption under the so-called co-decision procedure.

News & Updates

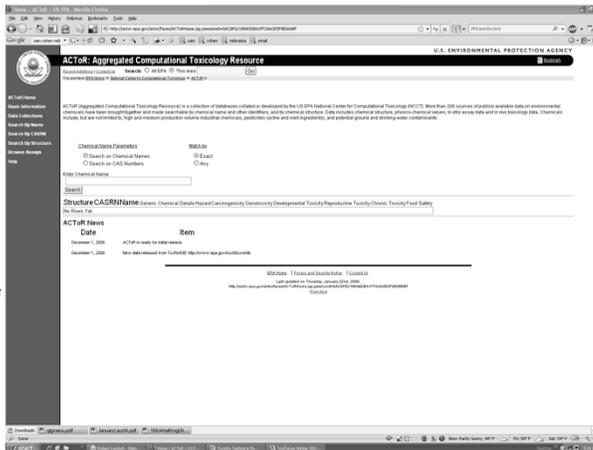
- 26.7.2006 REACH II - Call for tender - [Scientific and technical data](#) [See...](#)
- 16.7.2006 REACH Impact Assessment Study for UNCLAD/EC Industry Consortium. [See report](#) [See...](#)
- 7.7.2006 REACH II - Call for tender - [Scientific and technical data](#) [See...](#)
- 7.7.2006 See the letter to Press officers concerning arrival requirements and the Commission [Scientific and technical data](#) [See...](#)
- 6.7.2006 See the Press Release and the [Report on PCE](#) [See...](#)
- 19.6.2006 See the Further Impact assessment study in the European bodies production [Scientific and technical data](#) [See...](#)
- 14.6.2006 See the [Call for information](#) [See...](#)
- 4.6.2006 See the REACH II - Call for [tender](#) - [Deadline 9.9.2006](#) [See...](#)
- 27.4.2006 [See...](#)

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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>

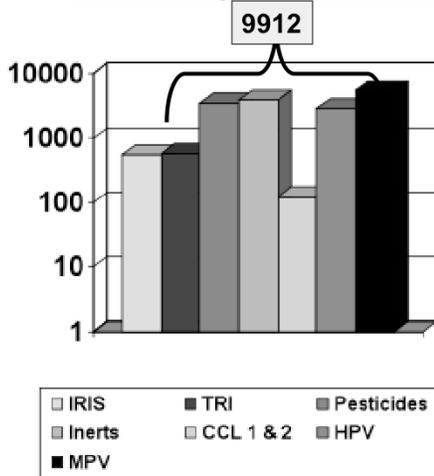


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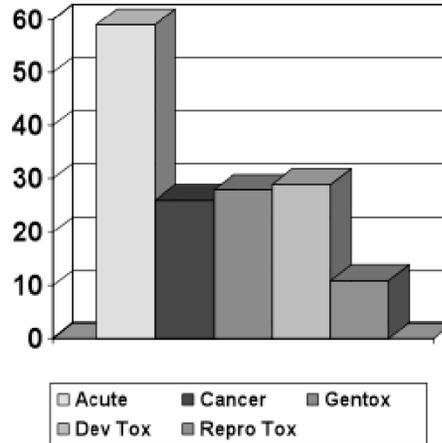
EPA's Need for Prioritization

Too Many Chemicals



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Too Little Data (%)



Judson, et al *EHP* (2009)



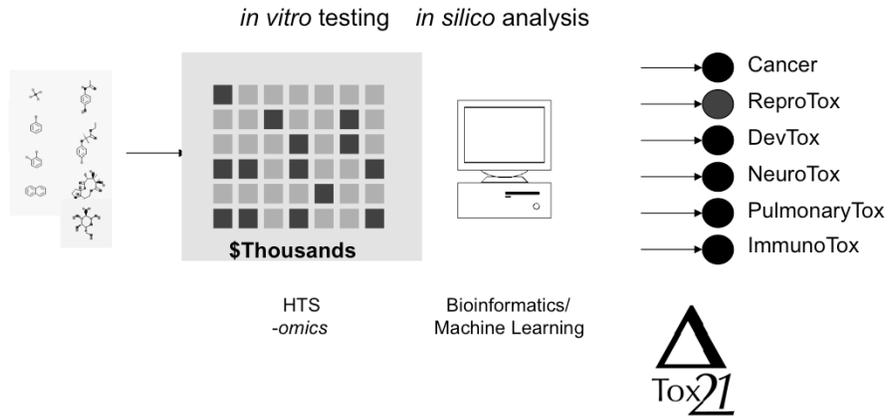
How Can We Prioritize?

- 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

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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, biotechnology, 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 exposures. They could also reduce the need for animal testing by substituting more laboratory tests based on human cells. This National Research Council report creates a far-reaching vision for the future of toxicity testing.

Toxicity tests on laboratory animals are conducted to evaluate chemicals—including pesticides, food additives, and industrial chemicals, and agricultural chemicals—for their potential to cause cancer, birth defects, and other adverse health effects. Information from toxicity testing serves as an important part of the basis for public health and regulatory decisions concerning toxic chemicals. Current test methods were developed incrementally over the past 50 to 60 years and are conducted using laboratory animals, such as rats and mice. Using the results of animal tests to predict human health effects involves a number of assumptions and extrapolations that remain controversial. Test animals are often exposed to higher doses than would be expected for typical human exposures, requiring assumptions about effects at lower doses or exposures. Test animals are typically observed for overt signs of adverse health effects, which provide little information about biological changes leading to such health effects. Other controversial laboratory tests cannot be applied to account for differences between test animals and humans. Finally, use of animals in testing is expensive and time consuming, and it sometimes causes ethical issues.

Today, technological evaluation of chemicals is poised to take advantage of the on-going revolution in biology and biotechnology. This revolution is making it increasingly possible to study the effects of chemicals using cells, cellular components, and tissues—particularly of human origin—rather than whole animals. These powerful new approaches could help to address a number of challenges facing the

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Tox21

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

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

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Future of Toxicity Testing

POLICYFORUM

TOXICOLOGY

Transforming Environmental Health Protection

FRANZ S. SCHERER, "Emerging Risk," John R. Bunker*

In 2003, the U.S. Environmental Protection Agency (EPA), with support from the U.S. National Toxicology Program (NTP), funded a project at the National Research Council (NRC) to develop a long-range research strategy for testing and assessment of chemicals. The project was to identify and assess potential pathways to meet existing regulatory needs. Challenges include the large number of substances that need to be tested and how to incorporate more information in predictive toxicology, computational systems, and information technology to help researchers to better assess potential risks, and to offer increased efficiency in design and cost (1-3). In response, the NRC conducted an advisory study and assessment of Environmental Agency programs to support the assessment of current toxicity testing, identified key issues, and developed a vision and implementation strategy to create a major shift in the assessment of chemical hazard and risk (4, 5).

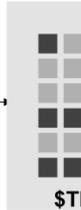
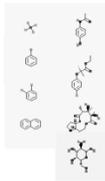
Although the NRC report heralded a new paradigm of chemical, computational and systems toxicology, progress has been slow. However, several public data sets and programs, such as the National Center for Computational Toxicology and Research (NCCCT) and the National Center for Chemical Genomics (NCCG), implemented with expertise in experimental toxicology, computational toxicology, and high-throughput technologies, respectively, have established a collaborative research program.

EPA, NCCG, AND NTP RESEARCH INITIATIVES

In 2004, the NTP advanced its vision and mission for the 21st century (6), which established initiatives to integrate high-throughput technologies, computational toxicology, and systems toxicology. The NTP also supported the development of the National Center for Computational Toxicology and Research (NCCCT) and the National Center for Chemical Genomics (NCCG), implemented with expertise in experimental toxicology, computational toxicology, and high-throughput technologies, respectively, have established a collaborative research program.

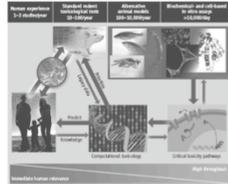
Throughout screening (HTS) and other automated screening assays into its testing program. In 2005, the EPA established the National Center for Computational Toxicology (NCCCT). Through these initiatives, NTP and EPA, with the NCCG, are progressing the evolution of toxicology from a predominantly descriptive science (based on historical data of target-specific, mechanism-based, biological observations, in vitro). As an example, below, in vivo and in vitro tests are being used to identify cellular responses after chemical exposure expected to result in adverse health effects (7). HTS methods are a primary means of discovery for drug development, and screening of 100,000 compounds per day is routine (8). However, developmental HTS methods do not identify test compounds at one concentration, usually between 2 and 10 µM, and below a high false-negative rate. In contrast, in the EPA, NCCG, and NTP work-based efforts, all compounds are tested at as many as 15 concentrations, generally ranging from 10 µM to 100 pM, to generate a concentration-response curve (9). This approach is highly applicable, provides significantly more false-positive and false-negative rates than the standard HTS methods (9), and facilitates multivariate comparisons. Finally, an interagency effort has been made to compare results among HTS screens; this is being expanded to allow comparisons with historical toxicology NTP and EPA data (http://toxcast.epa.gov/toxcast/HTSData). HTS and NTP are used as the NCCG, and other Molecular Libraries Initiative centers (http://mli.nih.gov/), and being made publicly available through Web-based databases (e.g., Tox21 data (http://tox21.ehponline.com)). In addition,

We propose a shift from primarily in vitro animal studies to more reliance on in vitro data, better integration, and computational modeling for toxicity assessment.



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



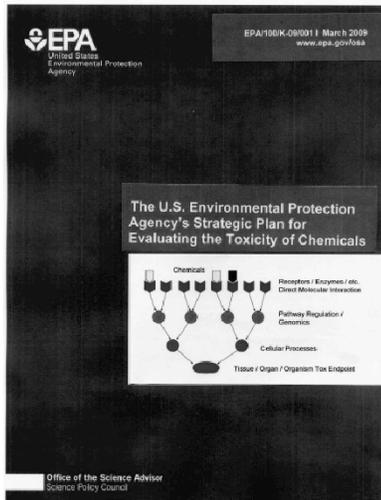
EPAs Contribution: The ToxCast Research Program

Office of Research and Development
National Center for Computational Toxicology

www.epa.gov/ncct/toxcast



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

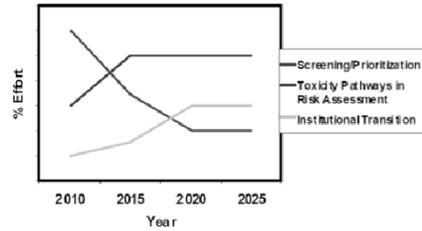


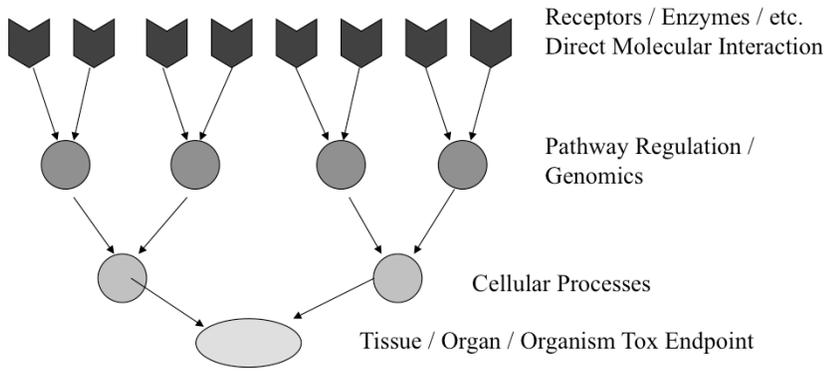
Figure 6. Relative (%) Emphasis of the Three Main Components of this Strategic Plan over its Expected 20-year Duration.

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



Toxicity Pathways

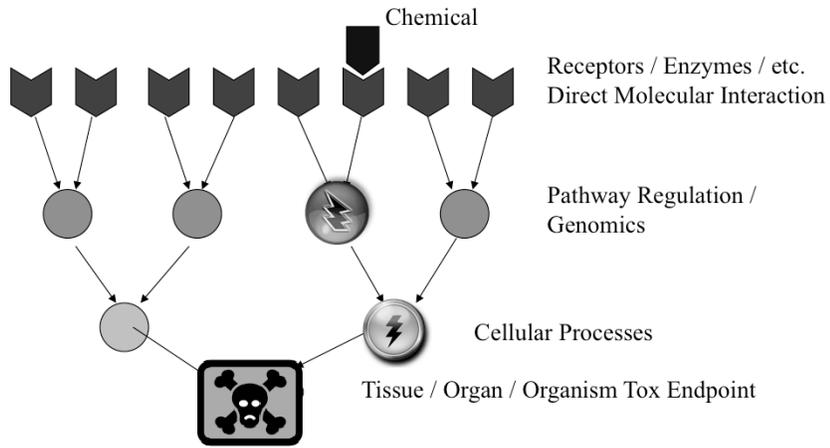


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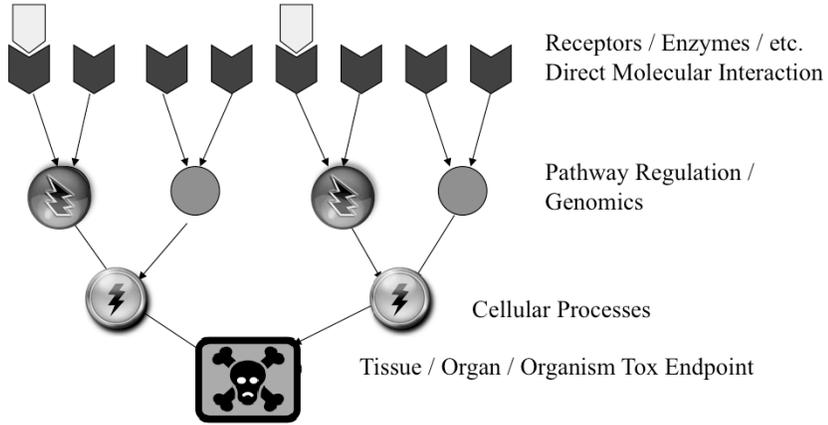
Toxicity Pathways



Office of Research and Development
National Center for Computational Toxicology



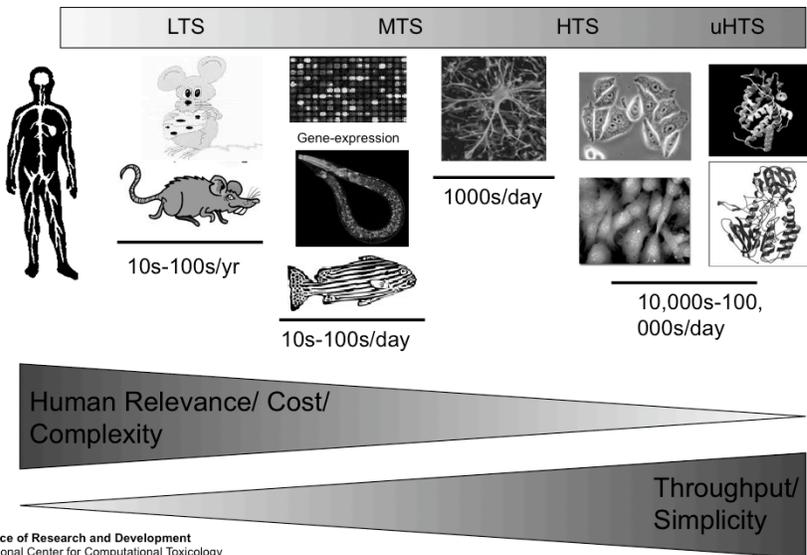
Toxicity Pathways





High-Throughput Screening Assays

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



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National Center for Computational Toxicology



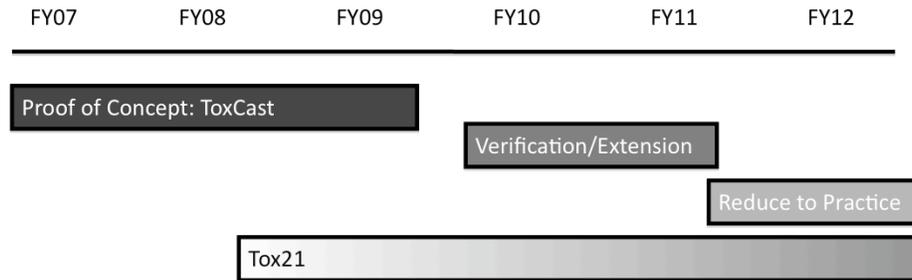
ToxCast™ Background

- Research program of EPA's National Center for Computational Toxicology
- Addresses chemical screening and prioritization needs for pesticidal inert, 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





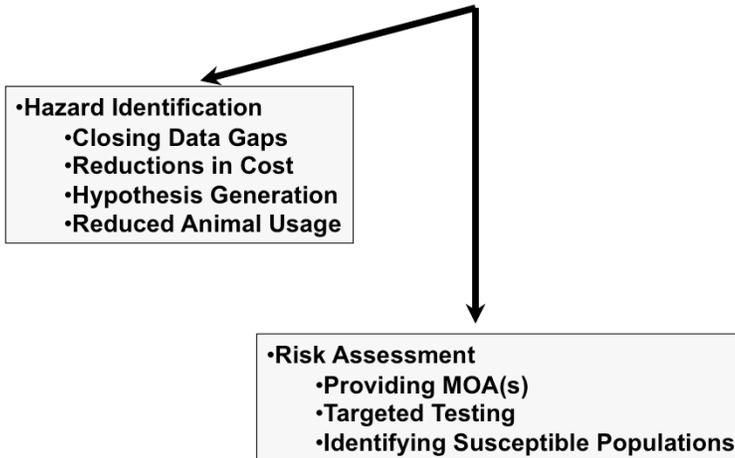
Implications for Success



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



Implications for Success



Implications for Success

• **Hazard Identification**

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

• **Ancillary Applications**

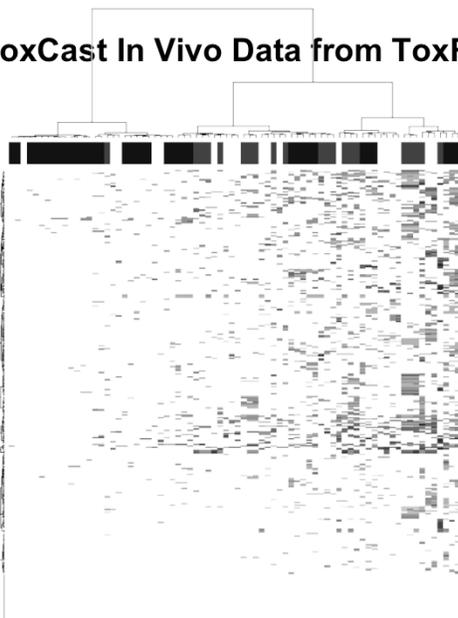
- Mixtures
- Chirals
- Nanomaterials
- Green Chemistry
- Lot variations

• **Risk Assessment**

- Providing MOA(s)
- Targeted Testing
- Identifying Susceptible Populations

ToxCast In Vivo Data from ToxRefDB

Chemicals

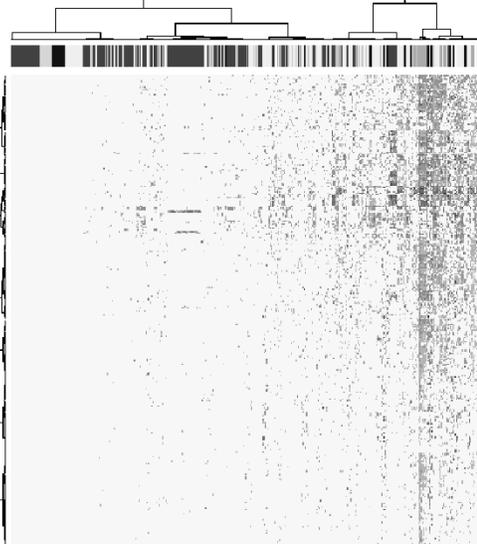


■ Chronic/Cancer
■ Multigeneration
■ Developmental

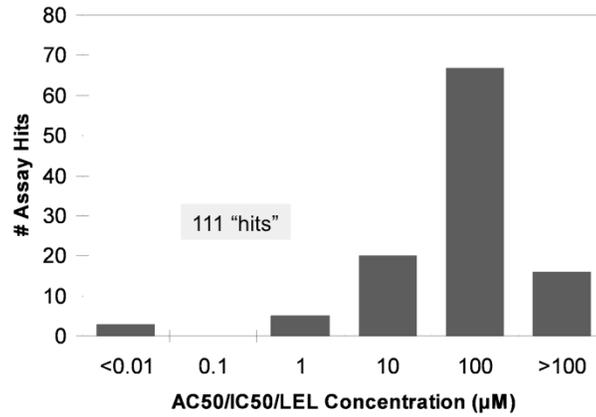
ToxCast In vitro data (467 assays)

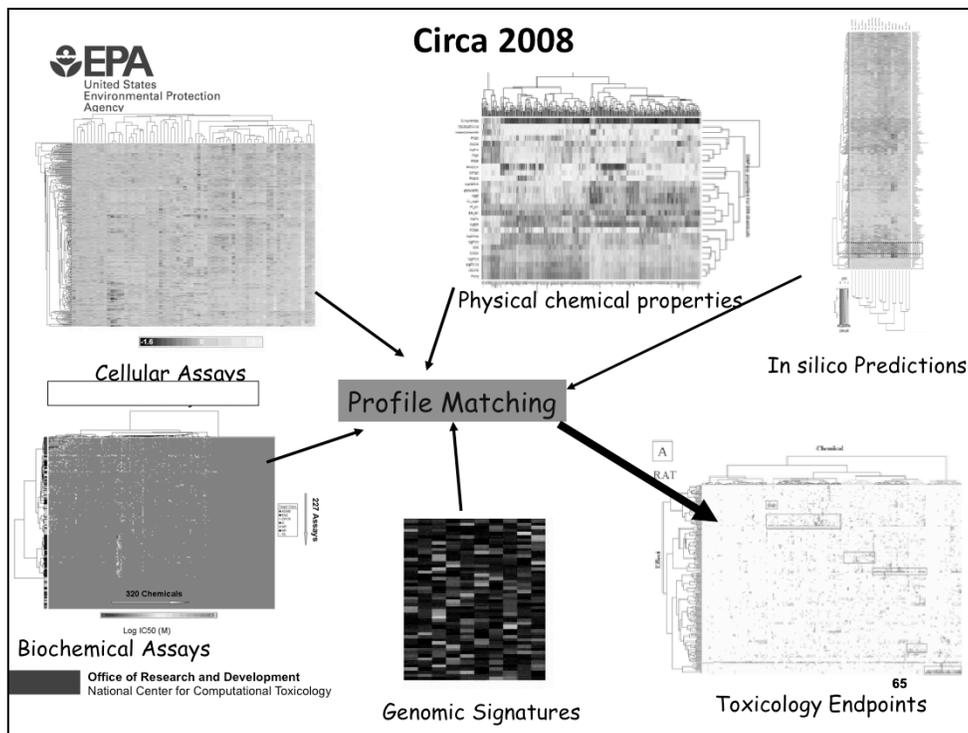
- Cell Free HTS
- Multiplexed TF
- Human BioMap
- HCS
- qNPAs
- XMEs
- Impedance
- Genotoxicity

Chemicals

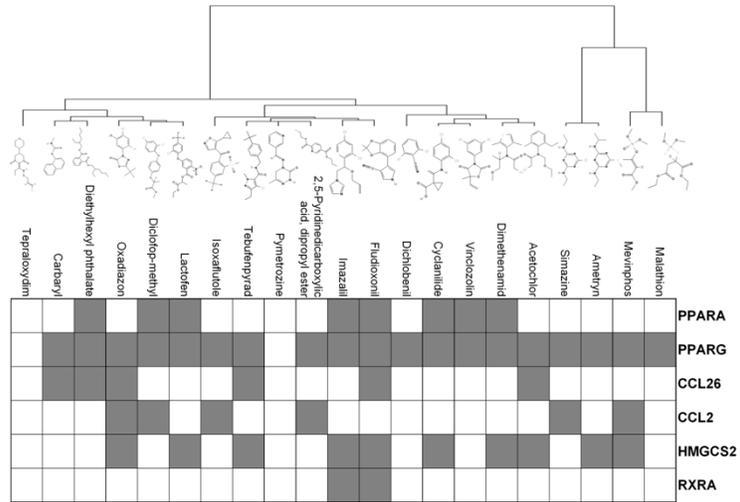


Bisphenol A

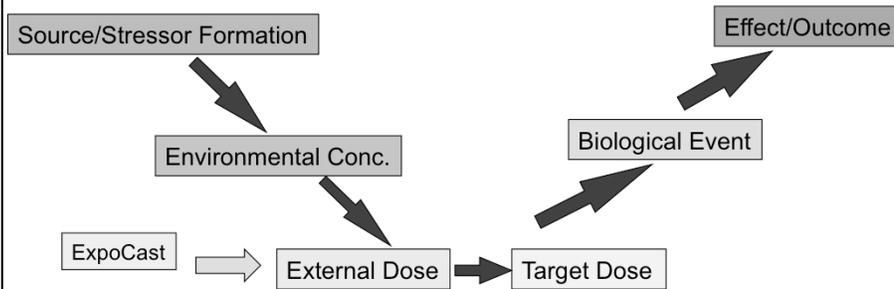




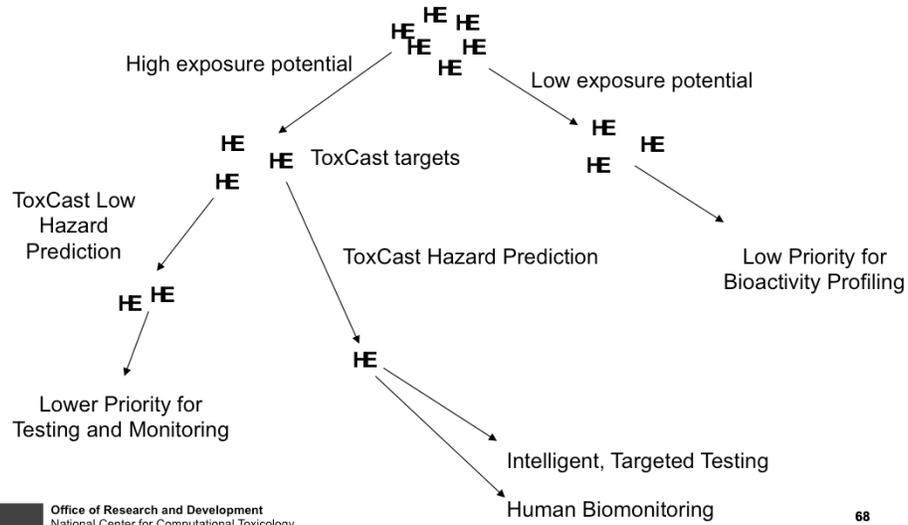
Rat Liver Tumor Correlations



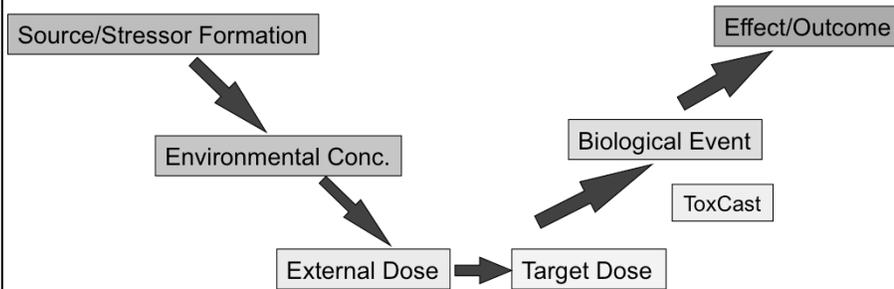
Applying Computational Toxicology Along the Source to Outcome Continuum



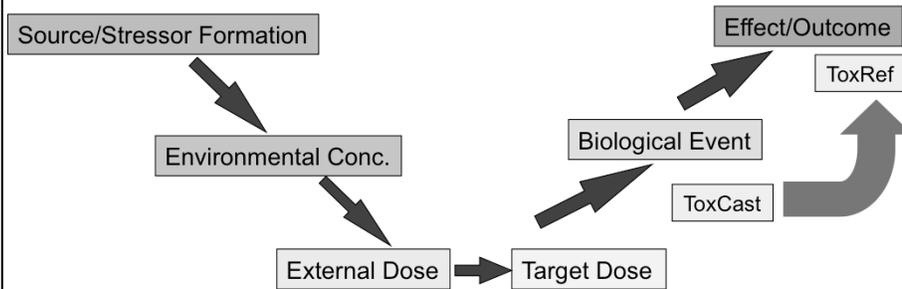
The Future State: Using Hazard and Exposure Information for Prioritizing Testing and Monitoring



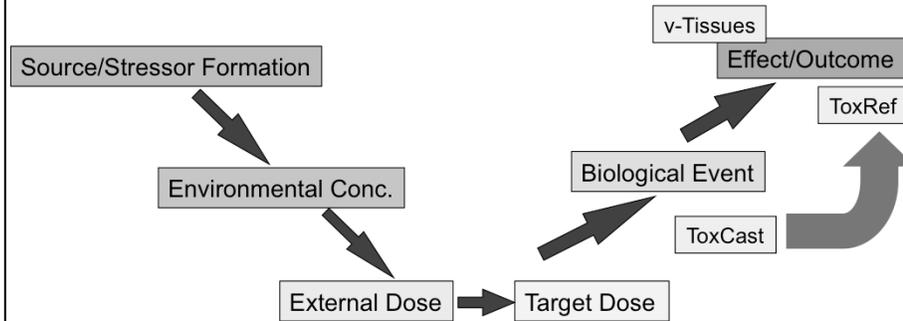
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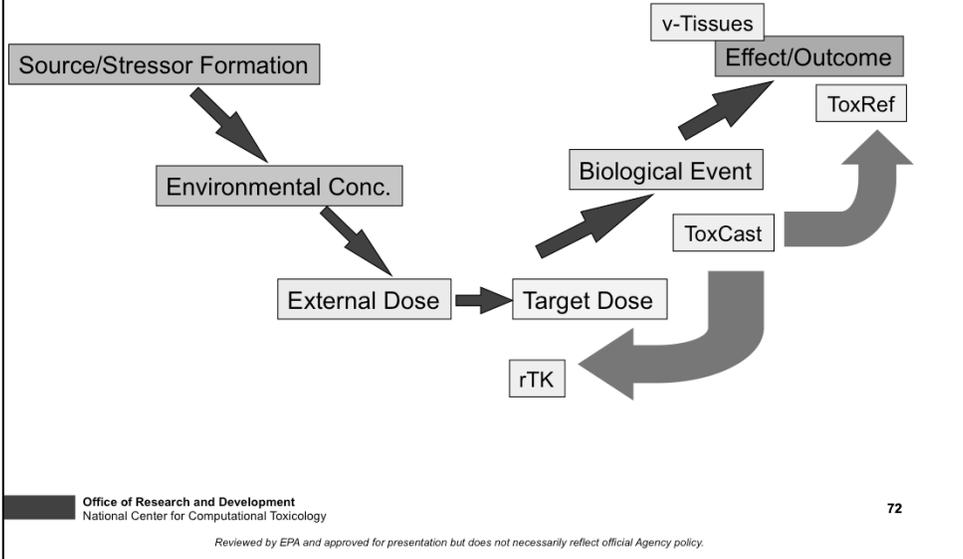
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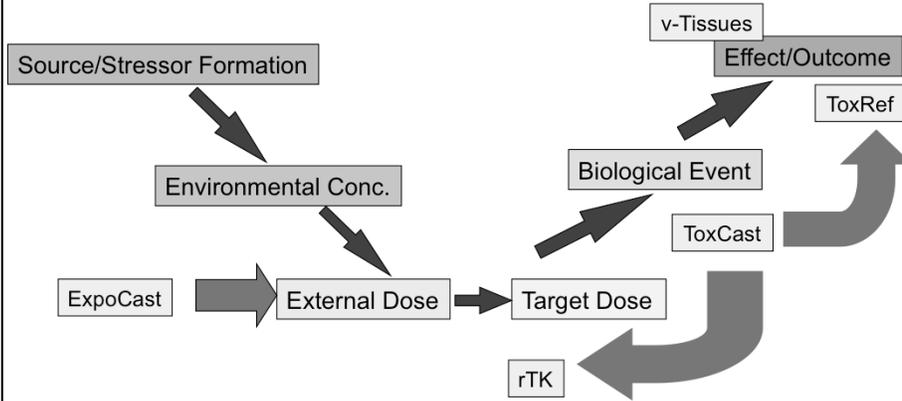
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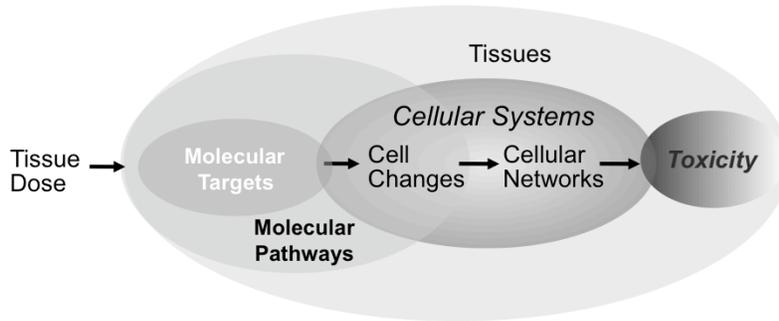
Applying Computational Toxicology Along the Source to Outcome Continuum



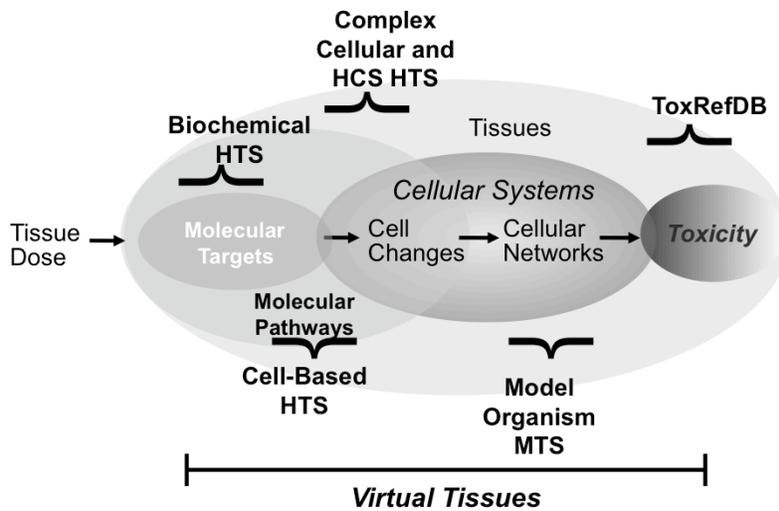
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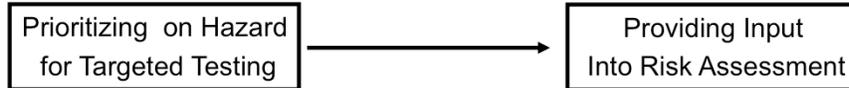
Predicting Human Toxicity: The Grand Challenge in Toxicology



Predicting Human Toxicity: The Grand Challenge in Toxicology



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.

For more information and archives of this and other [Risk e Learning](#) web seminars please refer to the Superfund Basic Research Program Risk e Learning web page:

http://tools.niehs.nih.gov/sbrp/risk_elearning/



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