

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY



ToxCast™ Data Analysis Summit

May 14-15, 2009

US EPA, Research Triangle Park, NC

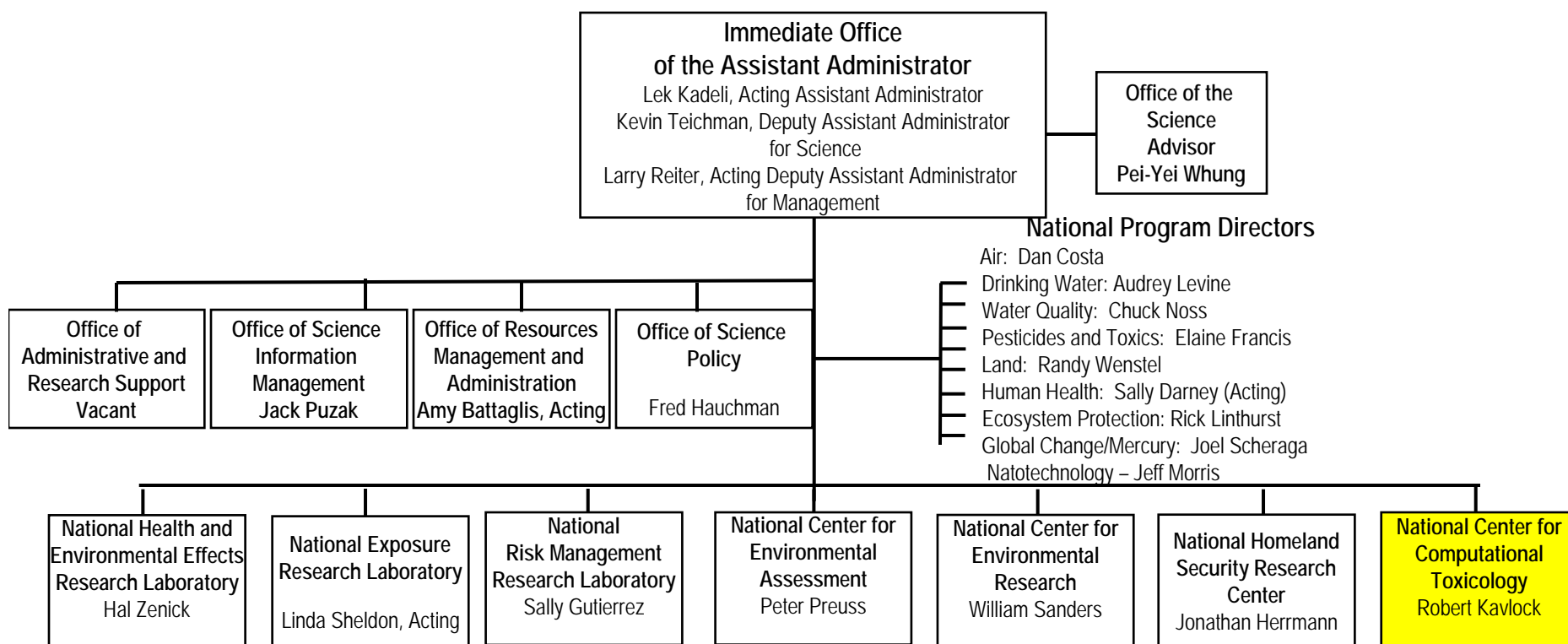
Robert Kavlock
Director, EPA's National Center for Computational Toxicology

EPA RTP

- 511 Acre Campus (shared with NIEHS)
- 2nd largest EPA facility (1.2m sq ft)
- Longest solar power lighted road
- 100% Green Power
- 1800 employees working in 500 labs
- Headquarters of two National Laboratories, a National Center and a Program Office

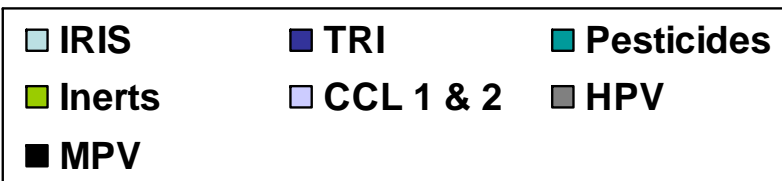
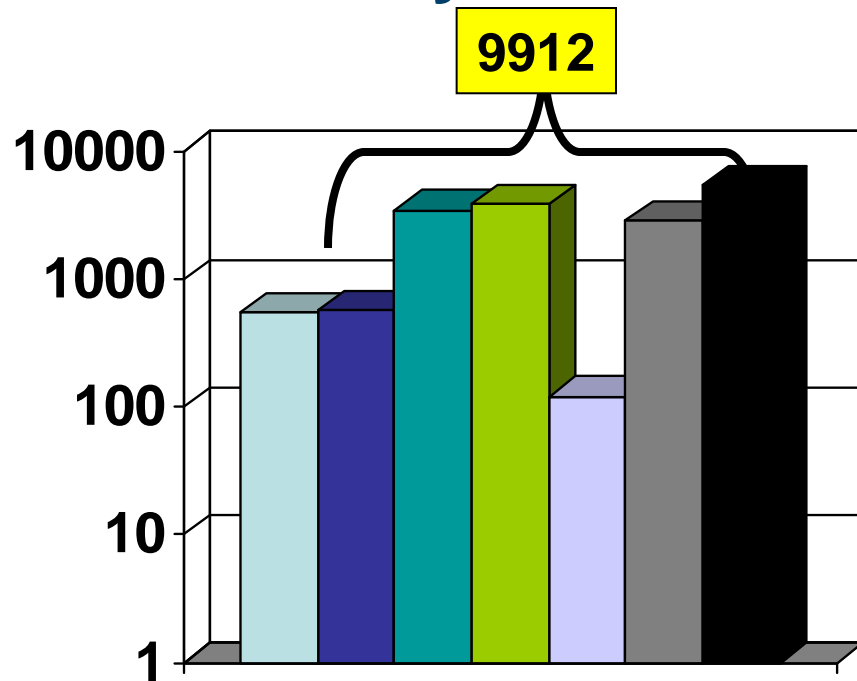


Office of Research and Development

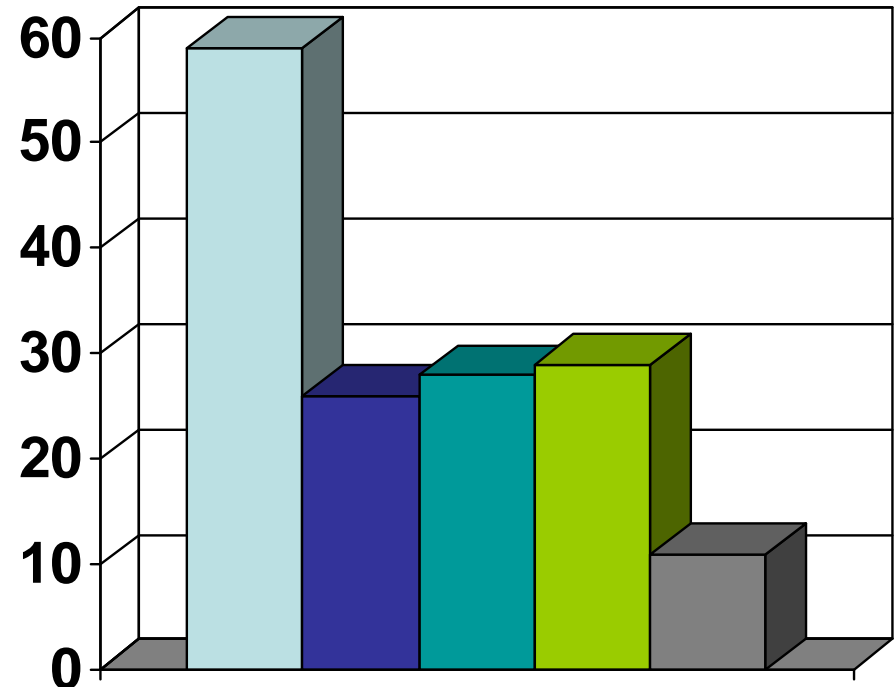


EPA's Need for Prioritization

Too Many Chemicals



Too Little Data (%)





“...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

Future of Toxicity Testing

POLICYFORUM

TOXICOLOGY

Transforming Environmental Health Protection

Francis S. Collins,^{1*} George M. Gray,^{2*} John R. Bucher^{3*}

We propose a shift from primarily in vivo animal studies to in vitro assays, in vivo assays with lower organisms, and computational modeling for toxicity assessments.

In 2005, 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 vision for toxicity testing and a strategic plan for implementing that vision. Both agencies wanted future toxicity testing and assessment paradigms to meet evolving regulatory needs. Challenges include the large numbers of substances that need to be tested and how to incorporate recent advances in molecular toxicology, computational sciences, and information technology, to rely increasingly on human as opposed to animal data; and to offer increased efficiency in design and costs (1–5). In response, the NRC Committee on Toxicity Testing and Assessment of Environmental Agents produced two reports that reviewed 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 (6, 7). Although the NRC reports have laid out a solid theoretical rationale, comprehensive and rigorously gathered data (and comparisons with historical animal data) will determine whether the hypothesized improvements will be realized in practice. For this purpose, NTP, EPA, and the National Institutes of Health Chemical Genomics Center (NCGC) (organizations with expertise in experimental toxicology, computational toxicology, and high-throughput technologies, respectively) have established a collaborative research program.

EPA, NCGC, and NTP Joint Activities
In 2004, the NTP released its vision and roadmap for the 21st century (1), which established initiatives to integrate high-

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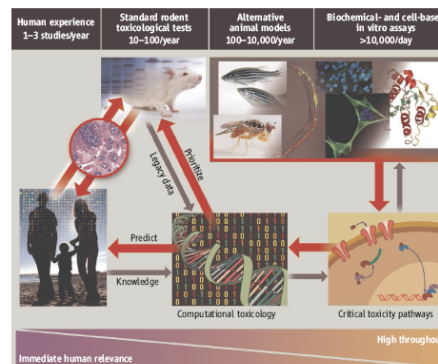
*The views expressed here are those of the individual authors and do not necessarily reflect the views and policies of their respective agencies.

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throughput screening (HTS) and other automated screening assays into its testing program. In 2005, the EPA established the National Center for Computational Toxicology (NCCT). Through these initiatives, NTP and EPA, with the NCGC, are promoting the evolution of toxicology from a predominantly observational science at the level of disease-specific models in vivo to a predominantly predictive science focused on broad inclusion of target-specific, mechanism-based, biological observations in vitro (1, 4) (see figure, below).

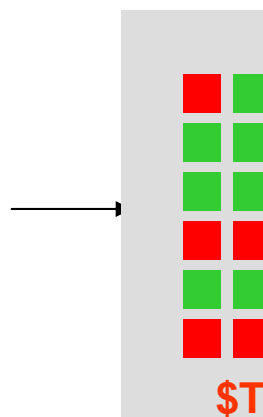
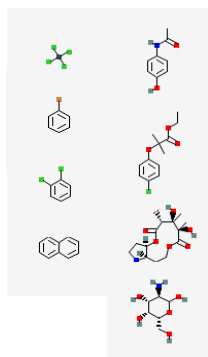
Toxicity pathways. In vitro and in vivo tools are being used to identify cellular responses after chemical exposure expected to result in adverse health effects (7). HTS methods are a primary means of discovery for drug development, and screening of >100,000 compounds per day is routine (8). However, drug-discovery HTS methods traditionally test compounds at one concentration,

usually between 2 and 10 μM, and tolerate high false-negative rates. In contrast, in the EPA, NCGC, and NTP combined effort, all compounds are tested at as many as 15 concentrations, generally ranging from ~5 nM to ~100 μM, to generate a concentration-response curve (9). This approach is highly reproducible, produces significantly lower false-positive and false-negative rates than the traditional HTS methods (9), and facilitates multiasay comparisons. Finally, an informatics platform has been built to compare results among HTS screens; this is being expanded to allow comparisons with historical toxicologic NTP and EPA data (<http://ncgc.nih.gov/pub/openhts>). HTS data collected by EPA and NTP, as well as by the NCGC and other Molecular Libraries Initiative centers (<http://mli.nih.gov/>), are being made publicly available through Web-based databases [e.g., PubChem (<http://pubchem.ncbi.nlm.nih.gov/>)]. In addition,



Transforming toxicology. The studies we propose will test whether high-throughput and computational toxicology approaches can yield data predictive of results from animal toxicity studies, will allow prioritization of chemicals for further testing, and can assist in prediction of risk to humans.

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

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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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Robots could reduce animal tests

U.S. scientists are taking the first step towards testing potentially hazardous chemicals on cells grown in a laboratory, without using live animals.

Two government agencies are looking into the merits of using high-speed automated robots to carry out tests.

The long-term goal is to reduce the cost, time and number of animals used in screening everything from pesticides to household chemicals.

The move follows calls for scientists to rely less on animal studies.

Robots would be able to carry out hundreds of thousands of chemical tests a day to identify chemicals with toxic effects.

Details were published in the journal Science and discussed at the annual meeting of the American Association for the Advancement of Science (AAAS) in Boston.

Faster and cheaper

Speaking in a live link-up, Dr. Francis Collins, Director of the National Human Genome Research Institute at the National Institute of Health (NIH), said

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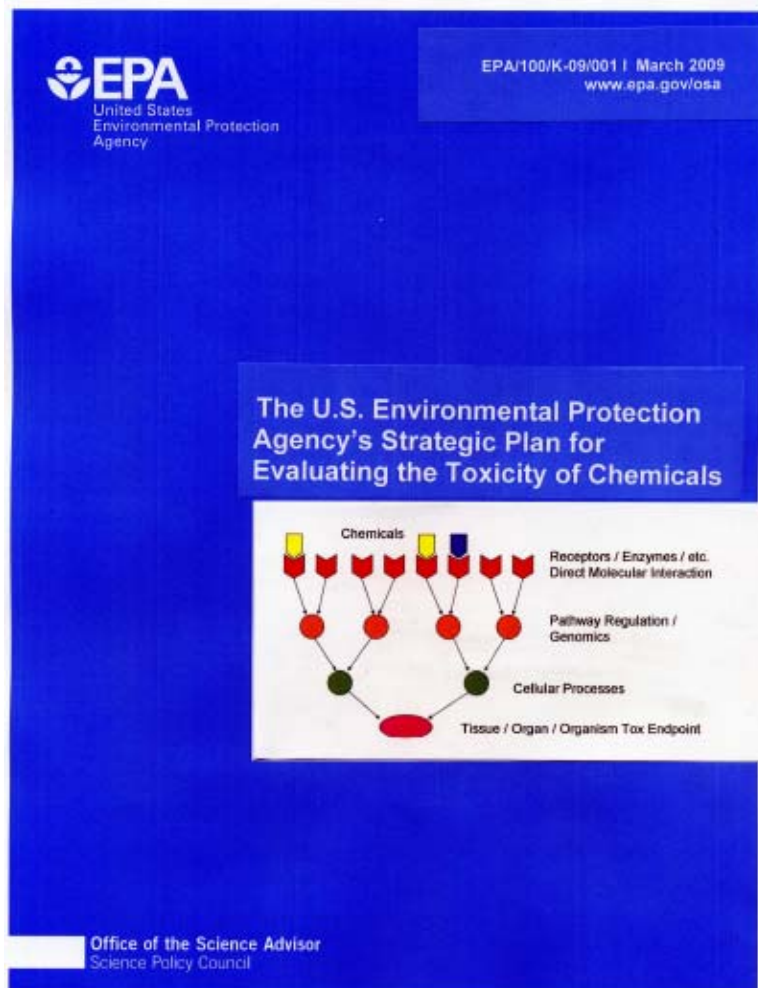
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EPA Reacts to Challenge of the NRC on the Future of Toxicity Testing



Strategic Goals

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

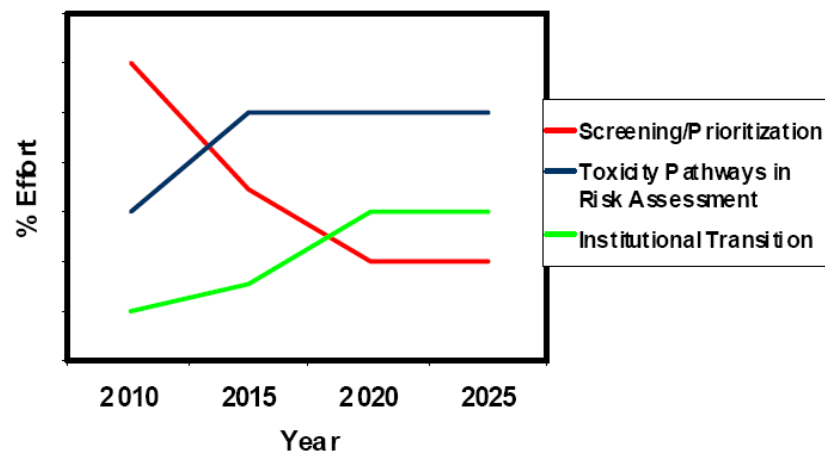
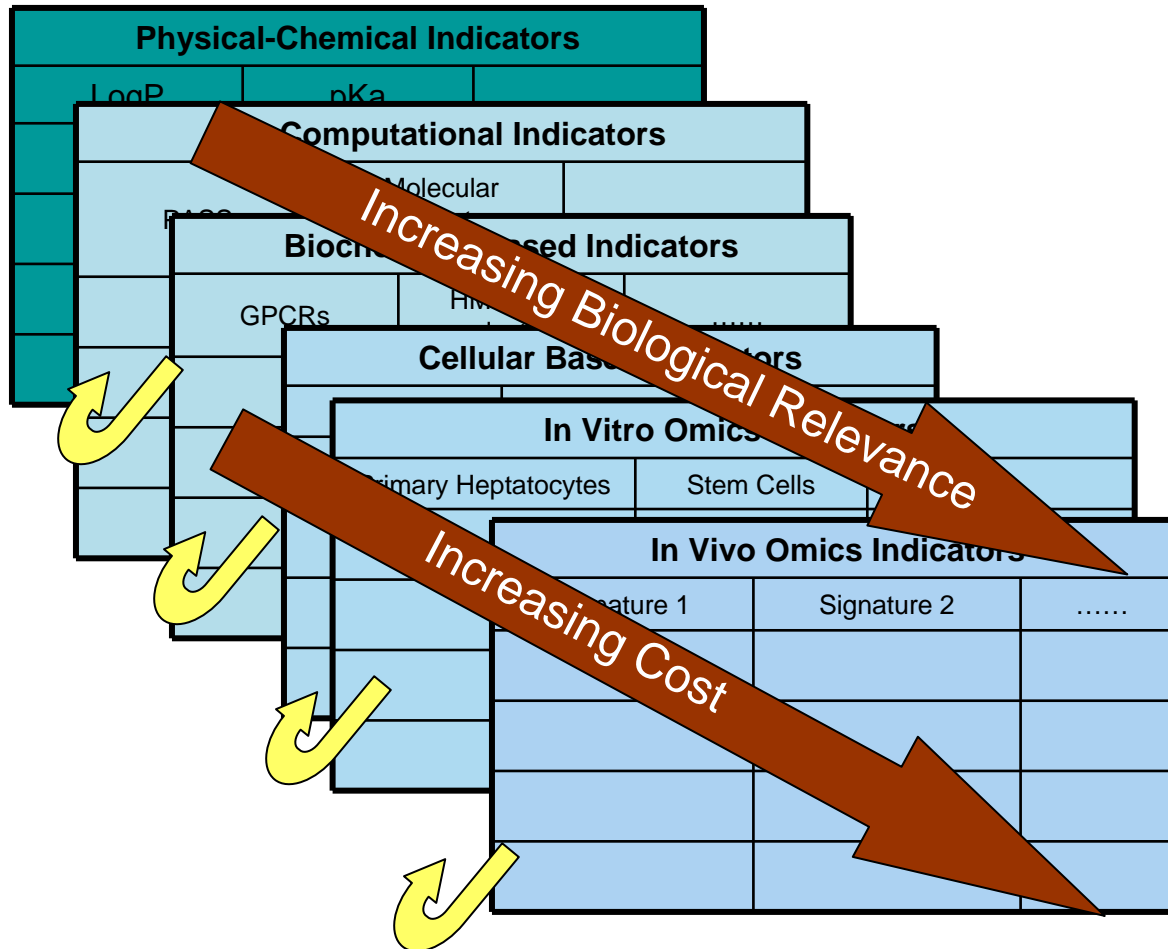


Figure 6. Relative (%) Emphasis of the Three Main Components of this Strategic Plan over its Expected 20-year Duration.

ToxCast Information Domains

Chemical Grouping
Bin 1
Bin 2
Bin 3
....
....
Bin



Prioritization Product Timeline

FY07

FY08

FY09

FY10

FY11

FY12

Proof of Concept: ToxCast

Verification/Extension

Reduce to Practice

Tox21



ToxCast Kick Off, April 2007

The ToxCast Team



Implications for Success



•Hazard Identification

- Prioritizing Chemicals
- Closing Data Gaps
- Efficient Animal Usage
- Better Resource Utilization

•Ancillary Applications

- Mixtures
- Chirals
- Nanomaterials
- Lot variations

•Risk Assessment

- Focusing on highest priority chemicals
- Providing Mode(s) of Action
- Targeted/Intelligent Testing
- Identifying Susceptible Populations

TDAS 1 Data Analysis Partners



Agenda Overview

- **Thursday**

- Welcoming and data overviews by EPA
- Selected platform presentations
- Photo opportunity
- Later afternoon poster session

- **Friday**

- Continuation of platform presentations
- Future directions (EPA staff)
- Open mic (one slide)
- Summary of presentation results (EPA)
- Concluding discussion on Phase I

Workshop Goals

- Present initial Phase I results
- Engage external scientific community in analysis of data
 - Exploration of approaches for model development
 - Strategies for prioritization
- Managing expectations
- Identification of data needs and future directions