

2009 International Workshop on Virtual Tissues:

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

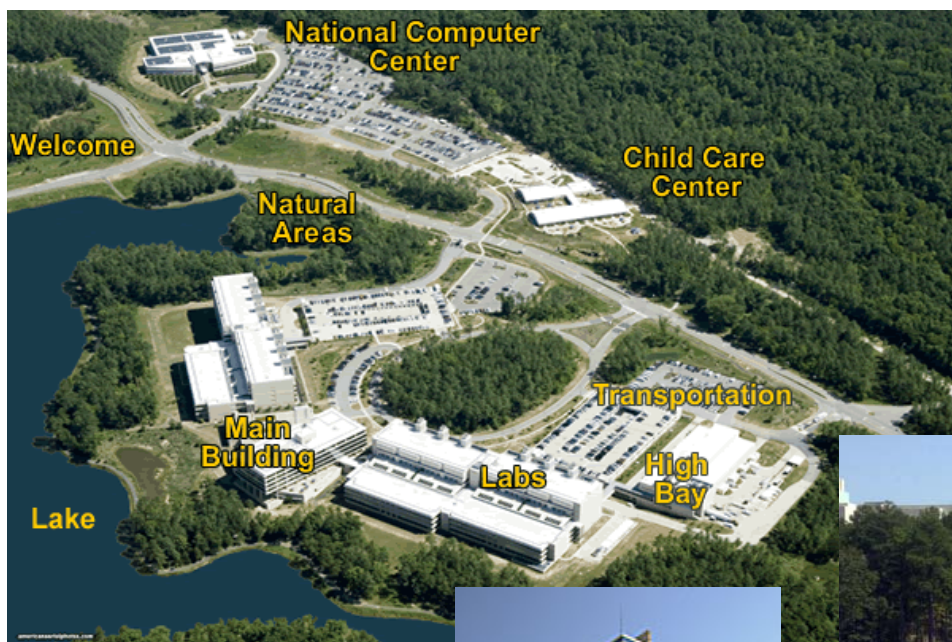
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY



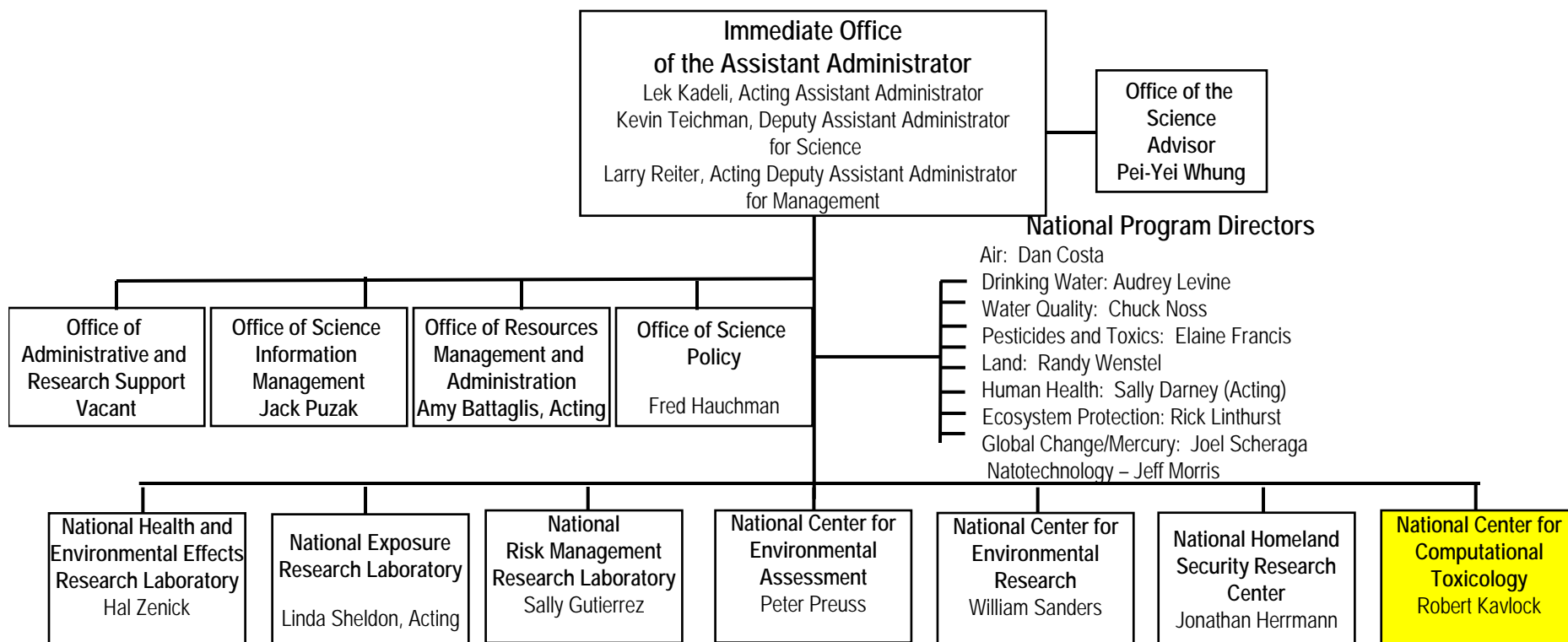
**COMPUTATIONAL
TOXICOLOGY**

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
- Top three ranking for postdocs



Office of Research and Development



Pesticide products contain both "active" and "inert" ingredients. The terms "active ingredient" and "inert ingredient" have been defined by Federal law, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), since 1947.

- An active ingredient is one that prevents, destroys, repels or mitigates a pest, or is a plant regulator, defoliant, desiccant or nitrogen stabilizer. By law, the active ingredient must be identified by name on the label together with its percentage by weight.
- An inert ingredient is simply any ingredient in the product that is not intended to affect a target pest. For example, isopropyl alcohol may be an active ingredient and antimicrobial pesticide in some products; however, in other products, it functions as a solvent and may be considered an inert ingredient. The law does not require inert ingredients to be identified by name and percentage on the label, but the total percentage of such ingredients must be declared.

Name Change: From Inert to Other Ingredients
In September 1997, the Environmental Protection Agency (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.

[Publications](#) | [Glossary](#) | [A-Z Index](#) | [Uoibs](#)

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Last updated on Wednesday, August 18th, 2004
URL: <http://www.epa.gov/oppr001/inerts/>

- How to Participate
- Who's Participating
- Information on HPV Chemicals
- HPV Robust Summaries, Test Plans & Comments
- Vol. Children's Chemical Eval. Pgm.
- Persistent, Bioaccumulative, and Toxic (PBT) Chemicals Rules
- Related Websites

- EDSP Overview
- Assay Development and Validation
- Priority Setting Activities
- Regulatory Aspect Program Documents
- Stakeholder Input
- Related Links

- Safewater Home
- CCL Home
- Frequent Questions
- CCL 2 List
- Related Activities & Dates

- 1. Registering Pesticides
- 2. Pesticide-Producing Establishments
- 3. Reregistration Laws
- 4. International Issues
- 5. Adverse Effects Reporting
- 6. Storage & Disposal
- 7. Restricted & Canceled Uses
- 8. Pesticide Tolerances
- 9. Registration Information Sources

Done



Done



Done

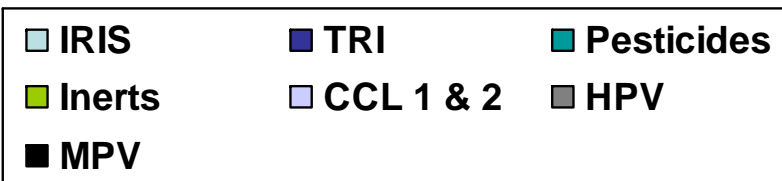
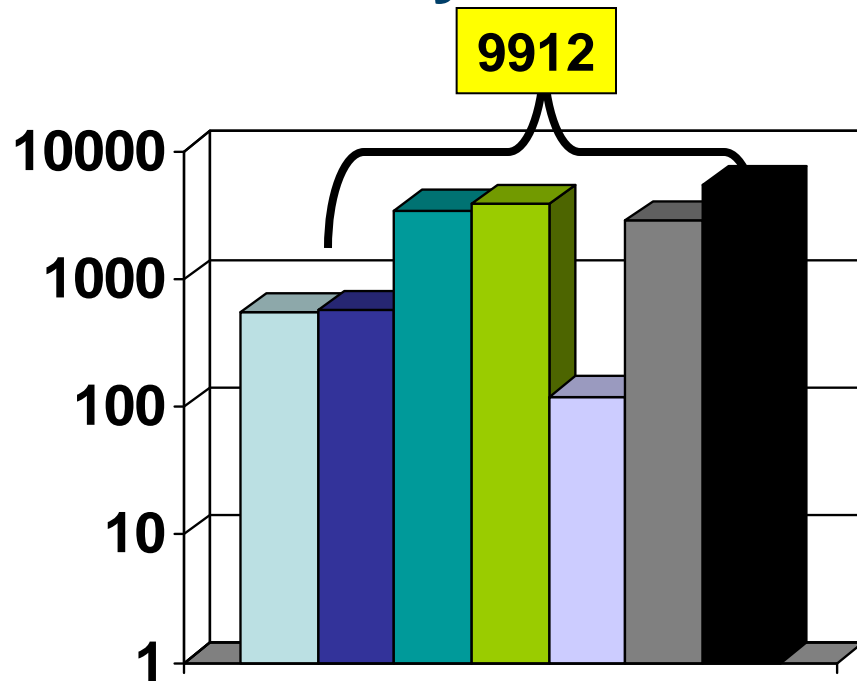


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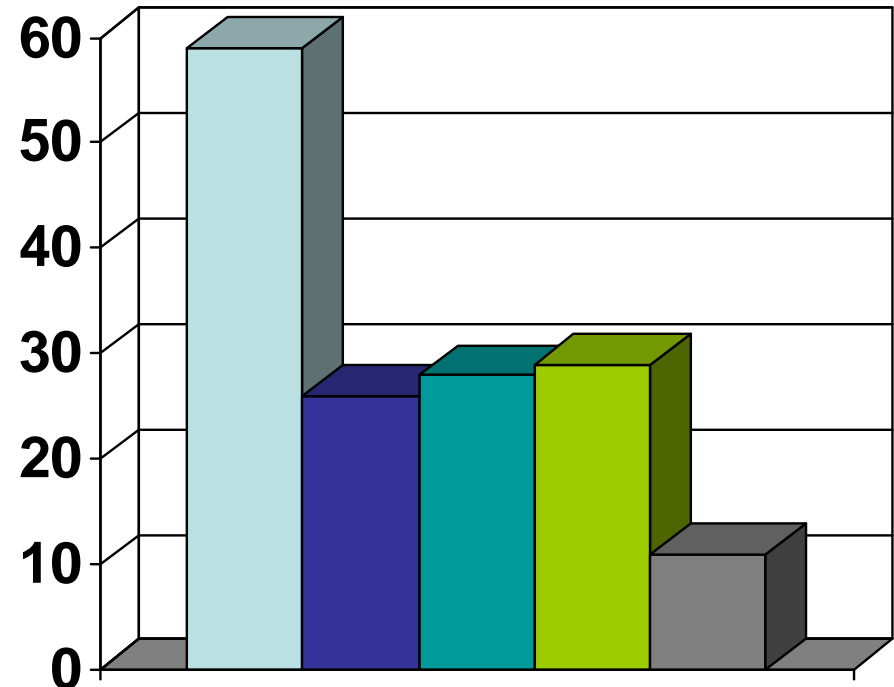


EPA's Need for Prioritization

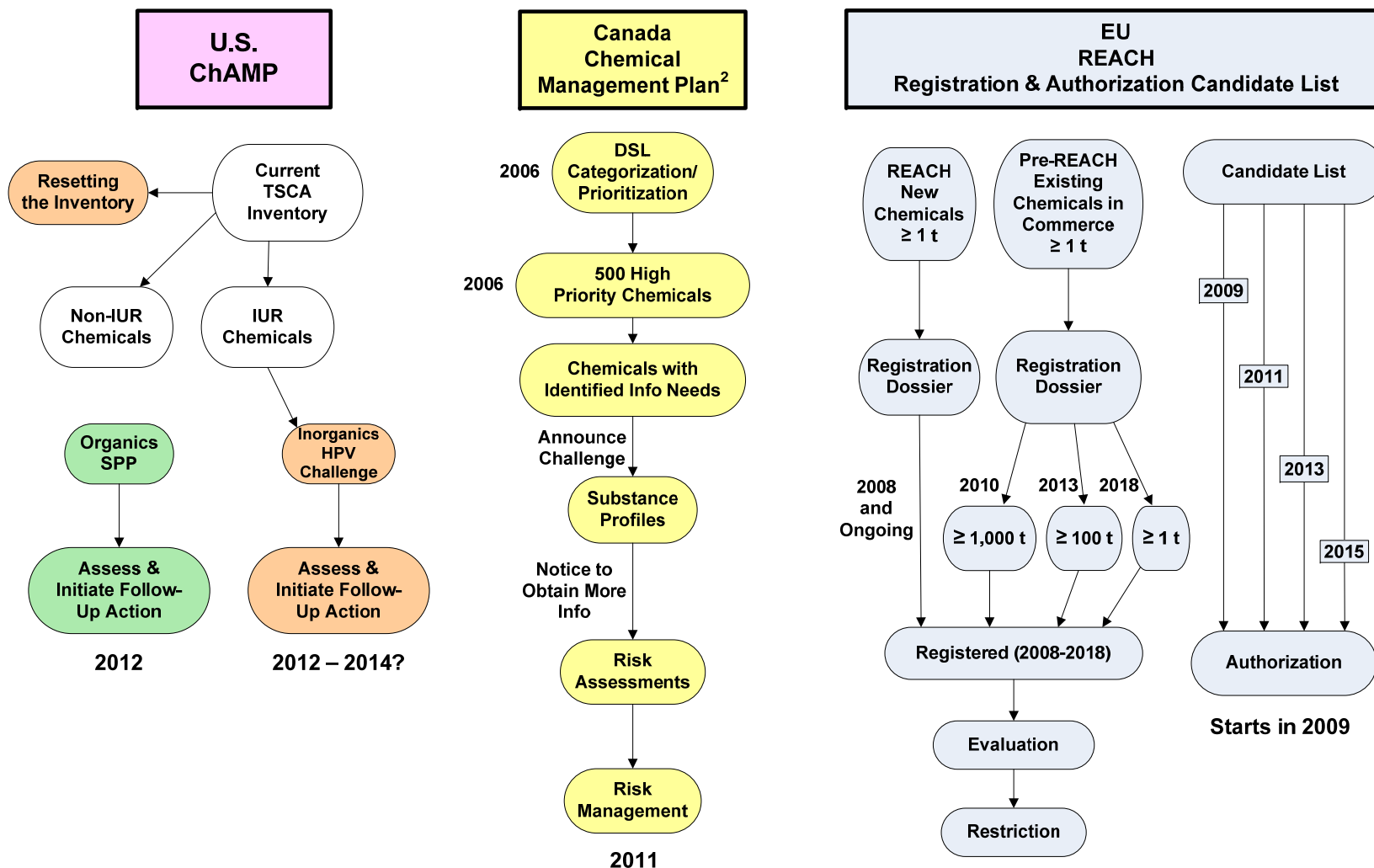
Too Many Chemicals



Too Little Data (%)



An International Problem



¹DSL = Canadian Environmental Protection Act Domestic Substances List

²Other aspects of the CMP are not shown on this figure.



“...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.

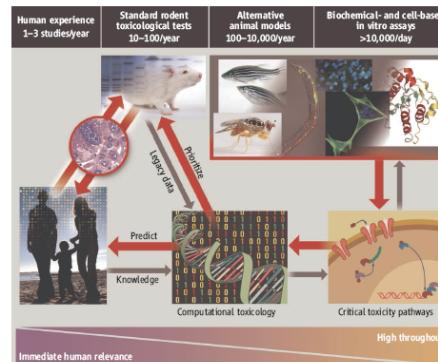
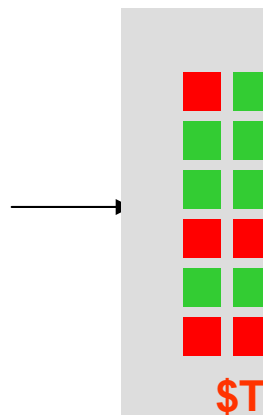
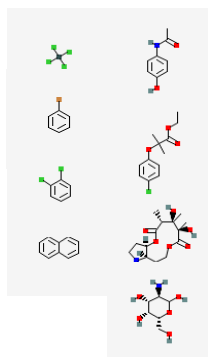
EPA, NCGC, and NTP Joint Activities

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

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,

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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.

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



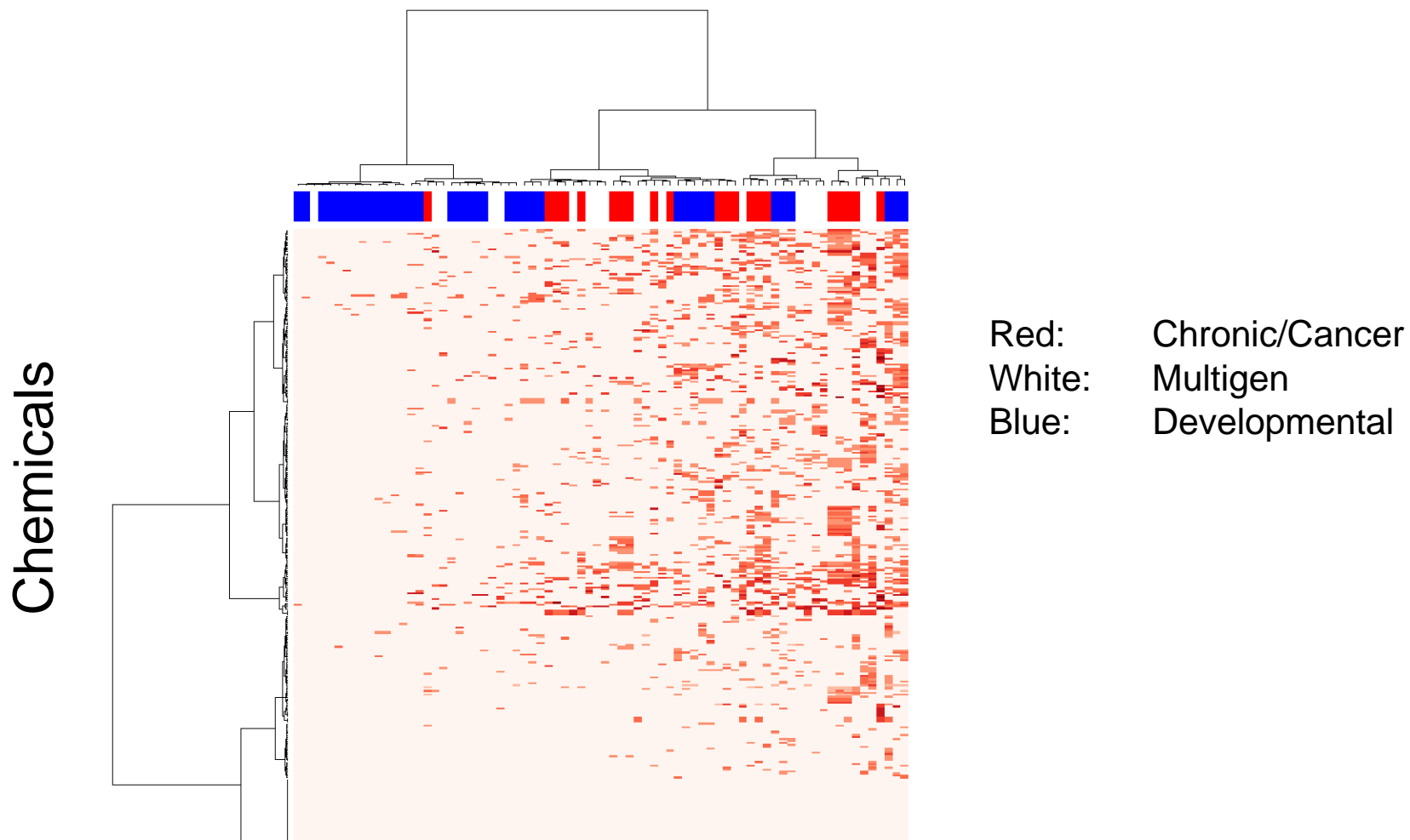
Downloaded from www.sciencemag.org on February 15, 2008

EPAs Contribution: The ToxCast Research Program









Office of Research and Development
National Center for Computational Toxicology

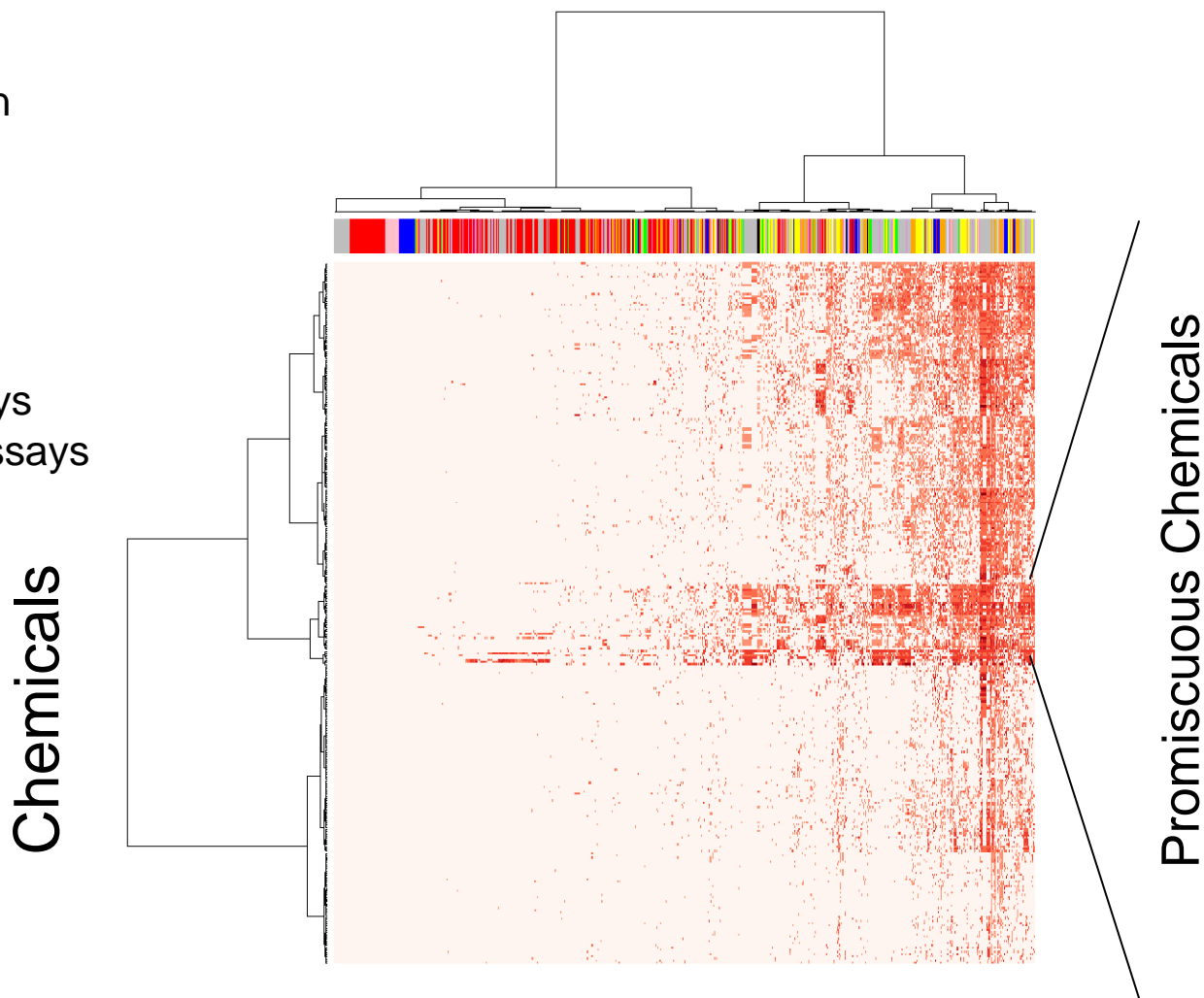
www.epa.gov/ncct/toxcast

ToxCast In Vivo Data from ToxRefDB

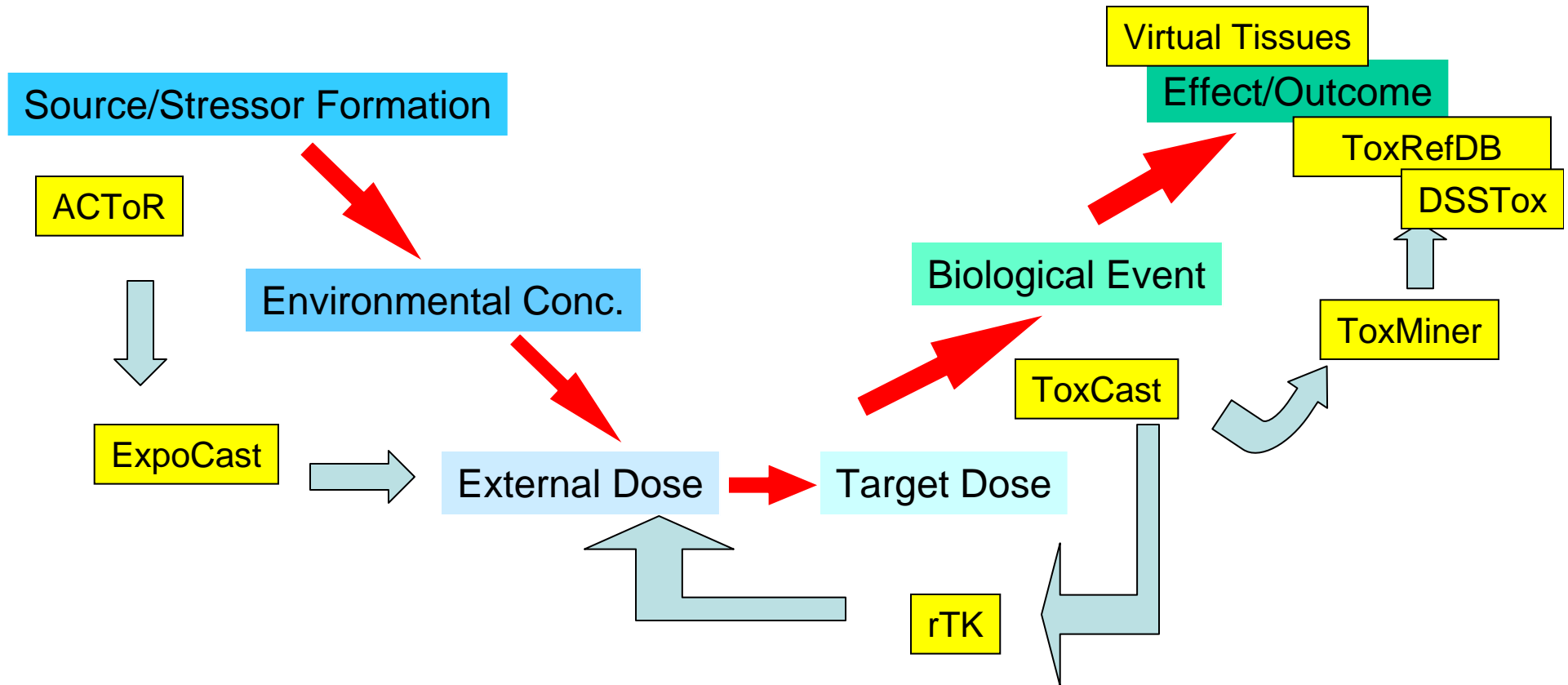


ToxCast In vitro data

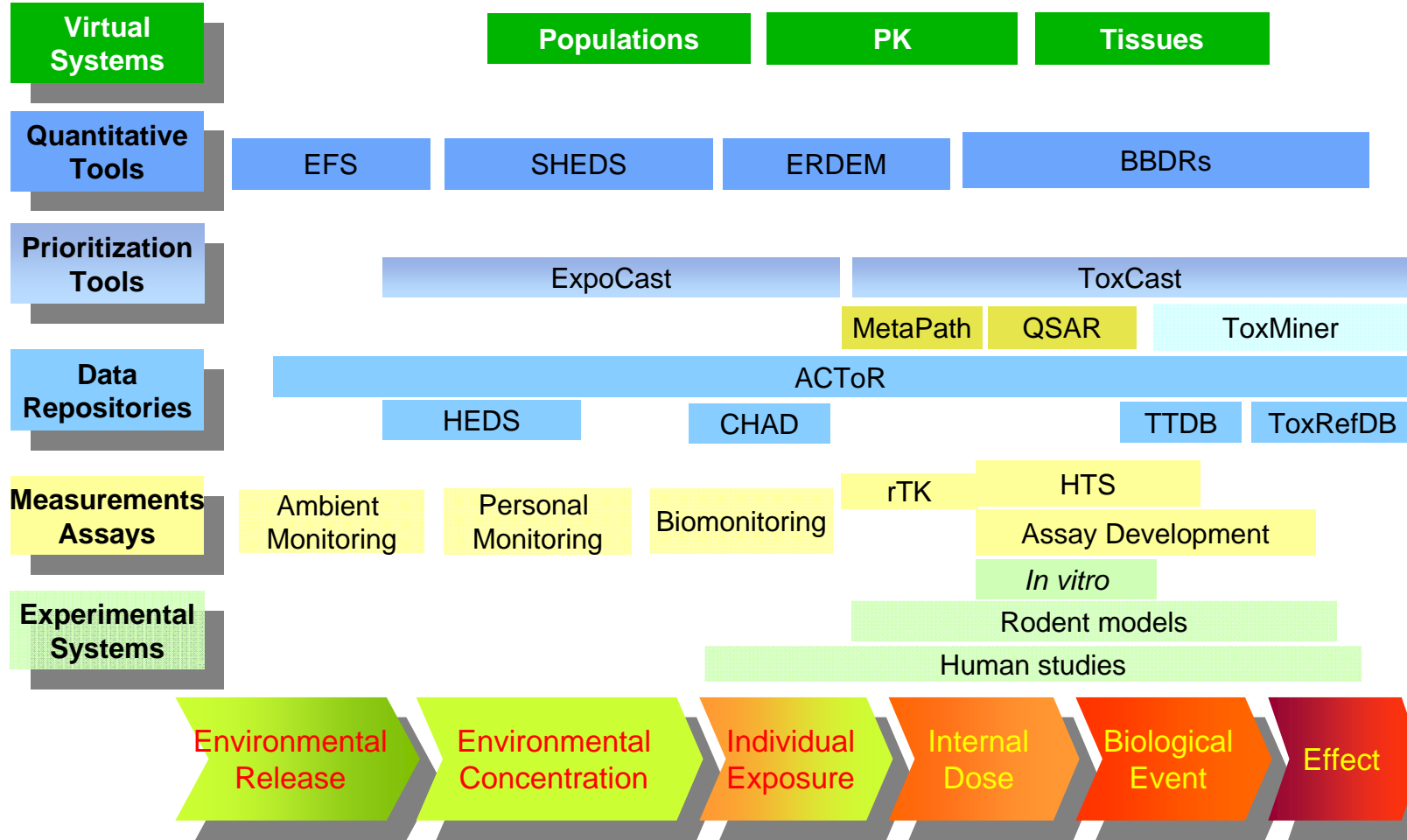
-  Novascreen
-  Attagene
-  BioSeek
-  Cellumen
-  CellzDirect
-  NCGC
-  Gene assays
-  Pathway assays



Applying Computational Toxicology Along the Source to Outcome Continuum



Contaminants Research in ORD



Improved Risk Assessment & Risk Management

v-Tissues: EPA Vision

- Gain deeper understanding of molecular and cellular pathways to efficiently analyze thousands of environmental contaminants
- Predict dose-dependent human adverse outcomes (development/cancer/immune etc)
 - Use *in vitro* data
 - Accurately model low-dose response
 - Evaluate role of genomic variation in response
- Reduce dependence on animal testing

v-Tissues 2009: Vision

- How do we link molecular activity to phenotypes?
- What is the state-of-the-art in modeling disease phenotypes *in silico*?
- What role do tissues play in understanding/simulating clinical outcomes?
- How far can we get with “Virtual Tissues” using *in vitro* data (reducing dependence on animals)?
- How do we leverage transatlantic collaboration to get there?

v-Tissues 2009: Scope

- Which translational research gaps can be bridged by Virtual Tissues?
- What are the short-term products and long-term applications?
- What key computational and experimental hurdles must be overcome?
- How can EU and US international collaborations help achieve these goals?

