EPA
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Environmental Protection
Agency

2009 International Workshop on Virtual Tissues:

Robert Kavlock
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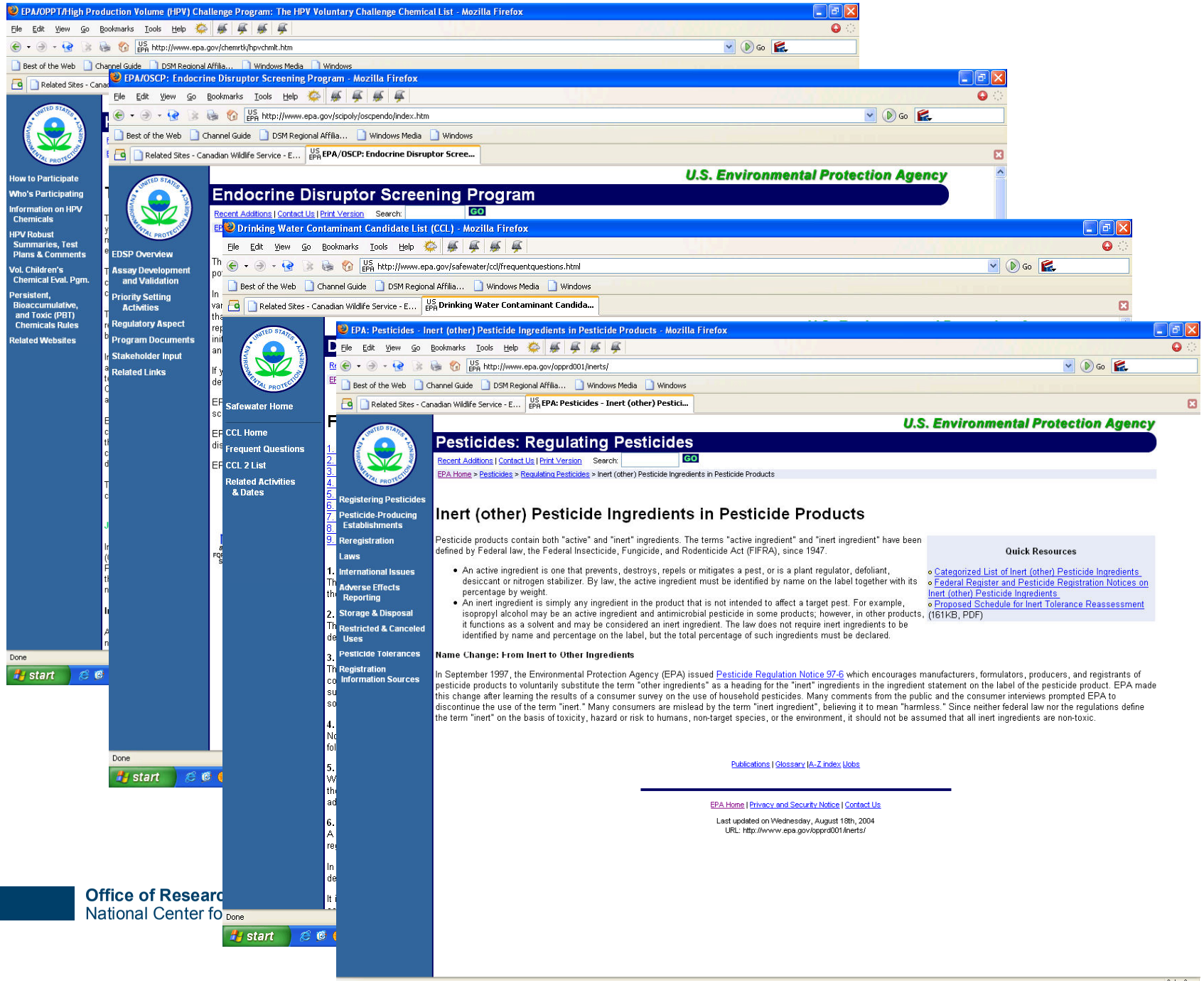
Office of Research and Development
National Center for Computational Toxicology

April 21 2009

United States Environmental Protection Agency

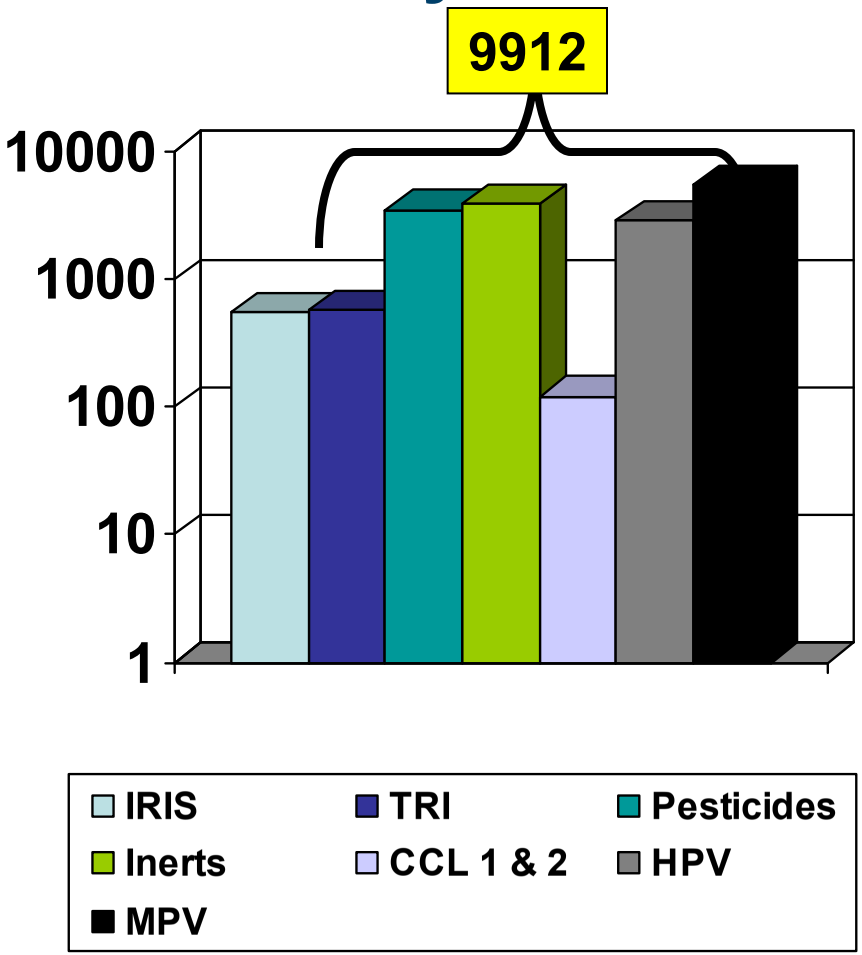
EPA RTP

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

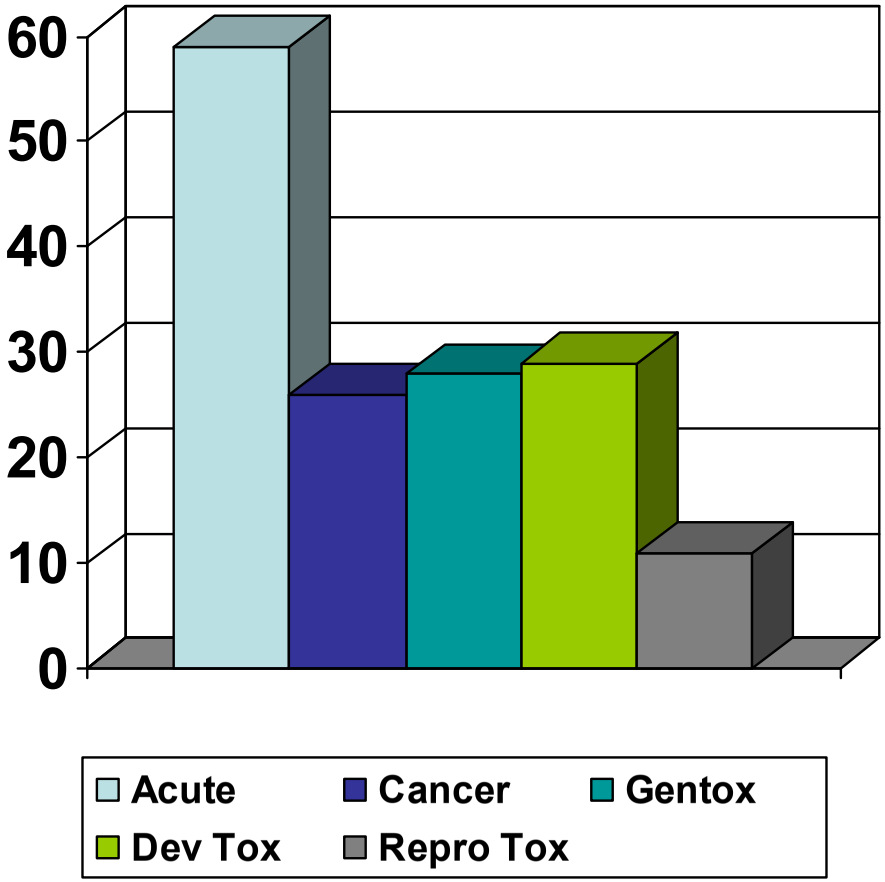

EPA/OPPT/High Production Volume (HPV) Challenge Program: The HPV Voluntary Challenge Chemical List - Mozilla Firefox
How to Participate
Who's Participating
Information on HPV Chemicals
HPV Robust Summaries, Test Plans & Comments
Vol. Children's Chemical Eval. Pgm.
Persistent, Bioaccumulative, and Toxic (PBT) Chemicals Rules
Related Websites
EPA/OSCP: Endocrine Disruptor Screening Program - Mozilla Firefox
U.S. Environmental Protection Agency
Endocrine Disruptor Screening Program
EDSP Overview
Assay Development and Validation
Priority Setting Activities
Regulatory Aspect
Program Documents
Stakeholder Input
Related Links
Drinking Water Contaminant Candidate List (CCL) - Mozilla Firefox
Safewater Home
CCL Home
Frequent Questions
CCL 2 List
Related Activities & Dates
EPA: Pesticides - Inert (other) Pesticide Ingredients in Pesticide Products - Mozilla Firefox
U.S. Environmental Protection Agency
Pesticides: Regulating Pesticides
Registering Pesticides
Pesticide-Producing Establishments
Reregistration
Laws
1. International Issues
Adverse Effects Reporting
Storage & Disposal
Restricted & Canceled Uses
Pesticide Tolerances
Registration Information Sources
Inert (other) Pesticide Ingredients in Pesticide Products
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.
Quick Resources
Categorized List of Inert (other) Pesticide Ingredients
Federal Register and Pesticide Registration Notices on Inert (other) Pesticide Ingredients
Proposed Schedule for Inert Tolerance Reassessment (161KB, PDF)
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 mislead 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 | Jobs
EPA Home | Privacy and Security Notice | Contact Us
Last updated on Wednesday, August 18th, 2004
URL: http://www.epa.gov/opprd001/inerts/

EPA's Need for Prioritization

Too Many Chemicals



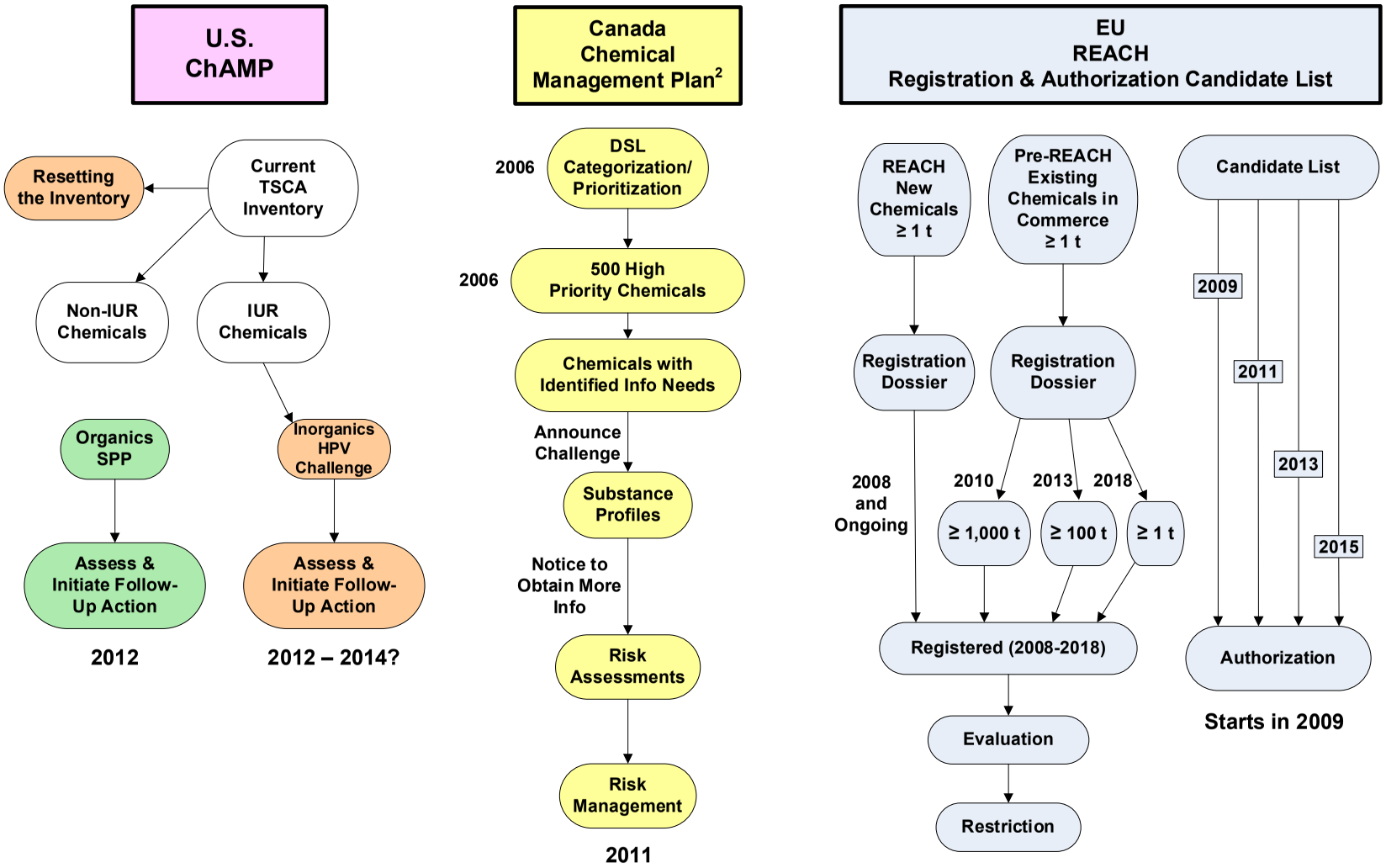
Too Little Data (%)



Judson, et al *EHP* (2009)

An International Problem

United States Environmental Protection Agency



[1] DSL = Canadian Environmental Protection Act Domestic Substances List

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

1,000 t = 2.2 M lbs.; 100 t = 220k lbs.; 1 t = 2.2k lbs.

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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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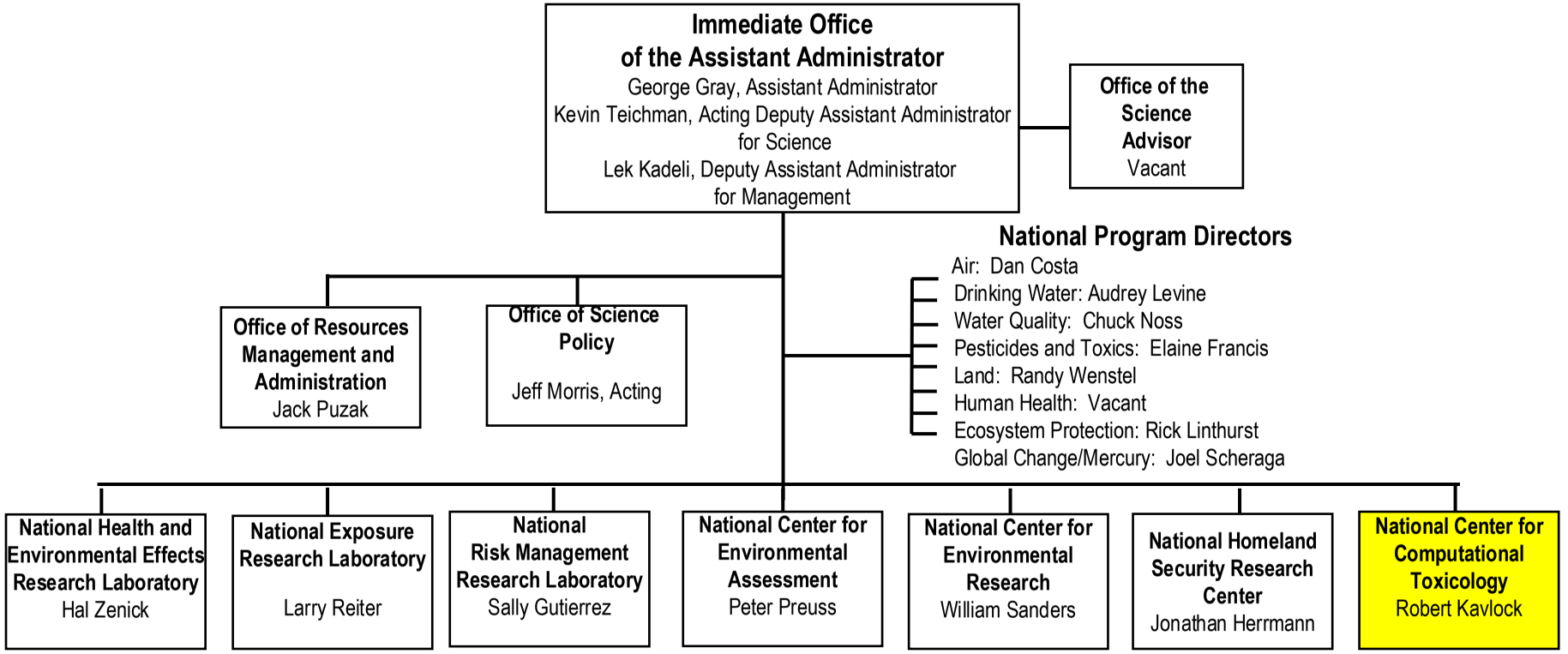
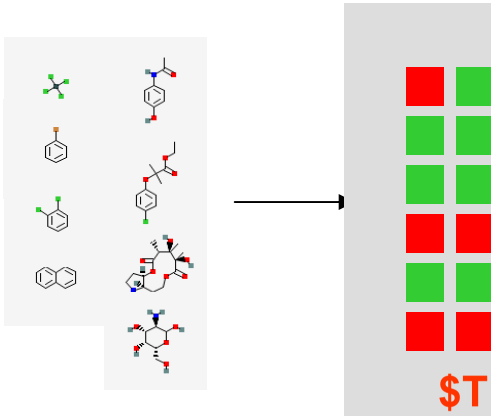
Office of Research and Development



Future of Toxicity Testing



POLICYFORUM

TOXICOLOGY

Transforming Environmental Health Protection

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.

Francis S. Collins,[1*†] George M. Gray,[2*] John R. Bucher[3*]

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 multiassay 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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*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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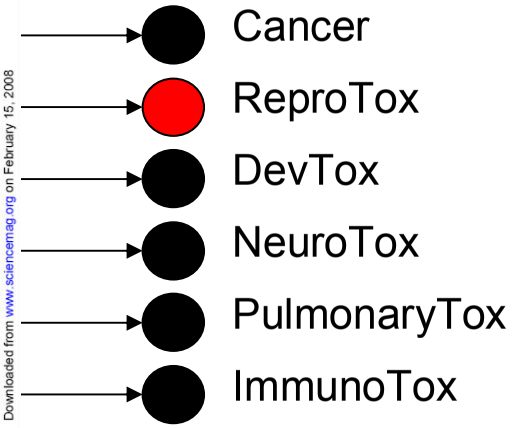
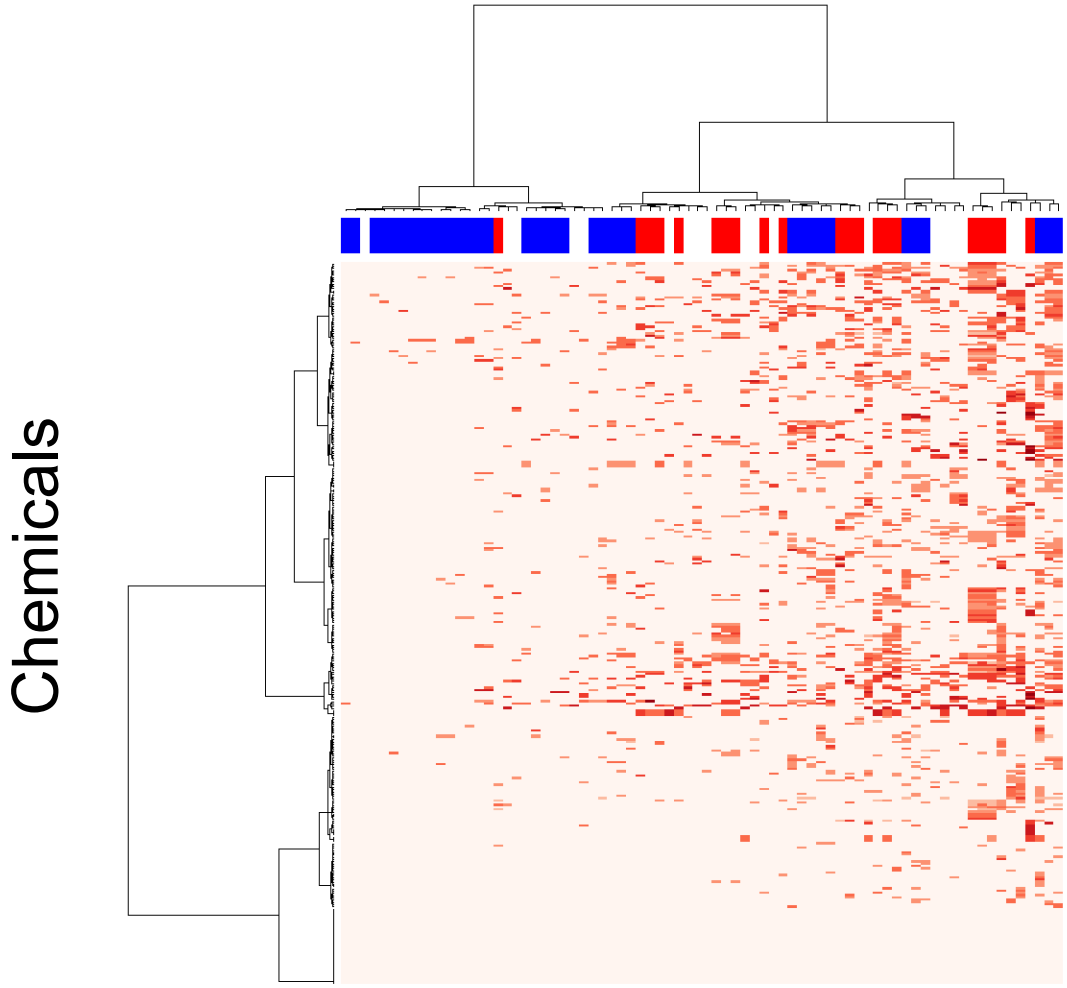


Tox21

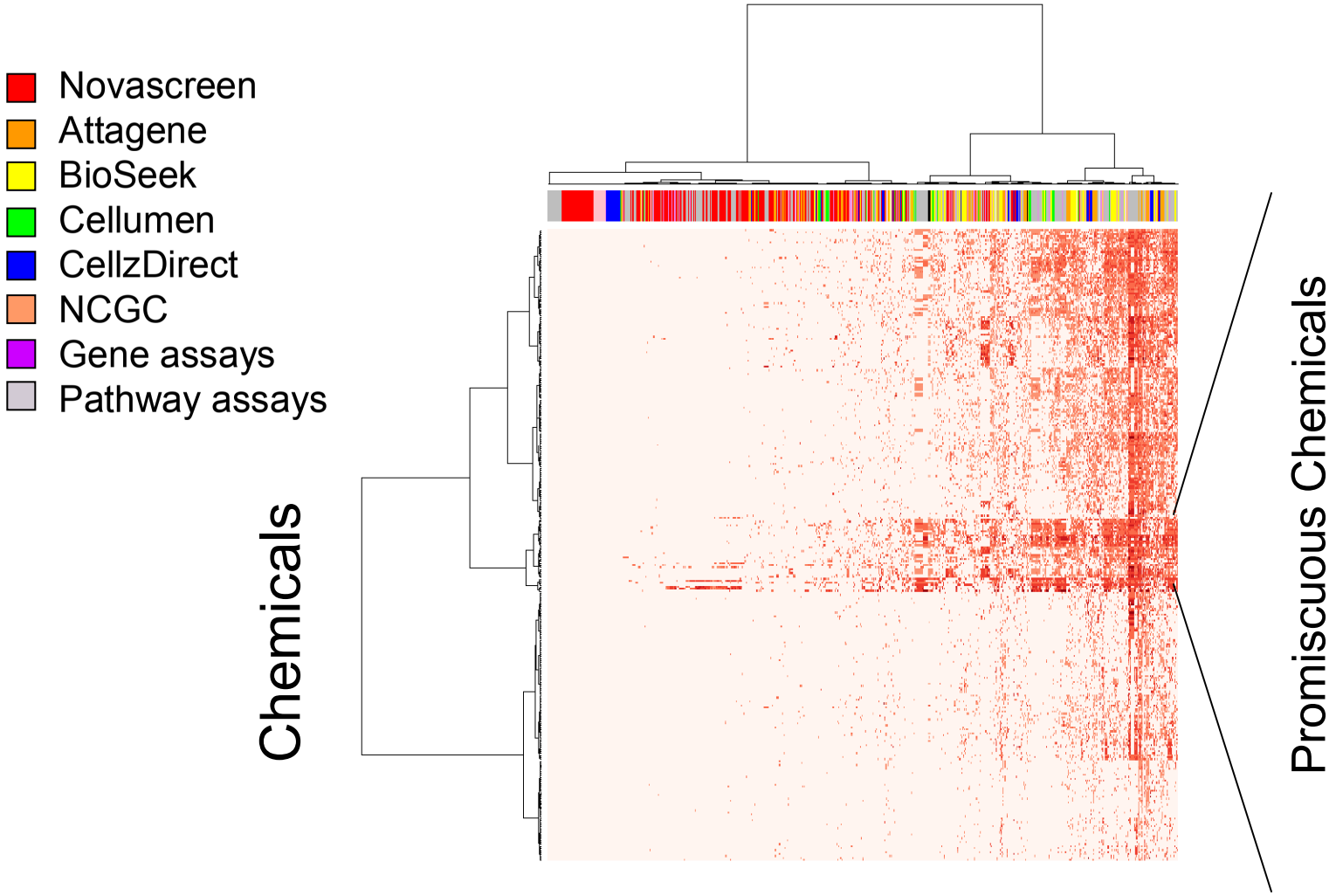
EPAs Contribution: The ToxCast Research Program

ToxCast In Vivo Data from ToxRefDB

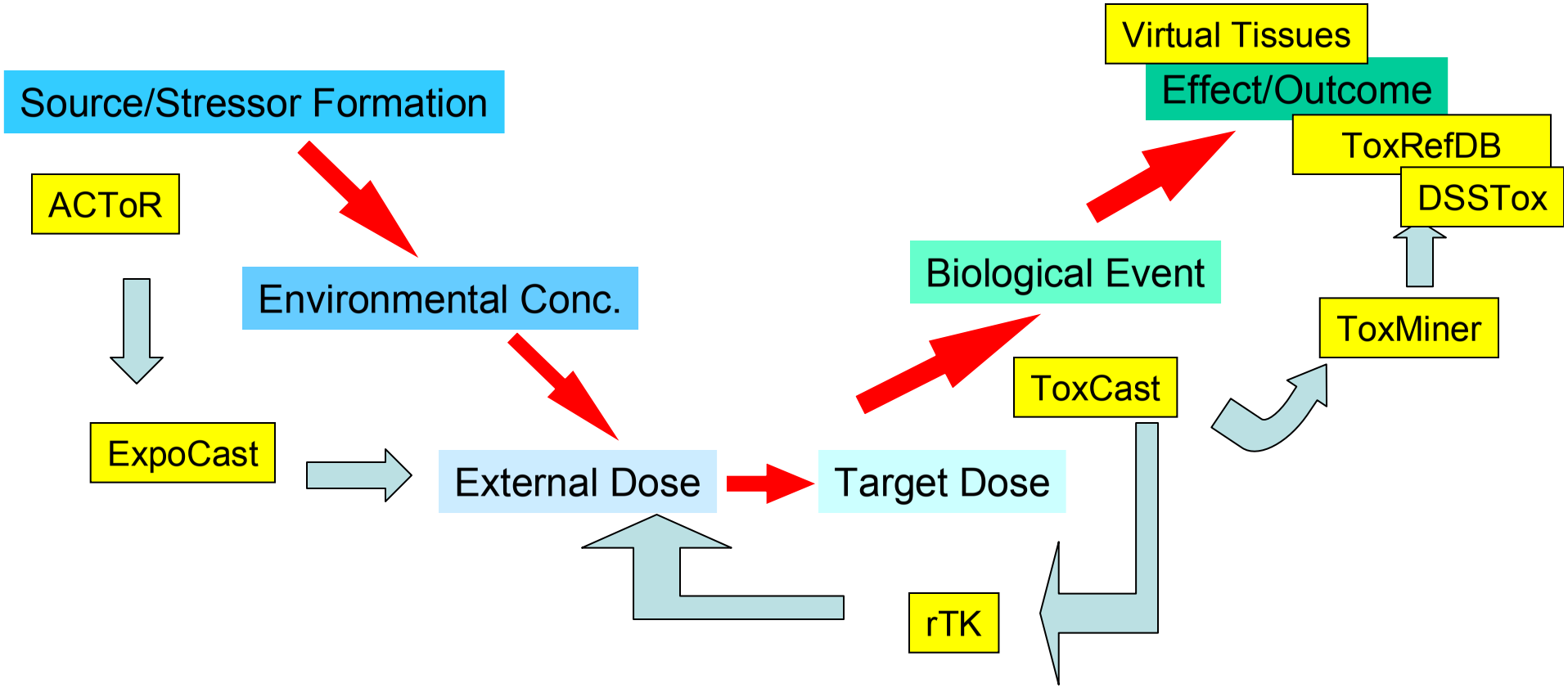


Red: Chronic/Cancer
White: Multigen
Blue: Developmental

ToxCast In vitro data



Applying Computational Toxicology Along the Source to Outcome Continuum



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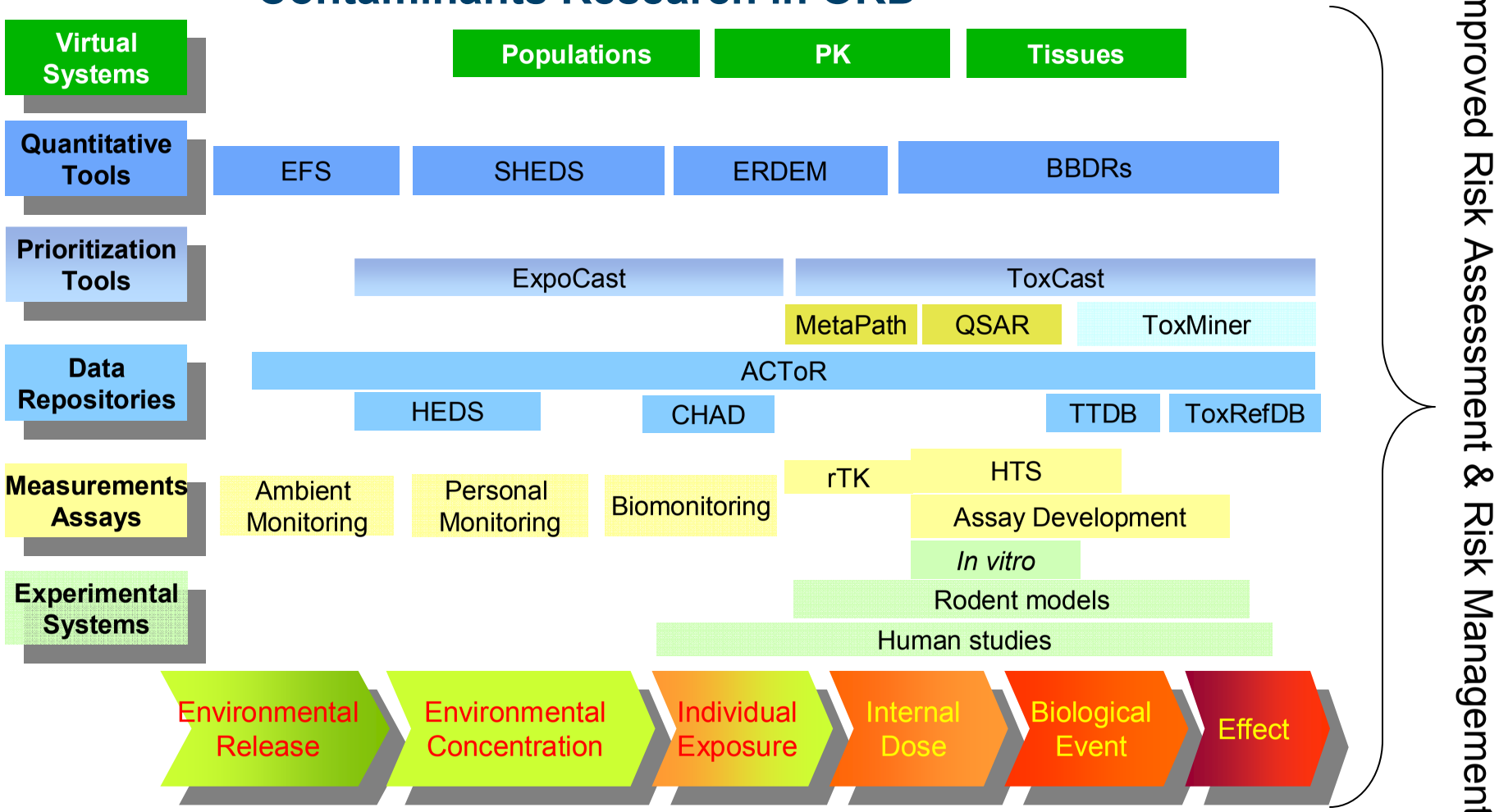
Contaminants Research in ORD



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

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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?

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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?

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