



# ***EPA's ToxCast Program for Predicting Toxicity and Prioritizing Environmental Chemicals***

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**Dix *et al.* (in press). The ToxCast Program for Prioritizing Toxicity Testing of Environmental Chemicals. *Toxicological Sciences*.**

***ToxCast is a research program to predict or forecast toxicity by evaluating a broad spectrum of chemicals and effects: physical-chemical properties, predicted bioactivities, HTS and cell-based assays, and genomics. Data will be interpretively linked to known or predicted toxicological properties to develop methods for chemical classification and prioritizing subsequent testing.***

# The Need for Toxiccast

OPPT/High Production Volume (HPV) Challenge Program: The HPV Voluntary Challenge Chemical List - Mozilla Firefox

File Edit View Go Bookmarks Tools Help

US EPA http://www.epa.gov/chemrtk/hpvchnlk.htm

Related Sites - Canada

Best of the Web Channel Guide DSM Regional Affili... Windows Media Windows

EPA/OSCP: Endocrine Disruptor Screening Program - Mozilla Firefox

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US EPA http://www.epa.gov/scipoly/oscp/index.htm

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Related Sites - Canada

Drinking Water Contaminant Candidate List (CCL) - Mozilla Firefox

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US EPA http://www.epa.gov/safewater/ccl/frequentquestions.html

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Related Sites - Canadian Wildlife Service - E...

EPA: Pesticides - Inert (other) Pesticide Ingredients in Pesticide Products - Mozilla Firefox

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US EPA http://www.epa.gov/oppr001/inerts/

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Related Sites - Canadian Wildlife Service - E...

U.S. Environmental Protection Agency

EUROPA - European Commission - Enterprise & Industry - REACH - Mozilla Firefox

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EUROPA http://europa.eu.int/comm/enterprise/reach/index\_en.htm

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Related Sites - Canadian Wildlife Service - E...

EUROPA - European Commission - Ent...

Enterprise and Industry

EUROPA > European Commission > Enterprise & Industry > Industry Sectors > REACH

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News & Updates

20.7.2005  
REACH IT - Call for tender - Questions and answers Set 2 / NEW

15.7.2005  
KPMG Impact Assessment Study for UNICE/CEIC Industry Consortium - Final report / NEW

8.7.2005  
REACH IT - Call for tender - Questions and answers Set 1 / NEW

7.7.2005  
See the letter (fr) from citizens concerning animal experiments and the Commission answer (fr) with the translation (en) / NEW

6.7.2005  
See the Press Release and the Report on SPORT / NEW

16.6.2005  
See the Further impact assessment study in the European textile production - Executive summary

14.6.2005  
See the Call for expressions of interest for technical assistance in relation to chemical affairs

8.6.2005  
See the REACH IT - Call for tender - deadline 9.6.2005

THE NEW EU CHEMICALS LEGISLATION - REACH

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 it 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.

Overview

Activities:

REACH Proposal

Proposal

Consultation

Impact Assessment

Trial runs

The White Paper

Information:

Calls

Links

Contact

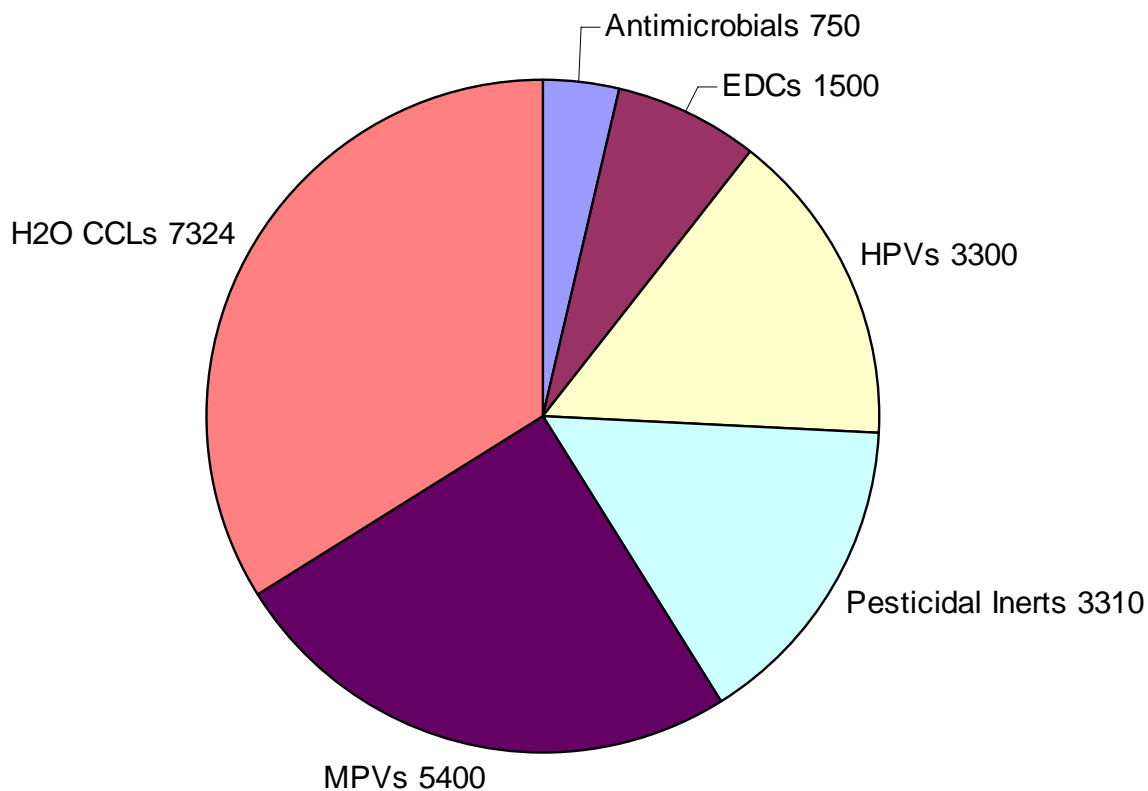
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http://www.epa.gov/pesticides/re

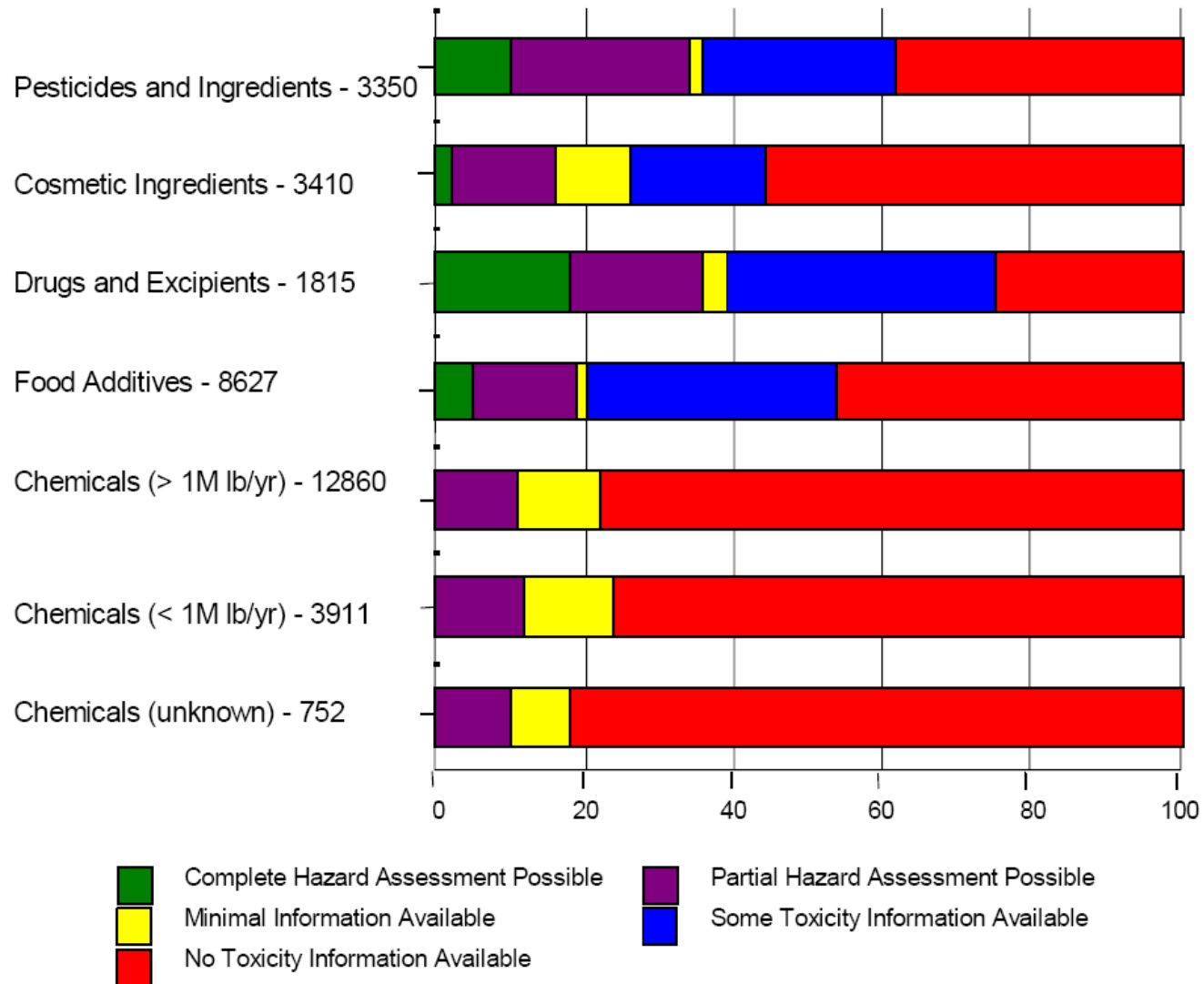
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# *Environmental Chemical Domains with Potential ToxCast Applications*



# Environmental Chemical Data Gaps

## Estimated Mean Percent in Selected Universe



*Strategies for Closing the Chemical Data Gap*

*by John S. Applegate and Katherine Baer*

# High-Throughput Screening: Utility Beyond Drug Discovery

*Definition: batch testing of large numbers of compounds for biological activity*

*Traditional Use: target-based approach to generate lead compounds for further drug development*

## Pharma: Drugable Proteome Interrogation

- Fliri, et al (2005); Biological spectral analysis: Linking biological activity profiles to molecular structure. *PNAS* 102:261.

## Agrochemical: Analysis of target species or model organisms

- Smith et al (2005); Targeting inputs and optimizing HTS for agrochemical discovery. *Comb. Chem & HTS* 8:577.
- Tietjen et al (2005); High throughput screening in agrochemical research. *Comb. Chem & HTS* 8:589.

## Basic Science: Providing molecular tools for cell biology

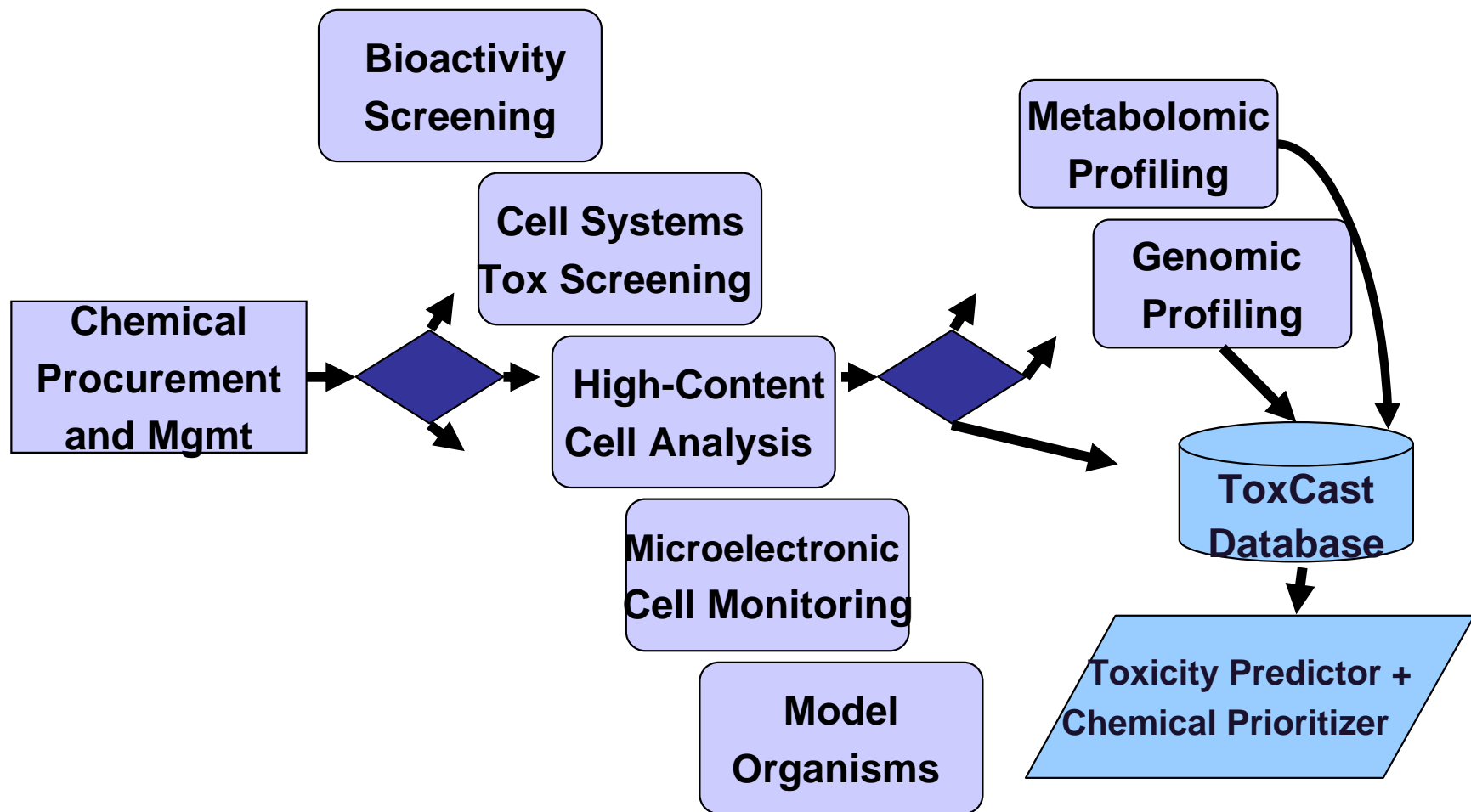
- Austin, et al (2004). NIH Molecular Libraries Initiative. *Science* 36:1138

# *HTS in Drug R&D vs Environmental Toxicology*

	Pharma	Toxico
Chemical Space	Narrow	Broad
Chemical Numbers	$10^4$ - $10^6$ ( $10^{60}$ )	$10^2$ - $10^4$
Intended MoA	Generally understood and narrow	May not exist
Target Potency	High	Generally low
Off Target Effects	Often understood	Poorly understood
Acceptance Rate	False negatives OK	False negative rate must be very low
Parent Activity	Design factor	Usually unknown

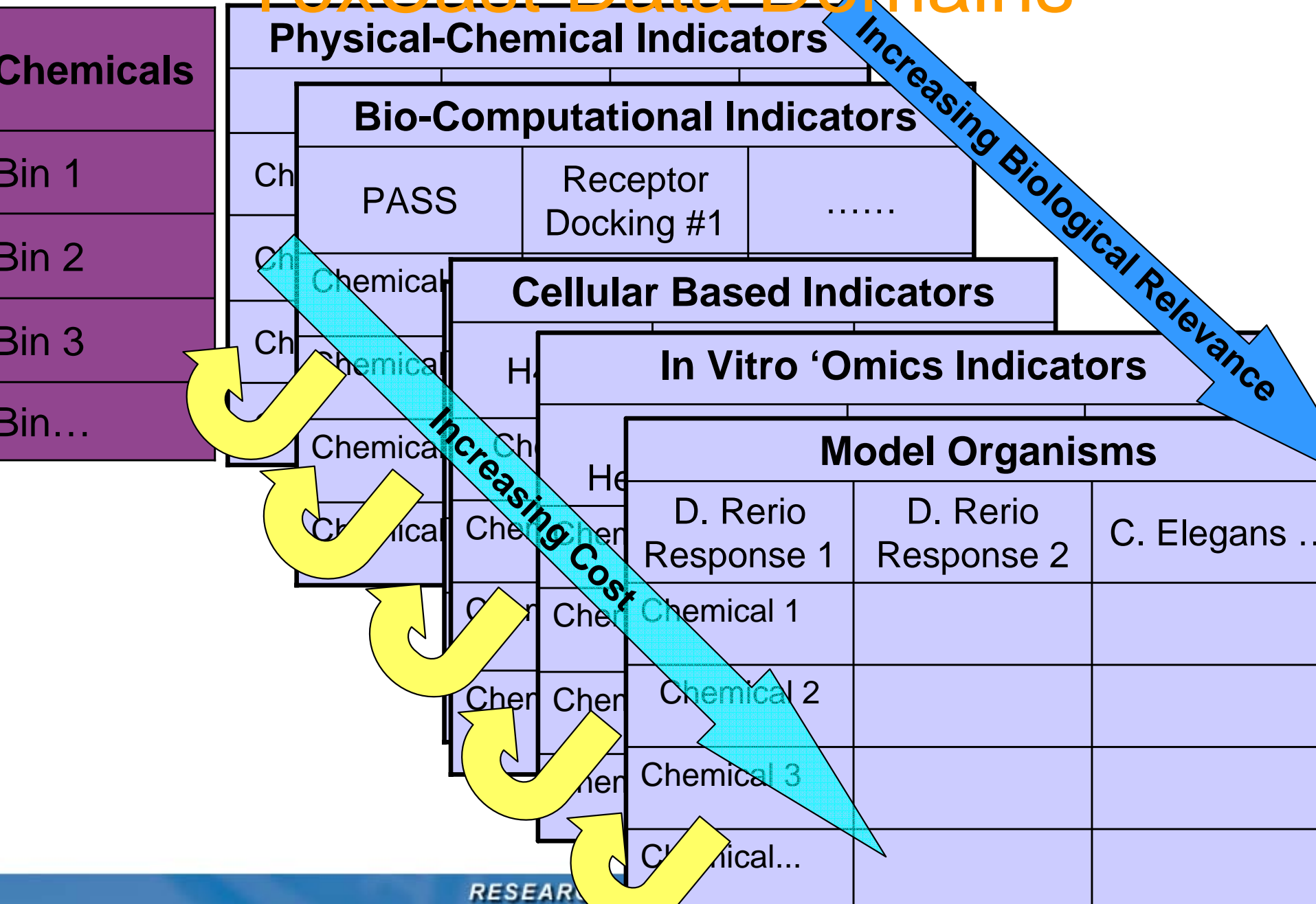


# ToxCast Program for Prioritizing Environmental Chemicals Based on Predicted Toxicity





# ToxCast Data Domains



# *Assay Coverage - Key Mechanisms / Toxicities*

- Cell cycle, apoptosis, DNA recombination and repair
- Transporters, channels, membrane receptors
- Signal transduction pathways
- Nuclear receptor mediated pathways
- Oxidative Stress
- Genotoxic and non-genotoxic carcinogenicity
- Developmental and reproductive toxicity
- Developmental neurotoxicity and immunotoxicity

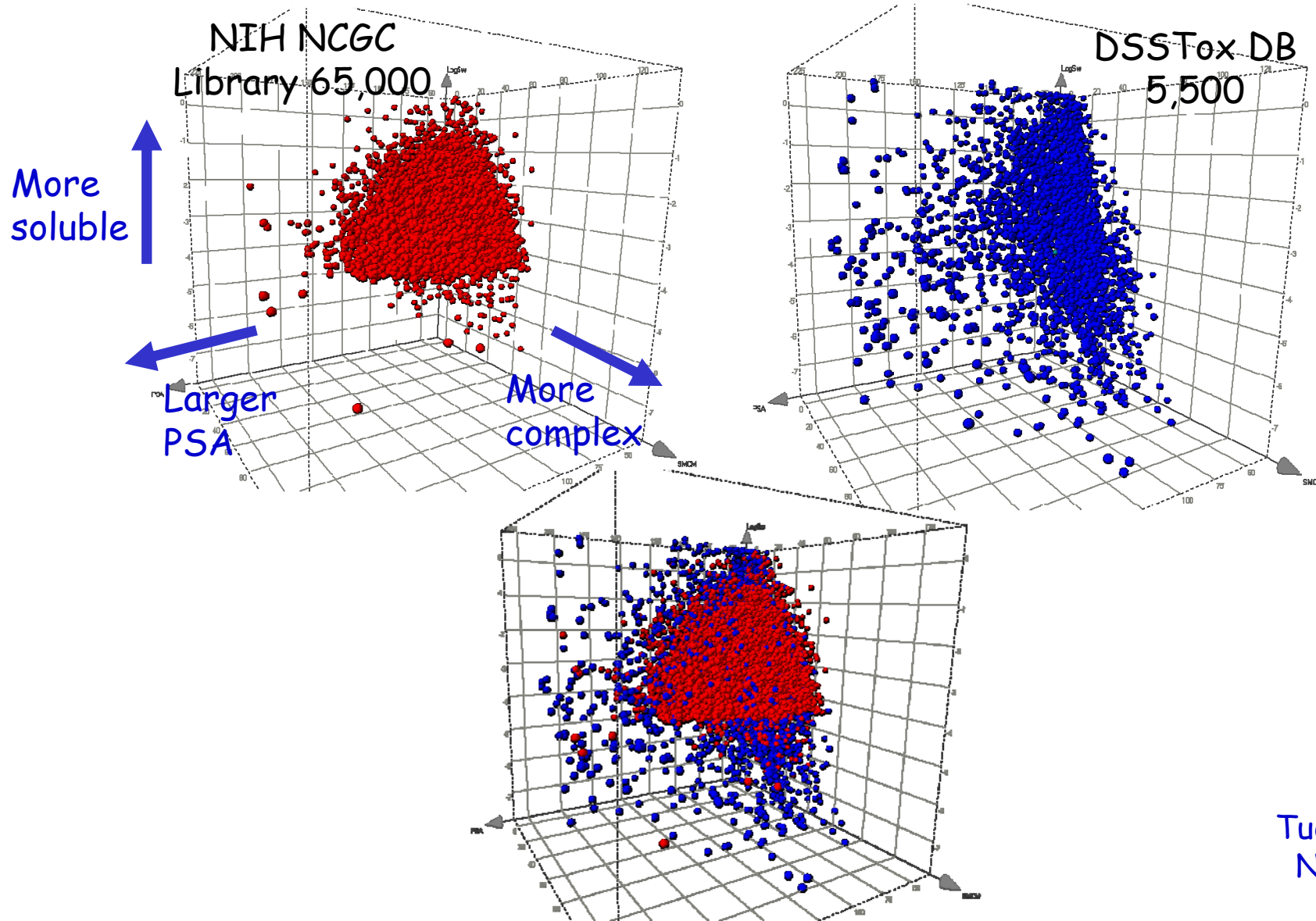
# *Assay Selection Considerations*

- Capacity (hundreds to thousands of chemicals)
- Cover broad spectrum of gene/protein families
- Utilize genomic, proteomic and/or metabolomic tools applied to cellular or organismal assays
- Currently available
- Model organisms (non-mammalian)
- Linkage to known toxicological MOA
- Ability to test in concentration-response format
- Biotransformation capability
- Minimizing false negative rates

# *Chemical Selection Considerations: Proof of Concept Chemicals*

- Require rich toxicological data for correlations with bioassay profiles
  - US Registered Pesticides (826)
    - 90 day, Chronic, Multigen, DevTox, (DNT), (IMT)
    - Designed with inherent biological activity
  - NTP Testing Program
  - Other Chemicals with rich information base
- 
- Pesticide Repository/OPP
    - Pesticide active ingredients
    - Analytical samples
    - ~400 obtained to date

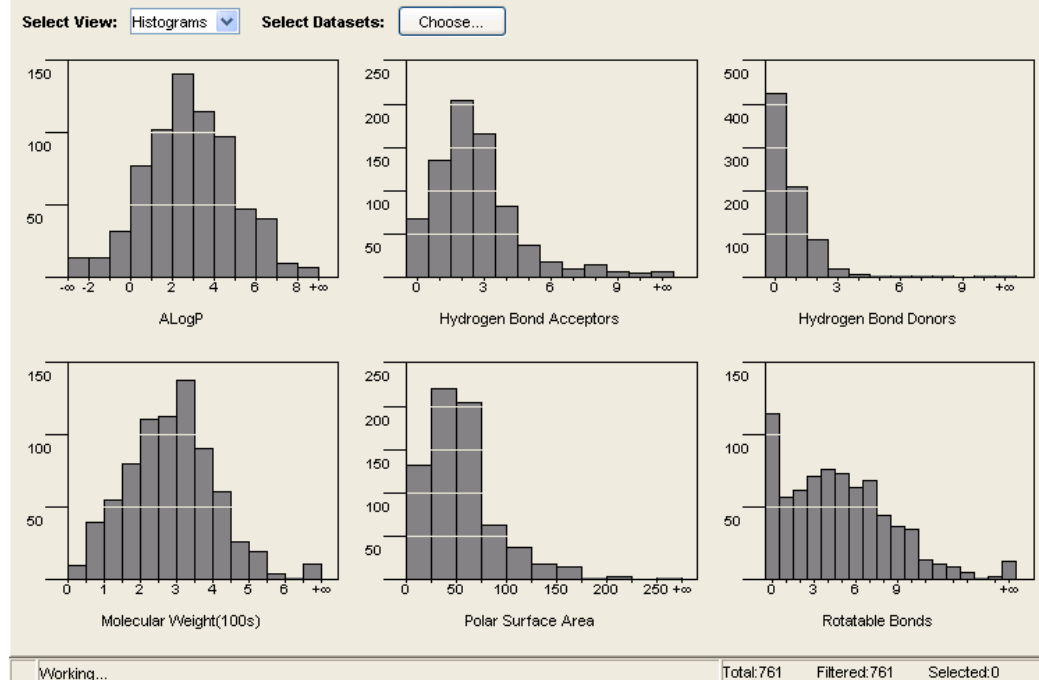
# Structural Diversity Comparison DSSTox Vs Pharma-Like Cmpds



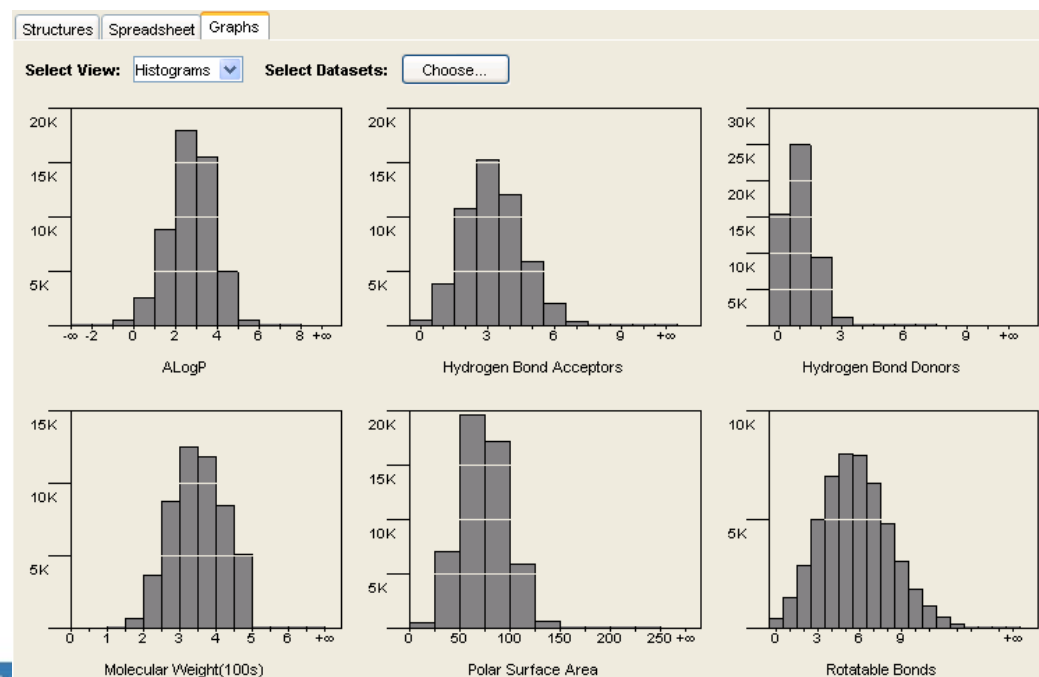
Tudor Oprea  
NM MLSC

# Chemical Diversity Comparison

EPA PTC Library



NCGC Chemical Genetics Library



# *Difficult Issues* *(the usual suspects)*

Extent to which concentration-response information is acquired (versus use of only some preset concentration)

Ability to detect 'protoxicants'

Solubility

How many assays are needed?

How many are affordable?

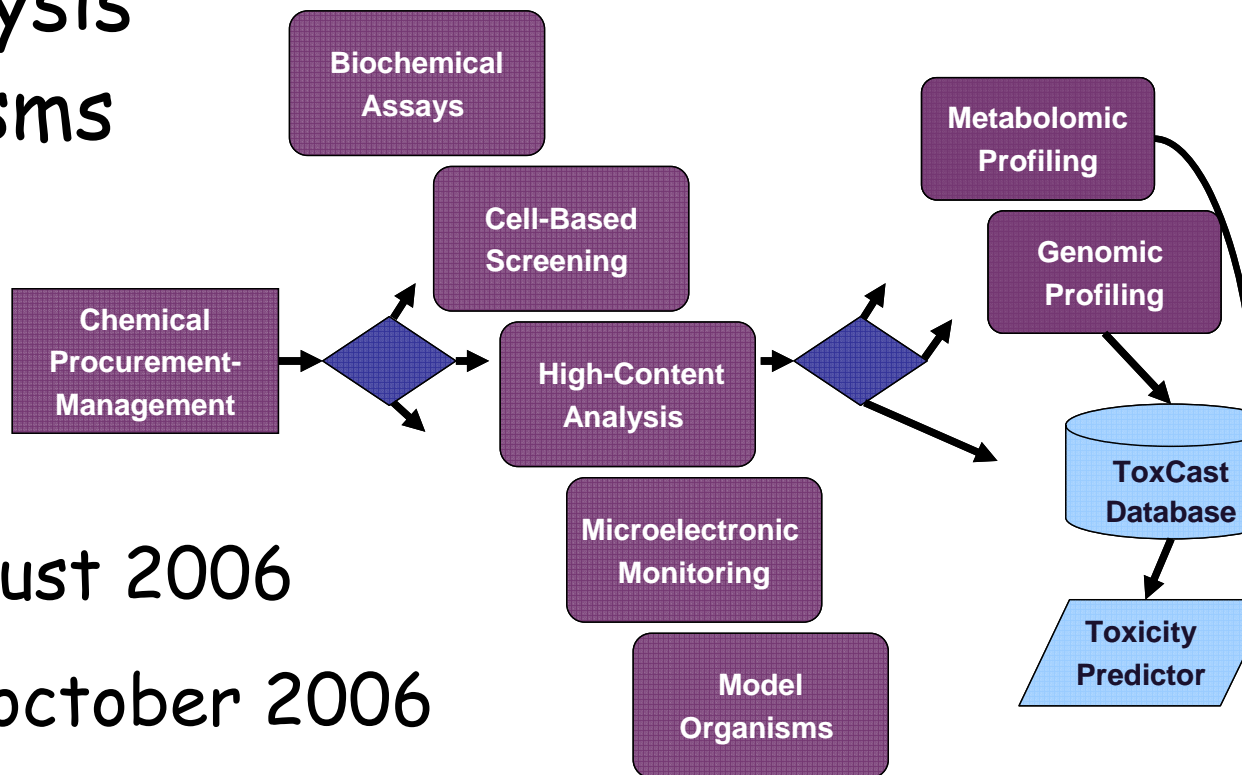
Coverage of mechanisms of developmental toxicity

- 17 Signaling Pathways identified by the NAS
- Highly conserved among metazoans



# ToxCast Contract RFPs

- Chemical Procurement/Management
- Biochemical Assays
- Cellular Systems
- Genomic Analysis
- Model organisms



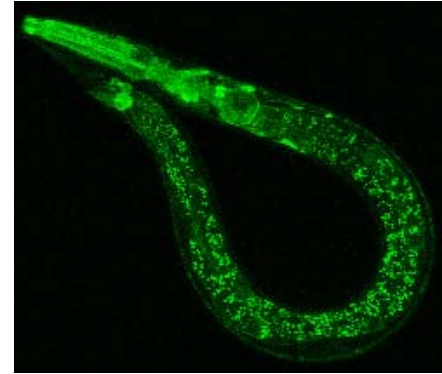
RFPs closing july-august 2006

Awards target date october 2006

# ToxCast Collaborations

NTP:

- HTS initiative (R. Tice)
- *C. elegans* assays (J. Freedman)

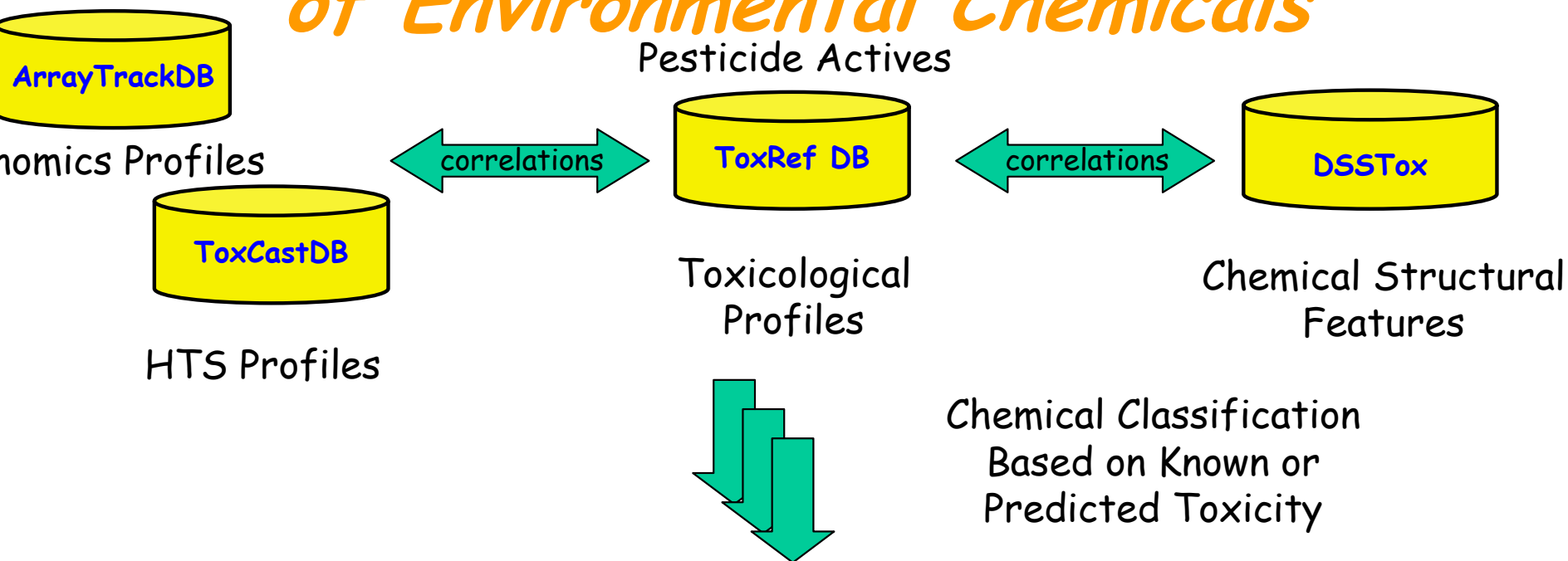


NIH NCGC: qHTS  
(C. Austin, J. Inglese)



OECD Molecular Screening  
(EPA/OPPTS)

# ToxCast Chemical Classification of Environmental Chemicals



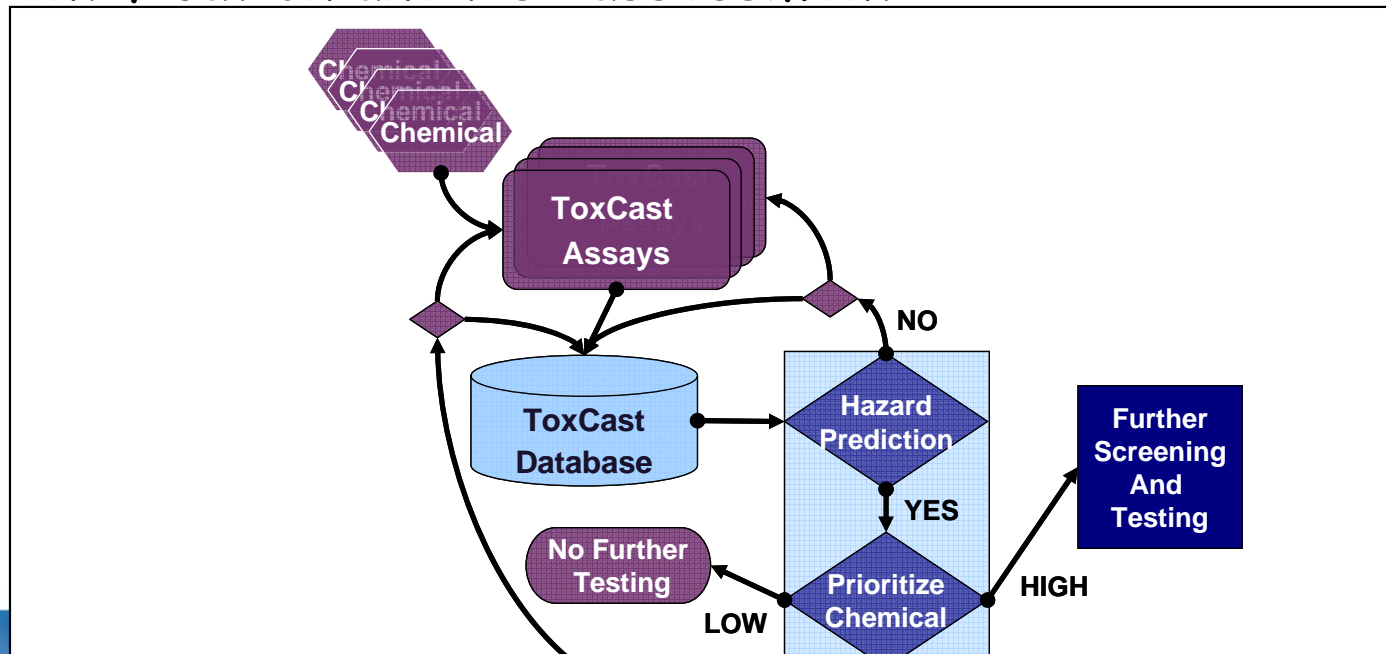
Profiles	Tox						
	Correlation Present	Liver Carcinogen	Kidney Carcinogen	DNT	NT	Liver Enzymes	Etc....
Chemical A	+	-	-	-	+	-	-
Chemical B	+	-	-	+	-	-	-
Chemical C	+	+	-	-	-	+	-
Chemical D	+	+	-	-	-	+	-
Chemical E	+	-	-	+	+	-	-
Chemical F	-	-	-	-	-	-	-

# *ToxCast- Potential Outcomes and Expansion Beyond Proof-of-Concept*

Availability of a science-based system to categorize chemicals of like properties and activities

- Increasing confidence as database grows
- Once operational, MOA leads for new chemicals
- Provide EPA Program Offices with a relatively inexpensive predictive tool box that heretofore has been seriously lacking

Improve the efficiency and effectiveness of the use of animals in hazard identification and risk assessment



# *Acknowledgements*

- NCCT
  - David Dix
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