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Agency

Prioritizing the Toxicity Testing of Environmental Chemicals at EPA

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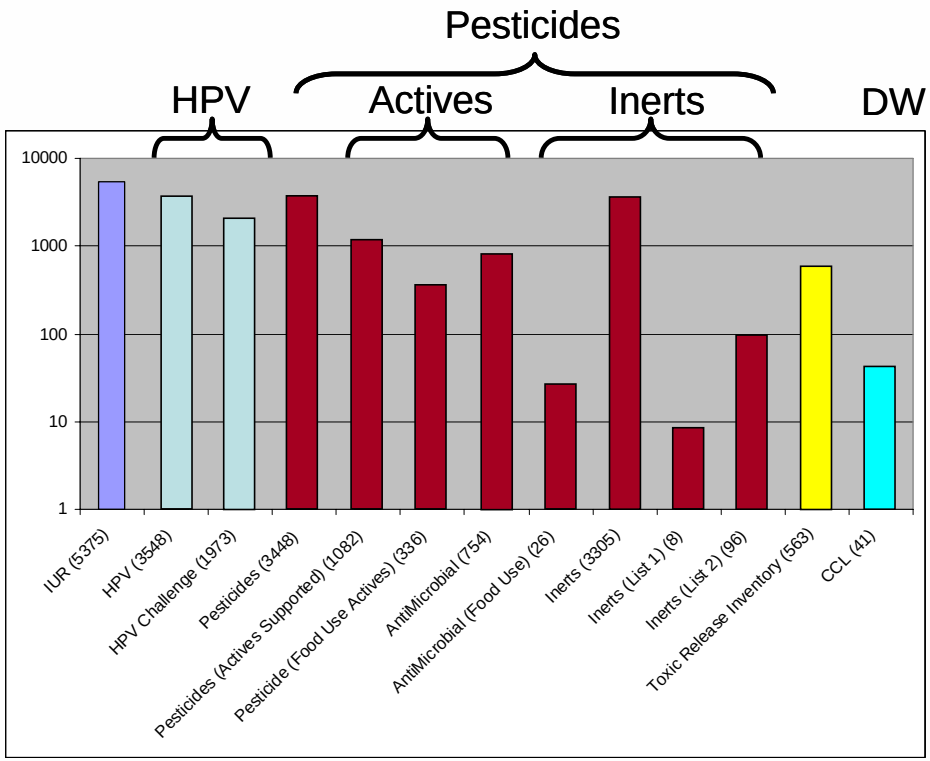
Ranking and Prioritizing Chemicals

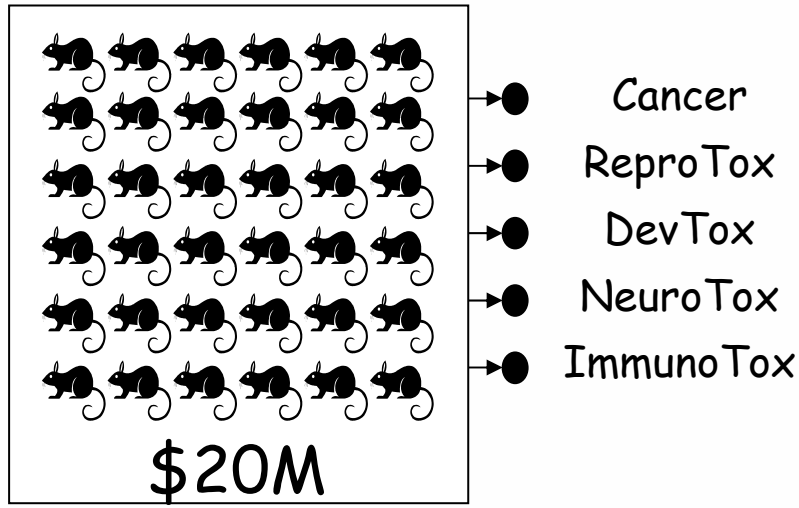
- Ranking for further testing
  - Identify compounds of greatest concern
  - Focus testing efforts
- Ranking for decision making
  - Challenge of consistent methods vs. chemical specific information
  - Differential uncertainty

ToxCast™ Addresses the Critical Need for Prioritization

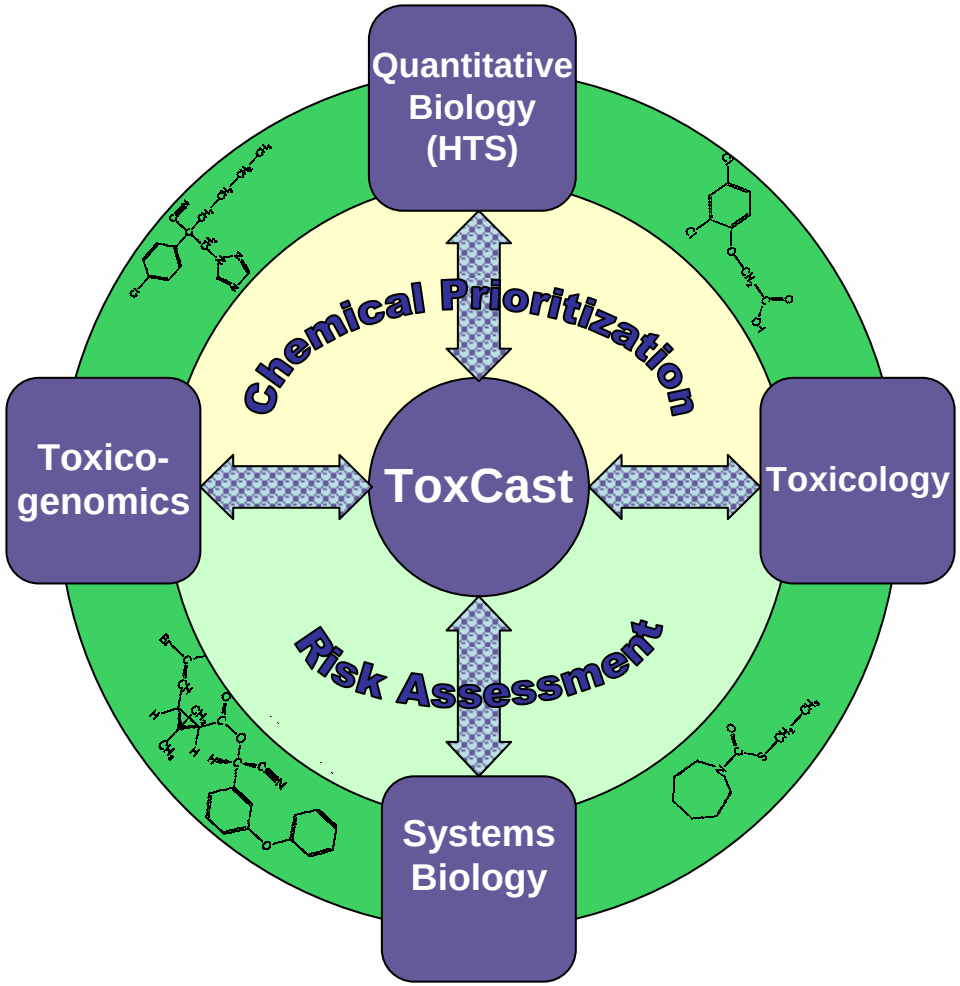
Too Many Chemicals



Too High a Cost



ToxCast Merges HTS and Genomics Technologies with Traditional Toxicology



The ToxCast Program for Prioritizing Toxicity Testing of Environmental Chemicals

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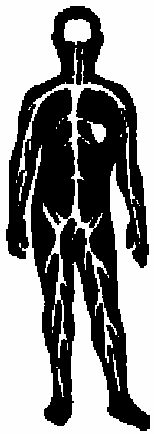
TOXICOLOGICAL SCIENCES **95(1)**, 5–12 (2007)
doi:10.1093/toxsci/kfl103
Advance Access publication September 8, 2006

The U.S. Environmental Protection Agency (EPA) is developing methods for utilizing computational chemistry, high-throughput screening (HTS), and various toxicogenomic technologies to predict potential for toxicity and prioritize limited testing resources toward chemicals that likely represent the greatest hazard to human health and the environment. This chemical prioritization research program, entitled "ToxCast," is being initiated with the purpose of developing the ability to forecast toxicity based on bioactivity profiling. The proof-of-concept phase of ToxCast will focus upon chemicals with an existing, rich toxicological database in order to provide an interpretive context for the ToxCast data. This set of several hundred reference chemicals will represent numerous structural classes and phenotypic outcomes, including tumorigens, developmental and reproductive toxicants, neurotoxicants, and immunotoxicants. The ToxCast program will evaluate chemical properties and bioactivity profiles across a broad spectrum of data domains: physical-chemical, predicted biological activities based on existing structure-activity models, biochemical properties based on HTS assays, cell-based phenotypic assays, and genomic and metabolomic analyses of cells. These data will be generated through a series of external contracts, along with collaborations across EPA, with the National Toxicology Program, and with the National Institutes of Health Chemical Genomics Center. The resulting multidimensional data set provides an informatics challenge requiring appropriate computational methods for integrating various chemical, biological, and toxicological data into profiles and models predicting toxicity.

High-Throughput Screening Assays

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

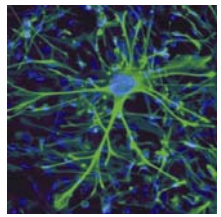
LTS	MTS	HTS	uHTS



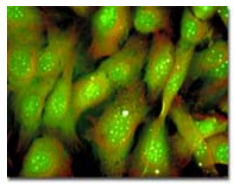
10s-100s/yr

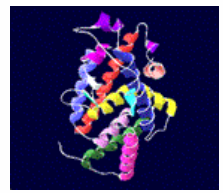
Gene-expression

10s-100s/day



1000s/day



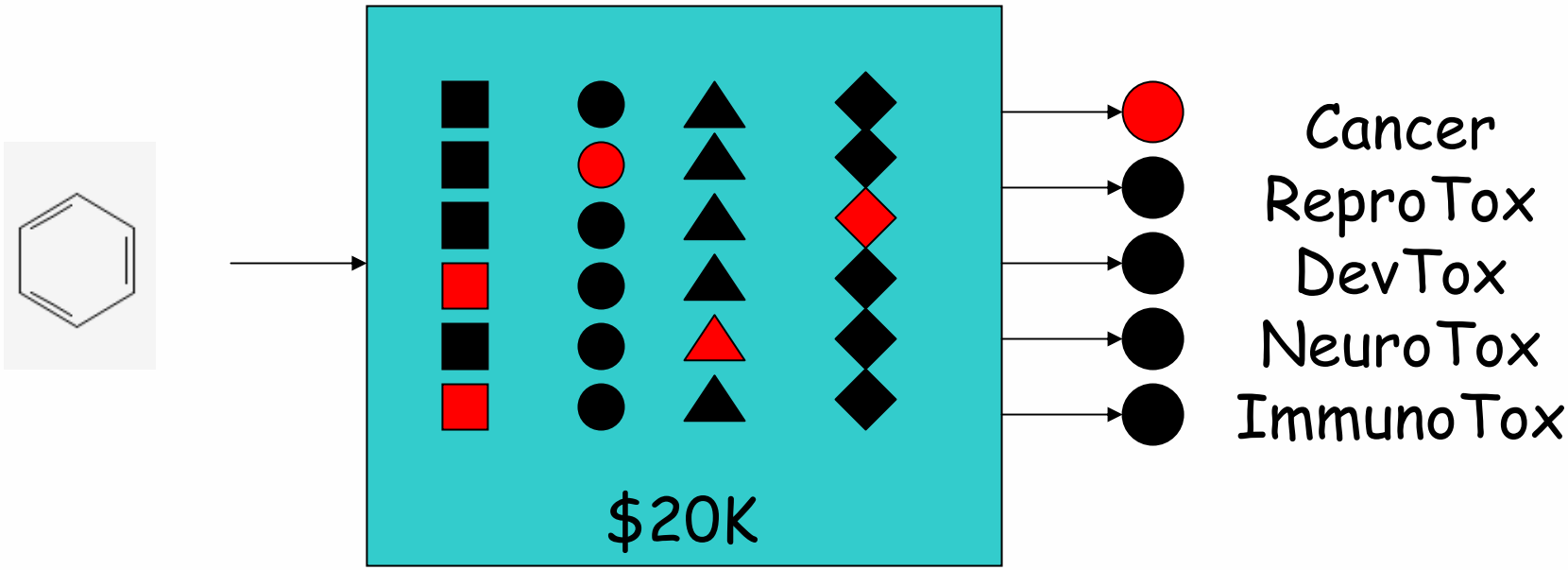


10,000s-
100,000s/day

Human Relevance/
Cost/Complexity

Throughput/
Simplicity

ToxCast™ will identify classifiers or signatures from HTS, HCS and genomics assays to predict hazard…



… and prioritize further testing of chemicals.

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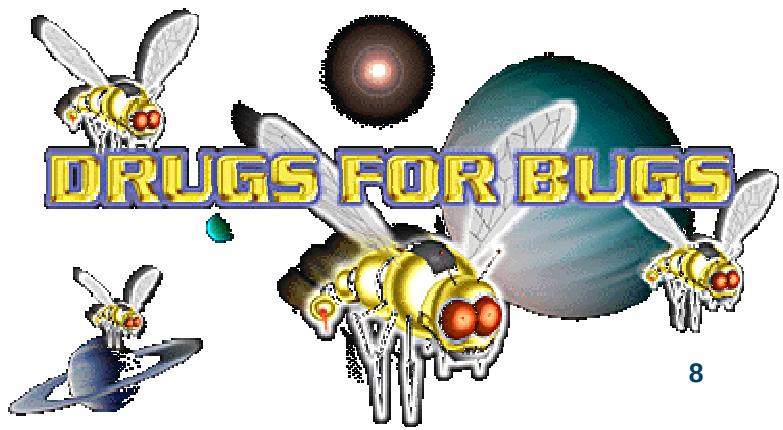
Examples of ToxCast Assays

- Biochemical Target Profiling
- High Content Cytotoxicity Assessment
- Transcription Factor Activity Profiling
- Gene Expression Profiling by Microarray and PCR

Pesticides as Proof of Concept

- ~800 Registered in the United States
- Wealth of Toxicological Information (~$19m)
  - Developmental, reproductive, chronic, etc
- Represent broad range of chemistries
  - Azoles, carbamates, pyrethroids, triazines, etc.
- Designed with biological activity in mind
  - Receptor binding, enzyme inhibition, cytoskeletal, etc.



http://micro.magnet.fsu.edu/pesticides/index.htm

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340 Candidate Chemicals for ToxCast Phase 1

- 317 pesticidal active ingredients
  - 299 with complete animal toxicity datasets
  - 7 metabolites
- 6 pesticidal inerts
- 17 industrial chemicals
  - 16 HPV (11 HPVchallenge)

Correlating HTS to Toxicity

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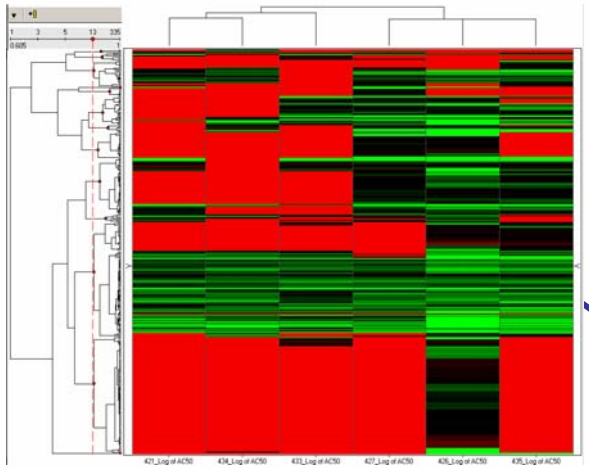
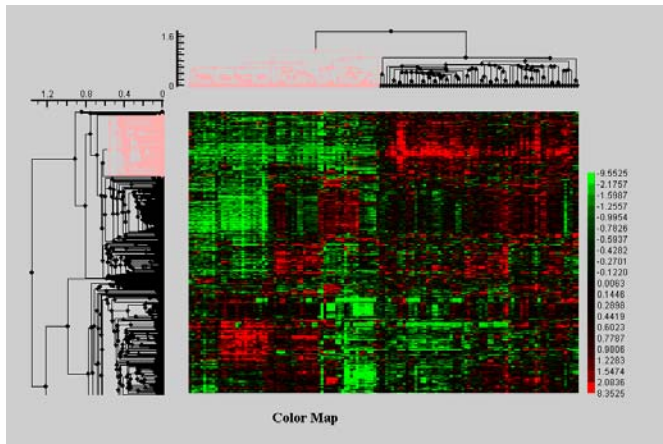
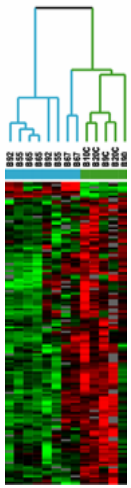


Cellular Assays

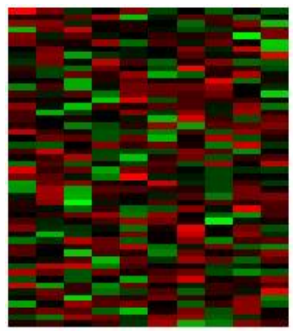


Physical chemical properties

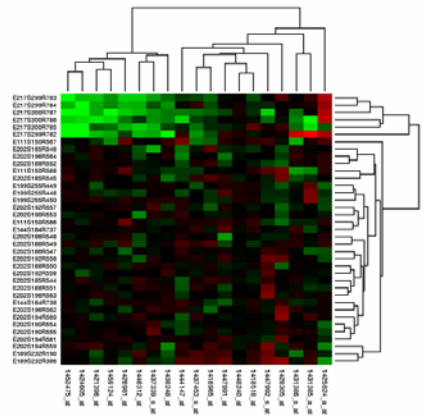
Profile Matching



Biochemical Assays



Genomic Signatures



Toxicology Endpoints

Finding Tests For Toxicity - Classification

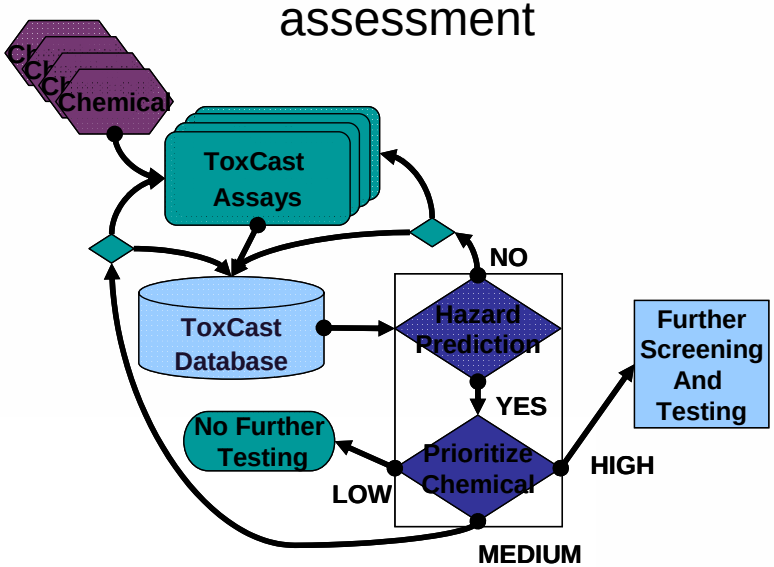
- Goal: Find “classifiers” that accurately predict endpoints
- Use all available data
  - ToxCast™ & public sources
  - HTS, HCS, genomics, physicochemical properties, calculated properties
- Properties of an ideal classifier
  - Accurate (low false positive & false negative rates)
  - Inexpensive and easy to measure for new chemicals
  - Easy to interpret – provides biological insight

Difficult Issues (the usual suspects)

- Endpoint data
- Extent to which concentration-response information is acquired (versus use of only single concentration)
- Ability to detect ‘protoxicants’
- Solubility
- How many assays are needed?
- How many assays are affordable?
- Ability to cover many mechanisms of toxicity

Phased Development of ToxCast

- Phase I Proof of Concept: derivation of first-generation ToxCast signatures based on known toxicity of 300 pesticide actives
- Phase II: Expansion and validation of ToxCast signatures with >1000 additional chemicals, most with partially characterized toxicity.
- Phase III: Application to thousands of environmental chemicals.
  - Delivering affordable, science-based system for categorizing chemicals
  - Increasing confidence as database grows
  - Identify potential mechanisms of action
  - Refine and reduce use of animals in hazard identification and risk assessment

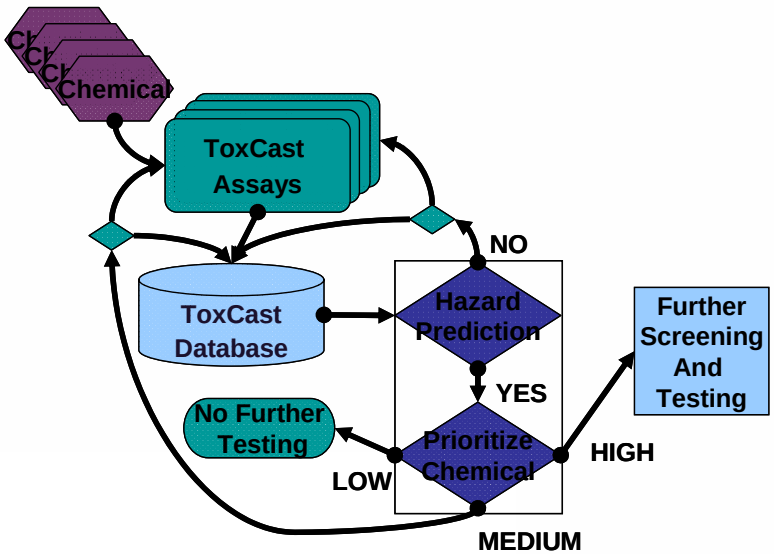


Programs

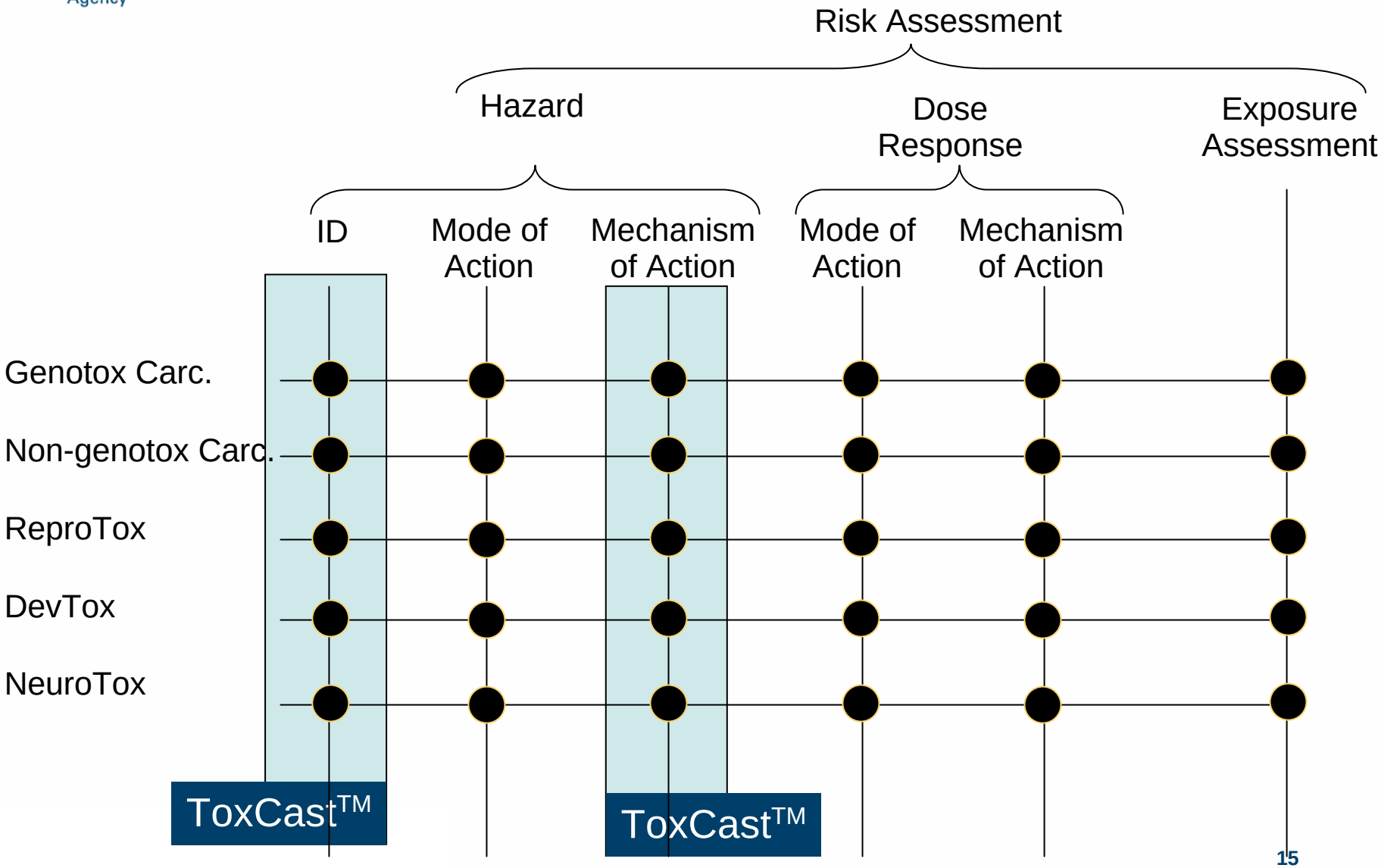
OPP- inerts, antimicrobials
OPPT- HPV, TRI, IUR
OSCP- EDC
OW- CCL

Phased Development of ToxCast

Phase	Number of Chemicals	Purpose
I	>300	Training and Cross-Validation
II	>1000	Validation and Prediction
III	thousands	Prediction and Prioritization



Roles for ToxCast™ in Chemical Prioritization and Risk Assessment



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Summary

- Prioritization for testing is important goal for EPA
- ToxCast is structured approach to developing a prioritization tool using modern biological and information management approaches
- Still need solid data on endpoints and analytic tools to inform decisions

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Thank You!