



ToxCast: A Concept for Prioritization/Categorization

BOSC Site Visit

National Center for Computational Toxicology

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Research Triangle Park NC

ToxCast– A Prioritization Concept

- Assumptions
 - ▶ Prioritization/Categorization is needed
 - ▶ Prioritization is not equivalent to screening
 - ▶ Need global coverage of potential outcomes
 - ▶ These outcomes are mediated by chemical-biological interactions
 - ▶ There is no current model
 - ▶ Technological advances can be employed
 - ▶ Cost is a factor in acceptance
- Pharmaceutical experience is helpful, but caveats
 - ▶ Focused on a target and perhaps a few off-targets
 - ▶ Accepts high false negative rate
- Build upon examples where mode/mechanism of action has already, or is being, employed in hazard or risk assessment

ToxCast Information Domains

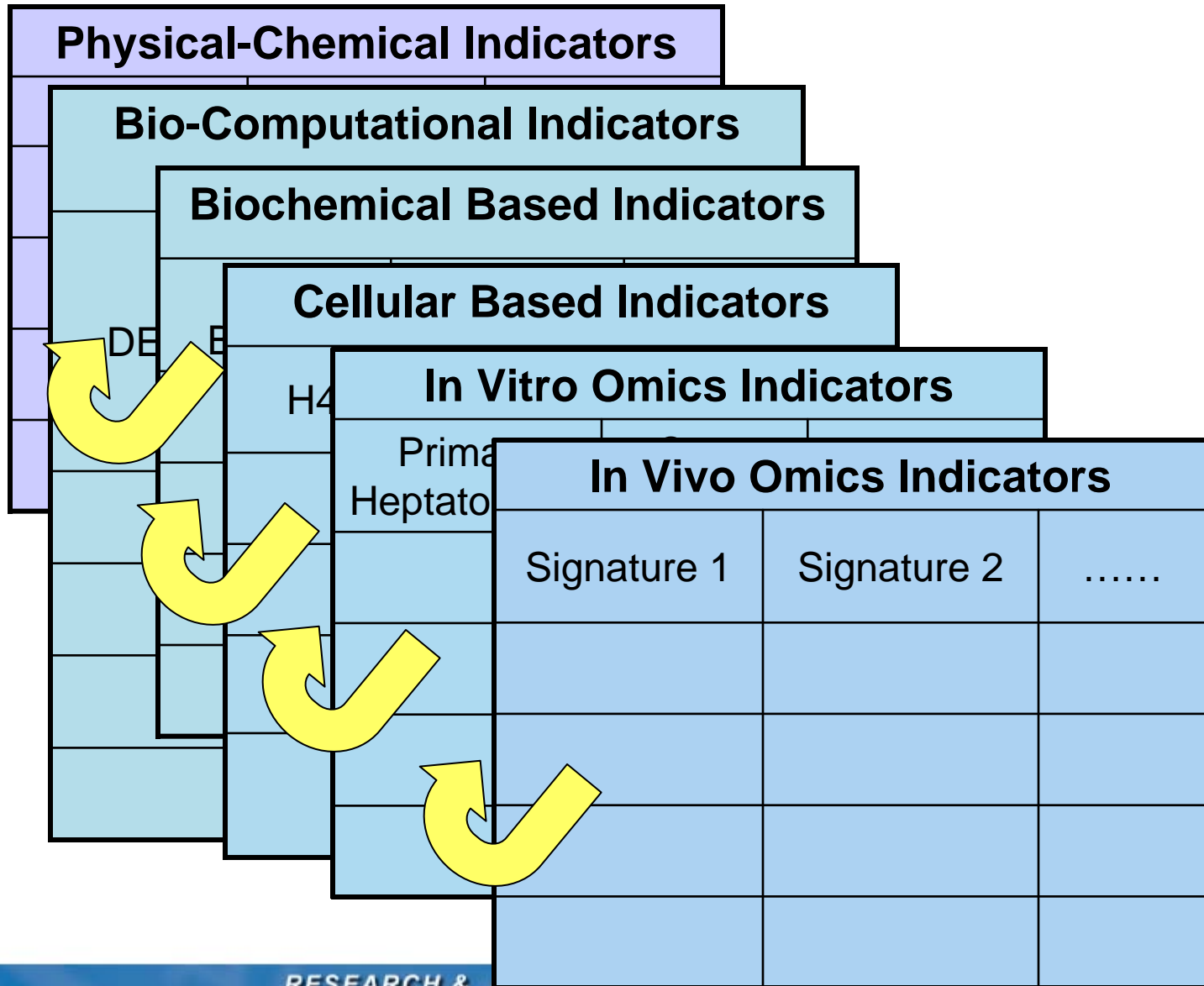
Reference Chemical	P-Chem	BioComp	Biochem	Cell	Omic 1	Omic 2
Bin 1						
Bin 2						
Bin 3						
Bin 4						
Bin 5						
Bin						

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

ToxCast Information Domains

Chemical Class
Bin 1
Bin 2
Bin 3
....
....
Bin



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Proposal

- Conduct a large scale Proof of Concept
- Work with chemicals of known toxicological phenotype
- Acquire information for various information domains
- Using clustering techniques to seek out patterns
- Determine if hazard outcomes can be discerned from the patterns

Benefits

- Ability to categorize or prioritize chemicals
 - ▶ Tool box of indicators across information domains
 - ▶ Cost effective approach for assessing potential to be biologically active agents
 - ▶ Potential targeting of outcomes of concern
- Flexibility
 - ▶ Adaptable to technological advances
 - ▶ Refinement of key indicators with experience
- Development of predictive models as database enlarges
- Involvement with Green Chemistry viewpoint
- Can lead to more effective and efficient use of animals in screening and testing

Limitations/Issues

- Chemical selection process
- Assay selection process
- Chemical management
- Signal to Noise
- Lack of metabolism in several domains
- Start with 'global' approach, or focus on a few "icities"?
- Coverage of developmental susceptibility
 - ▶ Use of the NAS Signaling Pathways??
 - ▶ ?????

Path Forward

- Consensus Building
 - Program Office Clients
 - BOSC
 - External Stakeholders
- Partnership Development
 - NIEHS/NTP, Pharma, Chemical Industry, OECD
- Deep Dive
 - IDEO
 - Workgroups of experts fleshing out details
- Funding
- Implementation