

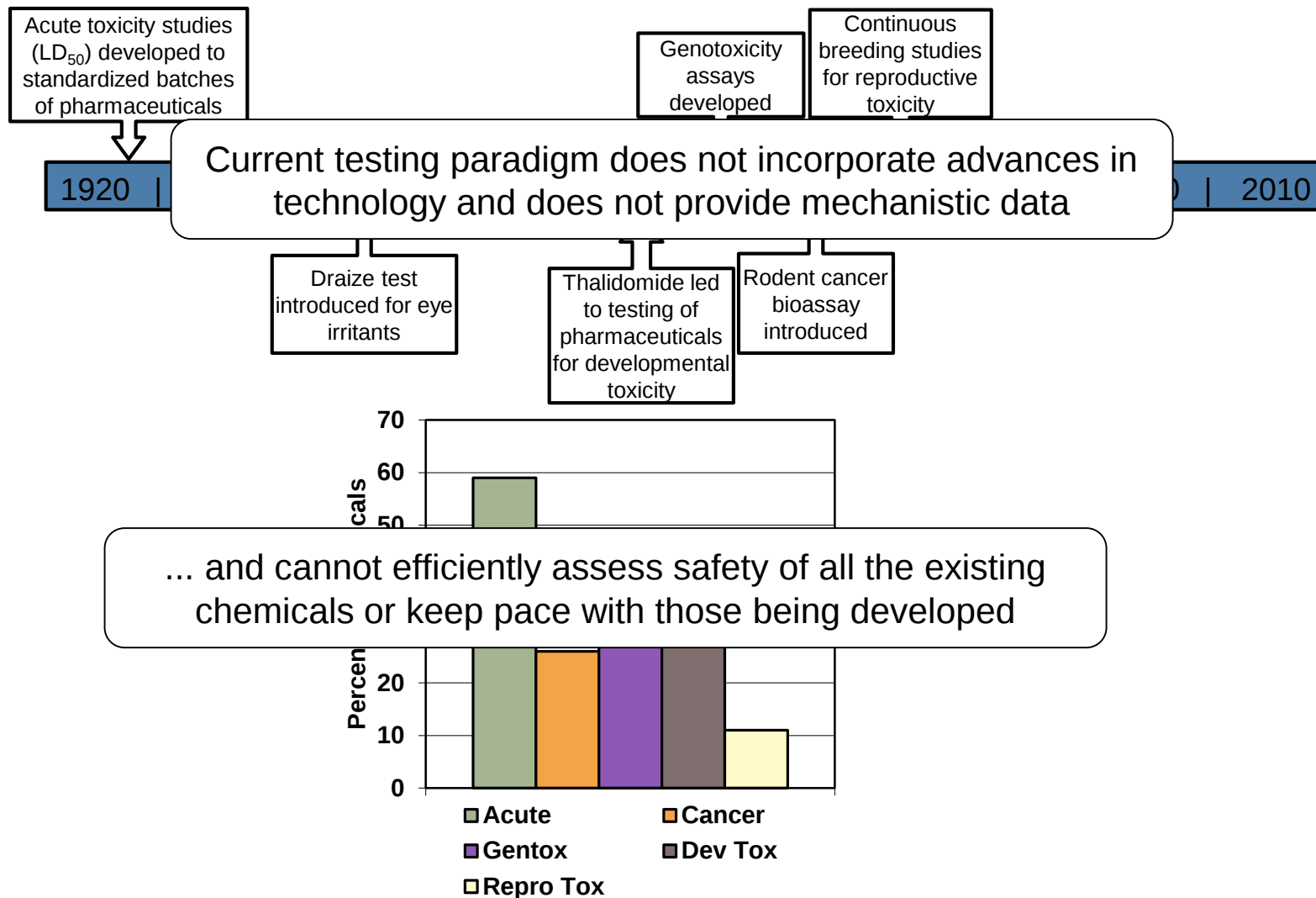
Application of High-Throughput In Vitro Assays for Risk-Based Chemical Safety Decisions of Environmental and Industrial Chemicals



Society of Toxicology Annual Meeting
March 25, 2015

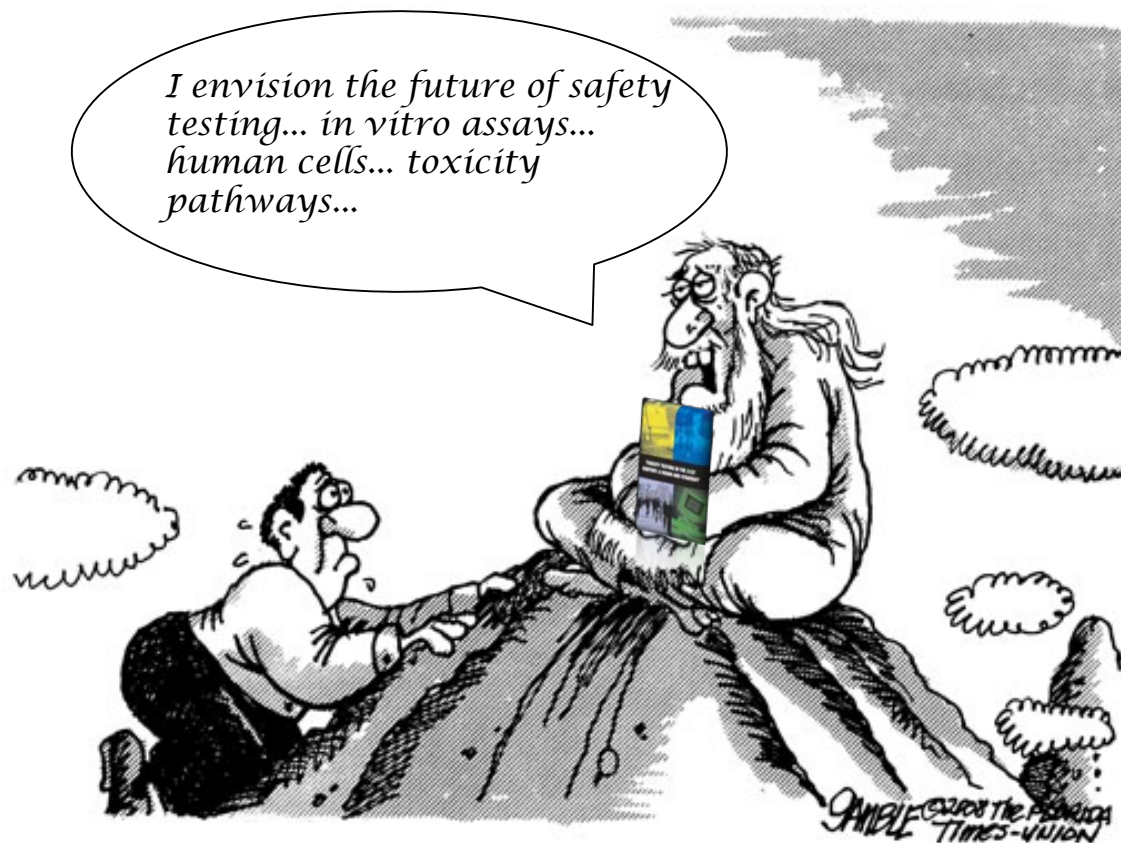
Rusty Thomas
Director
National Center for Computational Toxicology

Current System for Chemical Testing is Antiquated and Inefficient



Judson, et al *EHP* (2010)

In 2007, NRC Transformed Toxicology with a Future View

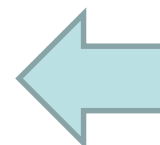
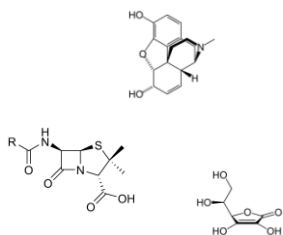
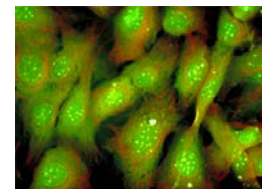
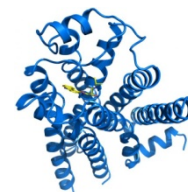


High Throughput Screening By Itself Leads is Incomplete



High-Throughput Screening is One Part of the Elephant...

HTS!

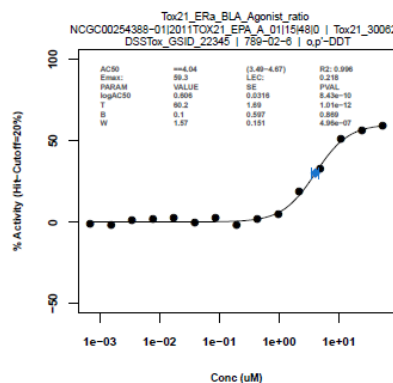


1,800 Chemicals in
Concentration Response

~300 Phase I
~700 Phase II
~800 E1K

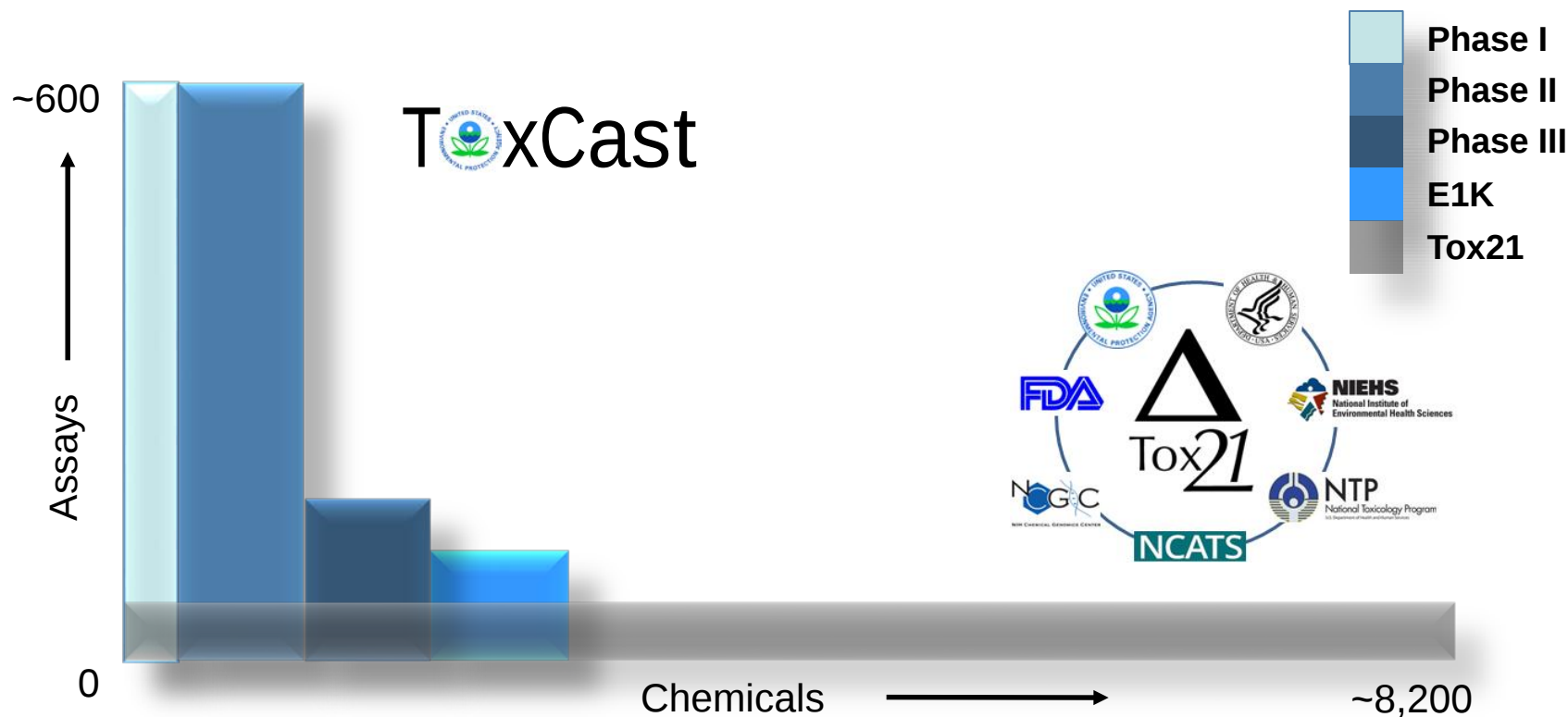
~700 Biochemical and Cell-
based High-throughput
Screening Assay Endpoints

(327 genes and 293
pathways)



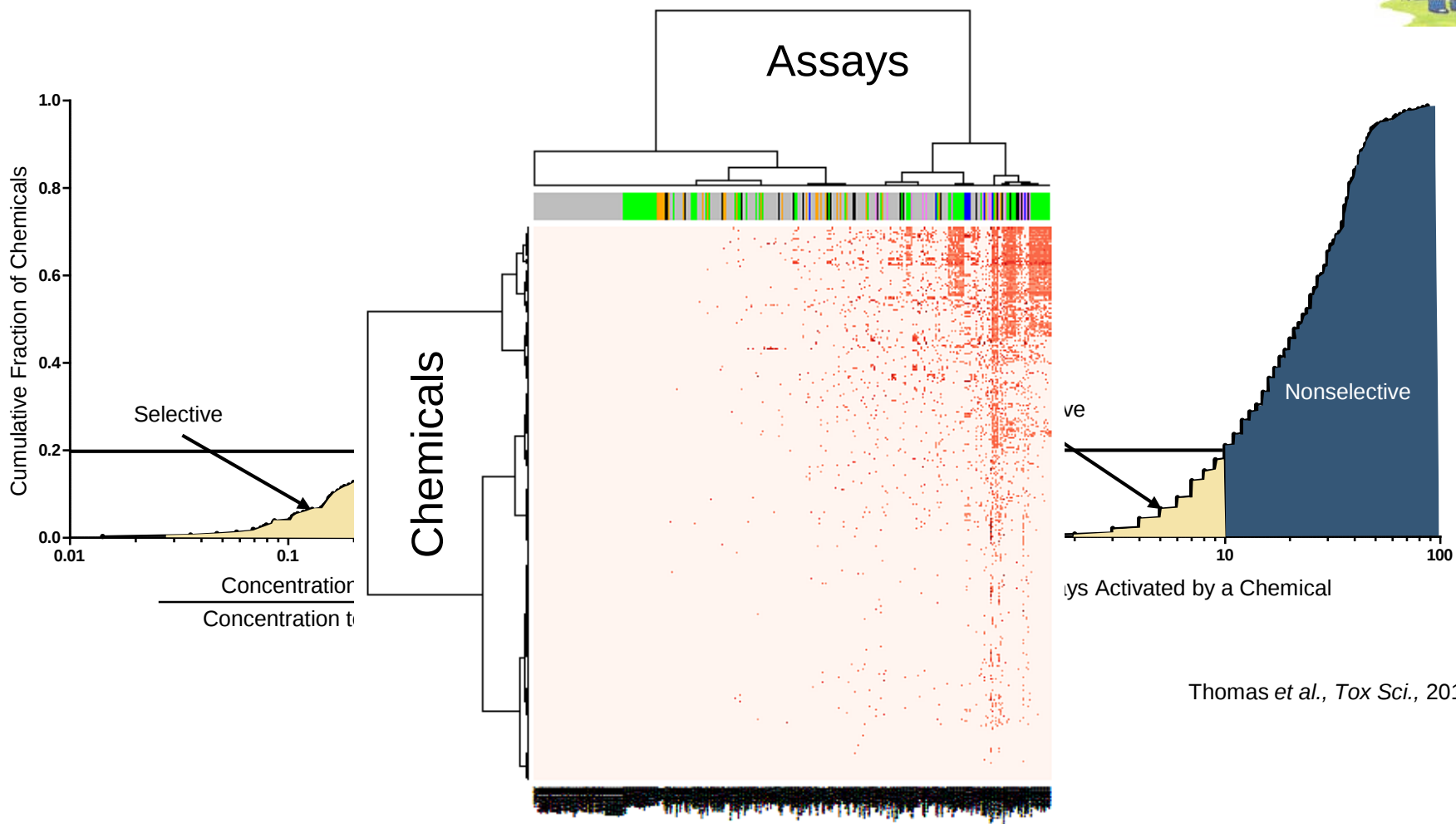
ToxCast and Tox21 Provide Complimentary Approaches

HTS!



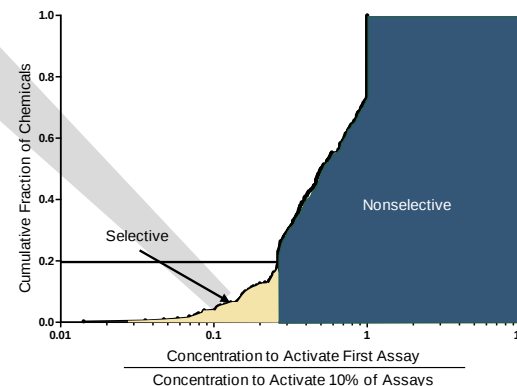
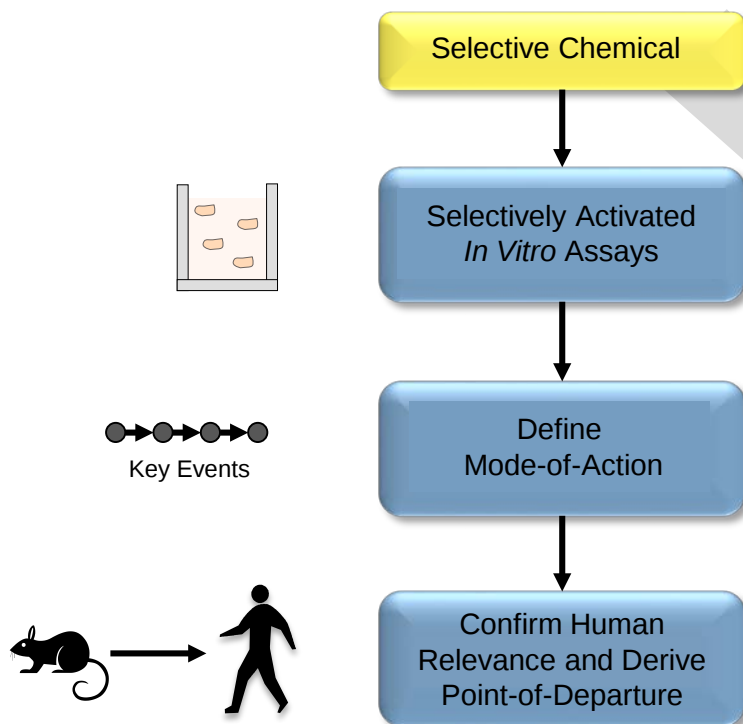
What Have We Learned From High-Throughput Screening?

HTS!

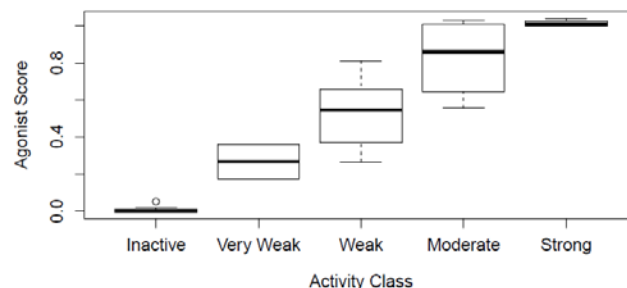
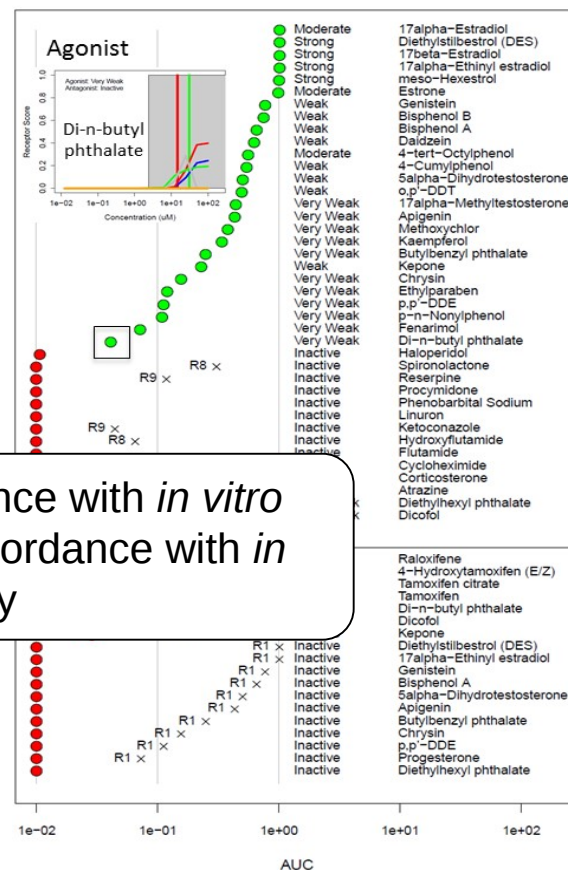
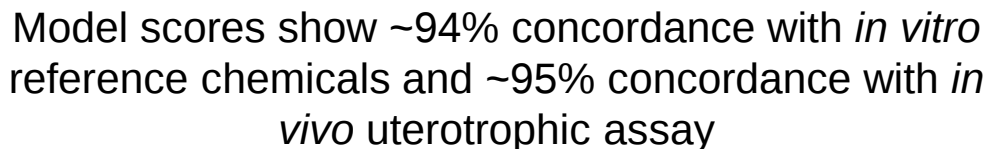


Thomas *et al.*, *Tox Sci.*, 2013

In Vitro Assay Selectivity as a Starting Point for AOPs



18 *In Vitro* Assays Measure ER-Related Activity

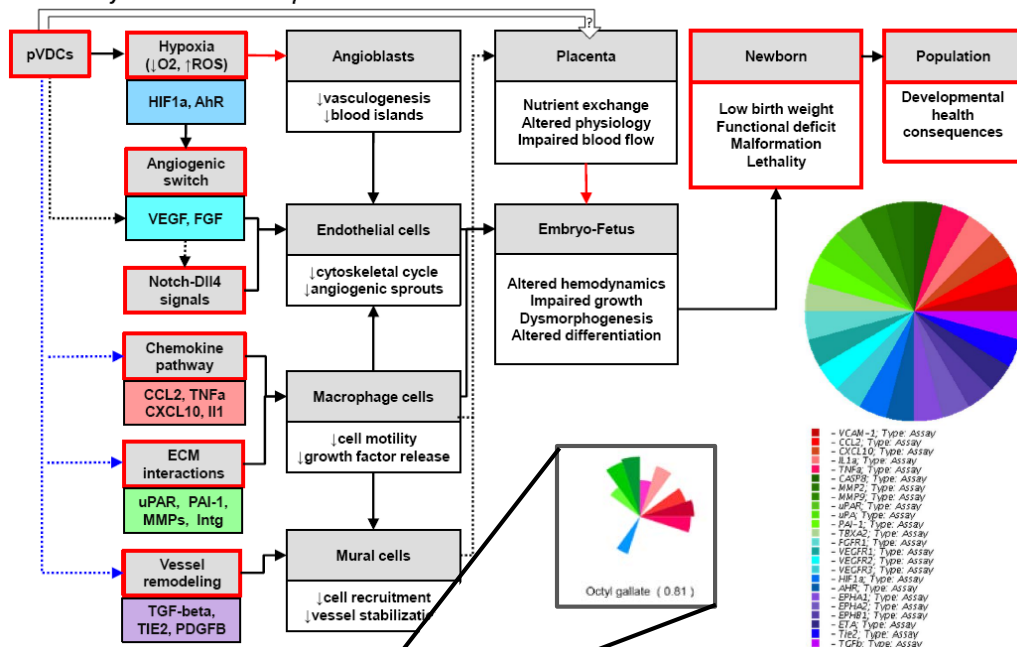


Integration of Assays for Multiple Key Events into AOPs

Systems
Models!

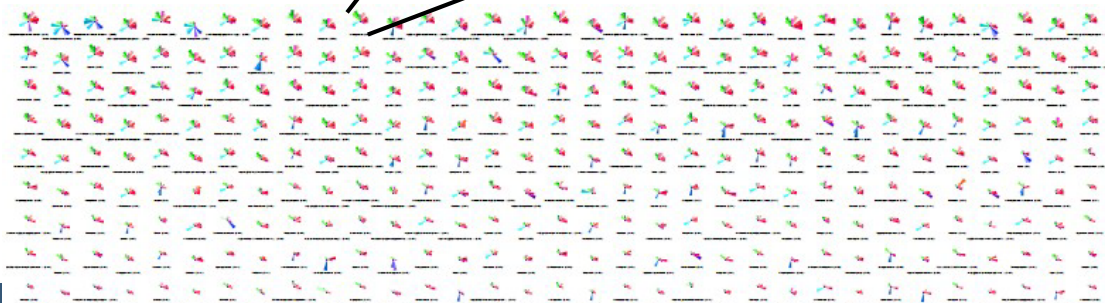
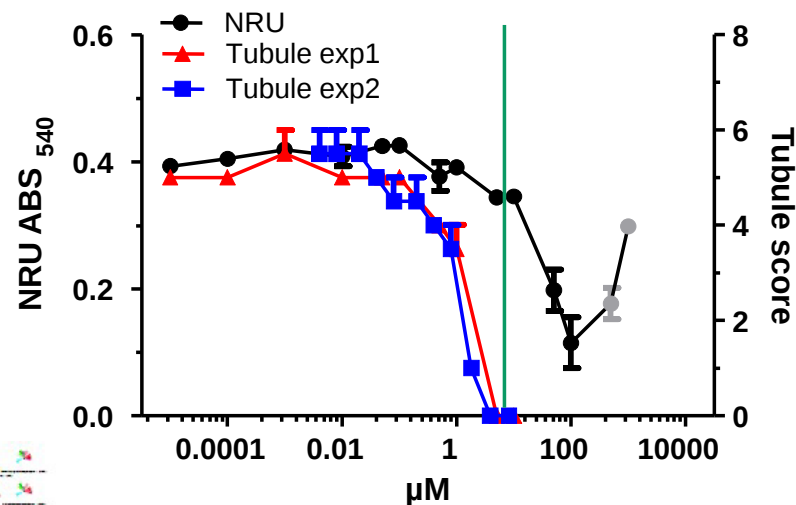


AOP: Embryonic Vascular Disruption Kleinstreuer et al., PLoS Comput Biol 9(4):e1002996, 2013

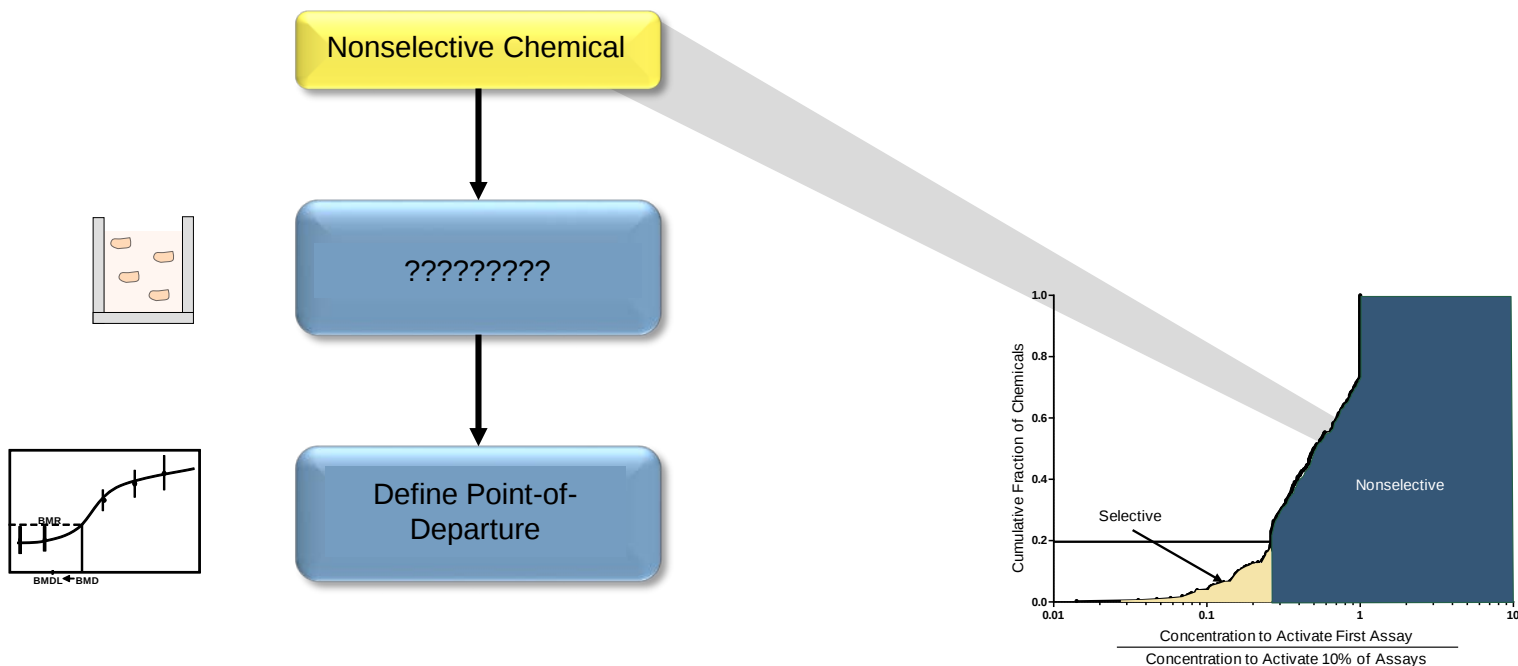


Human Tubulogenesis Assay (FICAM: T Heinonin)

Octyl gallate



What About the Non-Selective Chemicals?

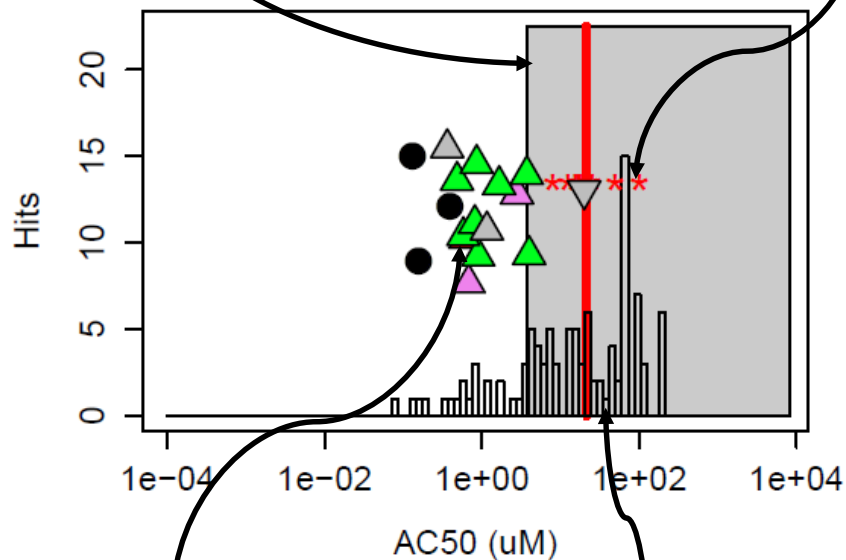


Non-Selectivity Closely Aligned with Cytotoxicity

Cytotoxicity Region

Cytotox assays

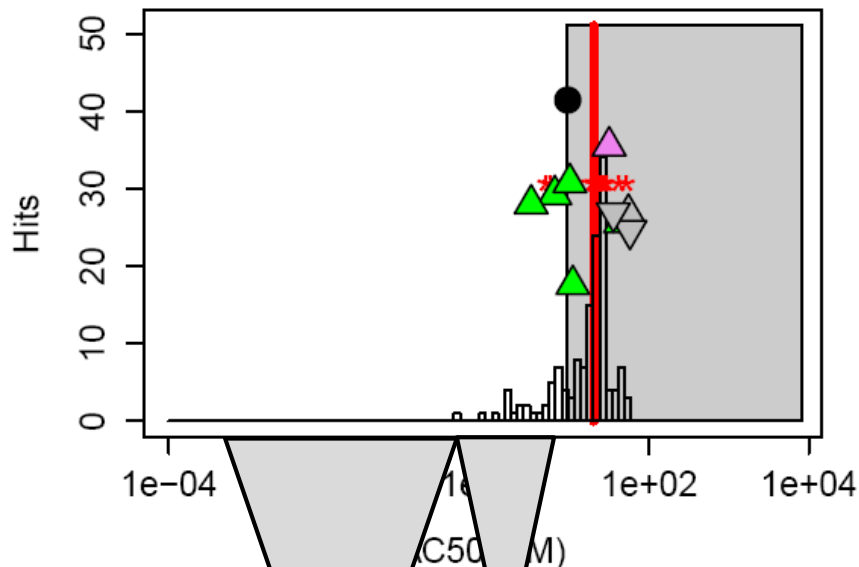
80-05-7 : Bisphenol A



AC50s for
ER assays

Histogram
counting hits

1034-01-1 : Octyl gallate

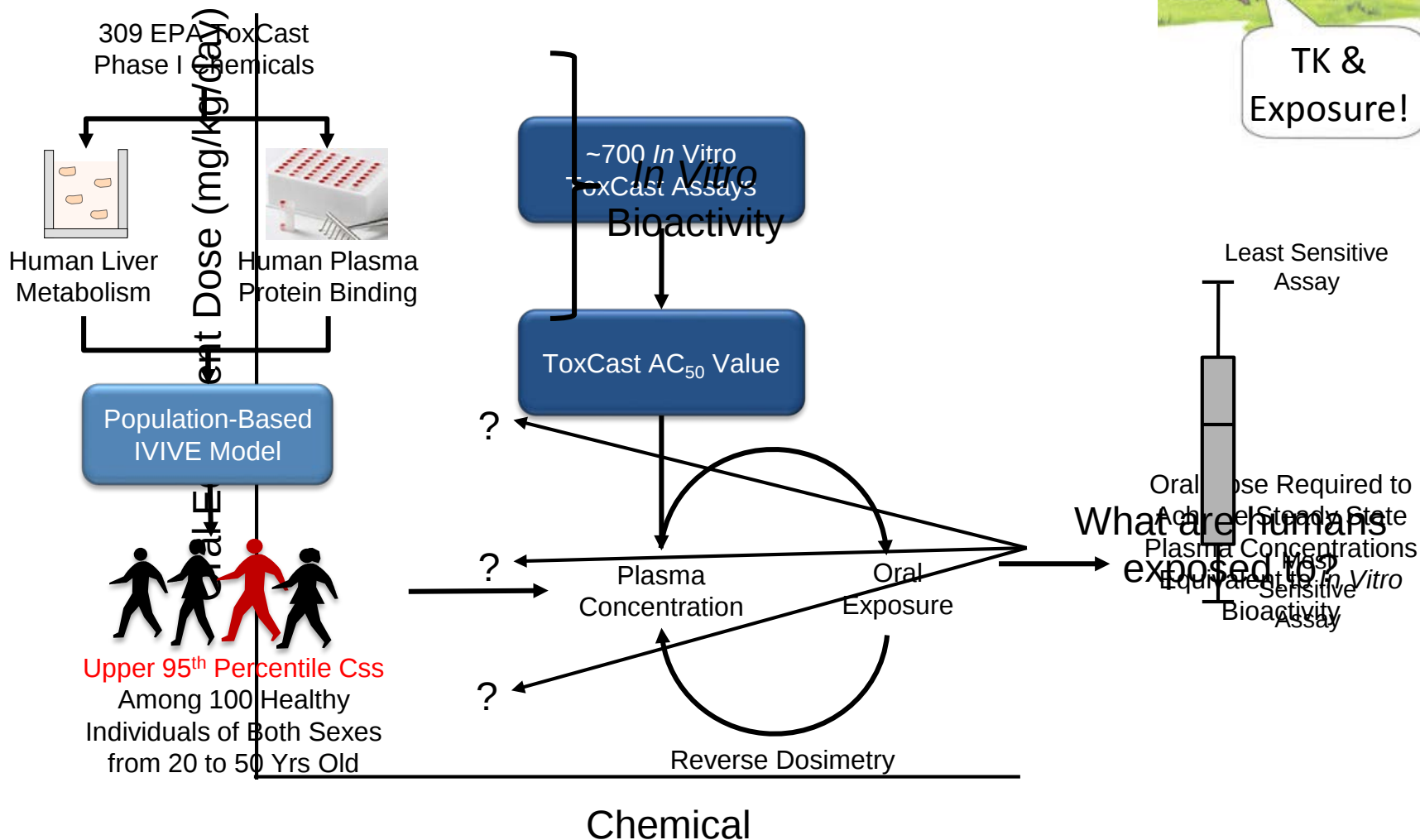


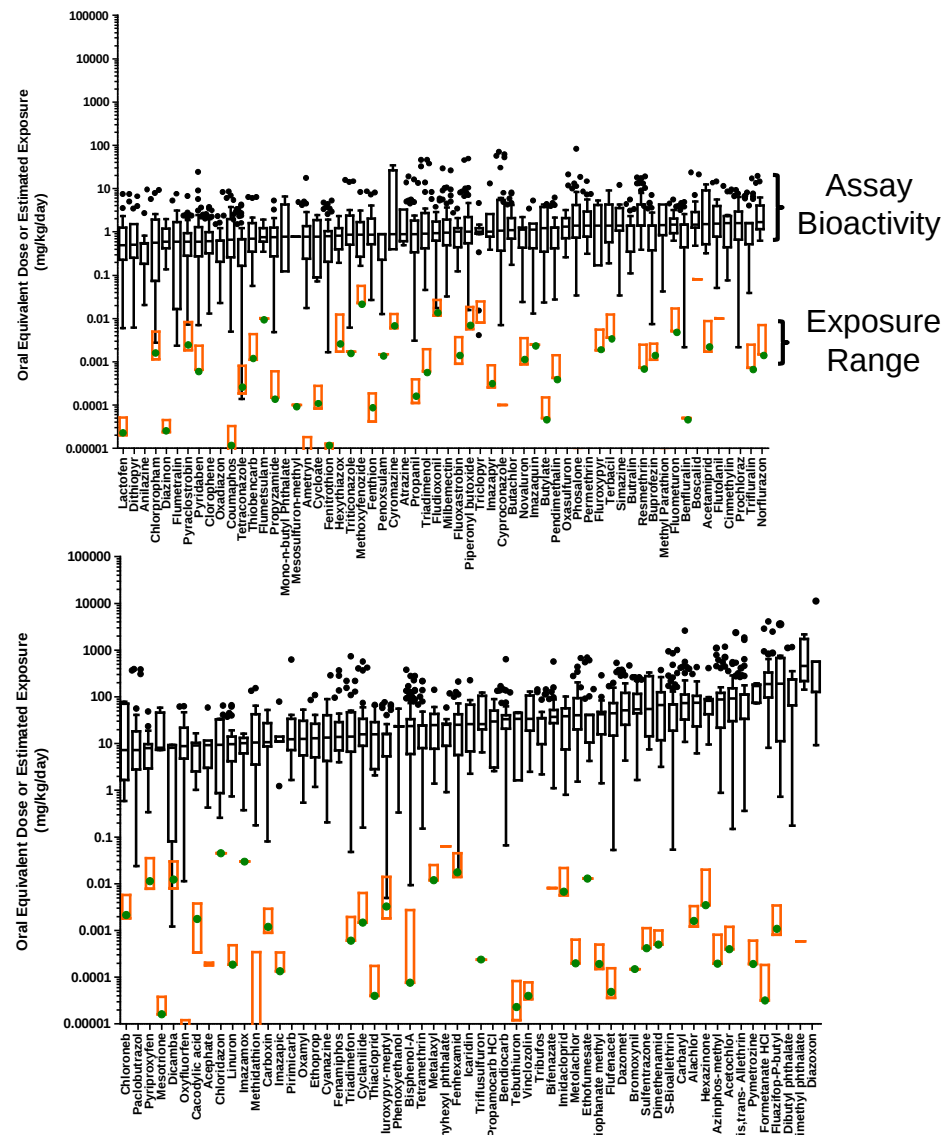
Only region of concentration range
getting hit in biological activity tests
activity/cytotoxicity

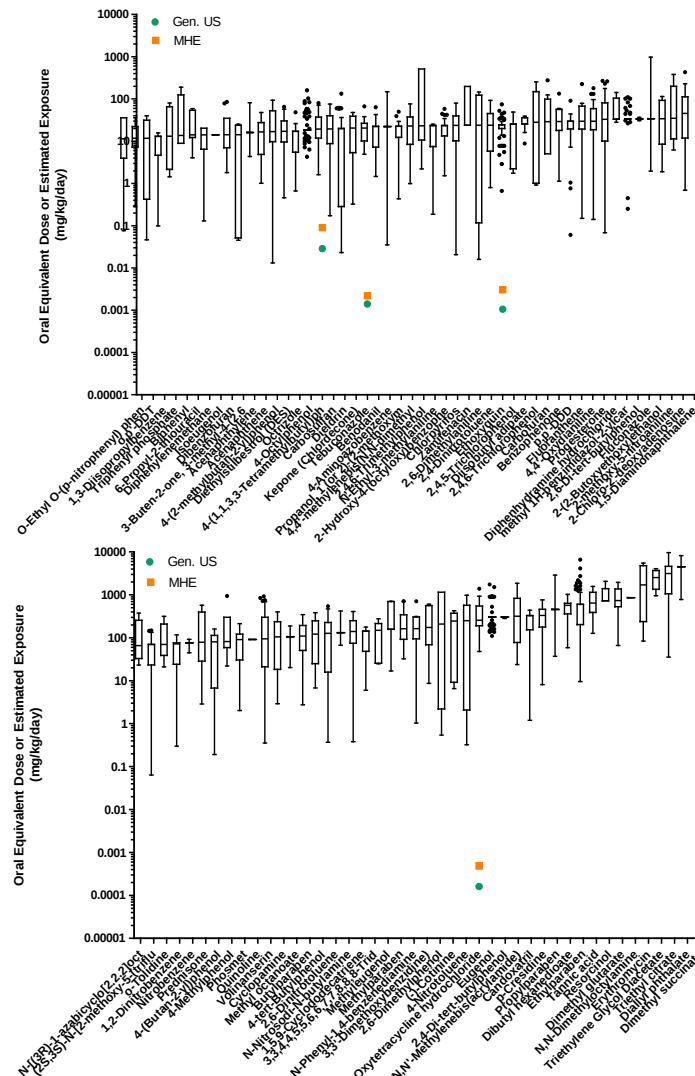
TK & Exposure Are Other Parts of the Elephant...



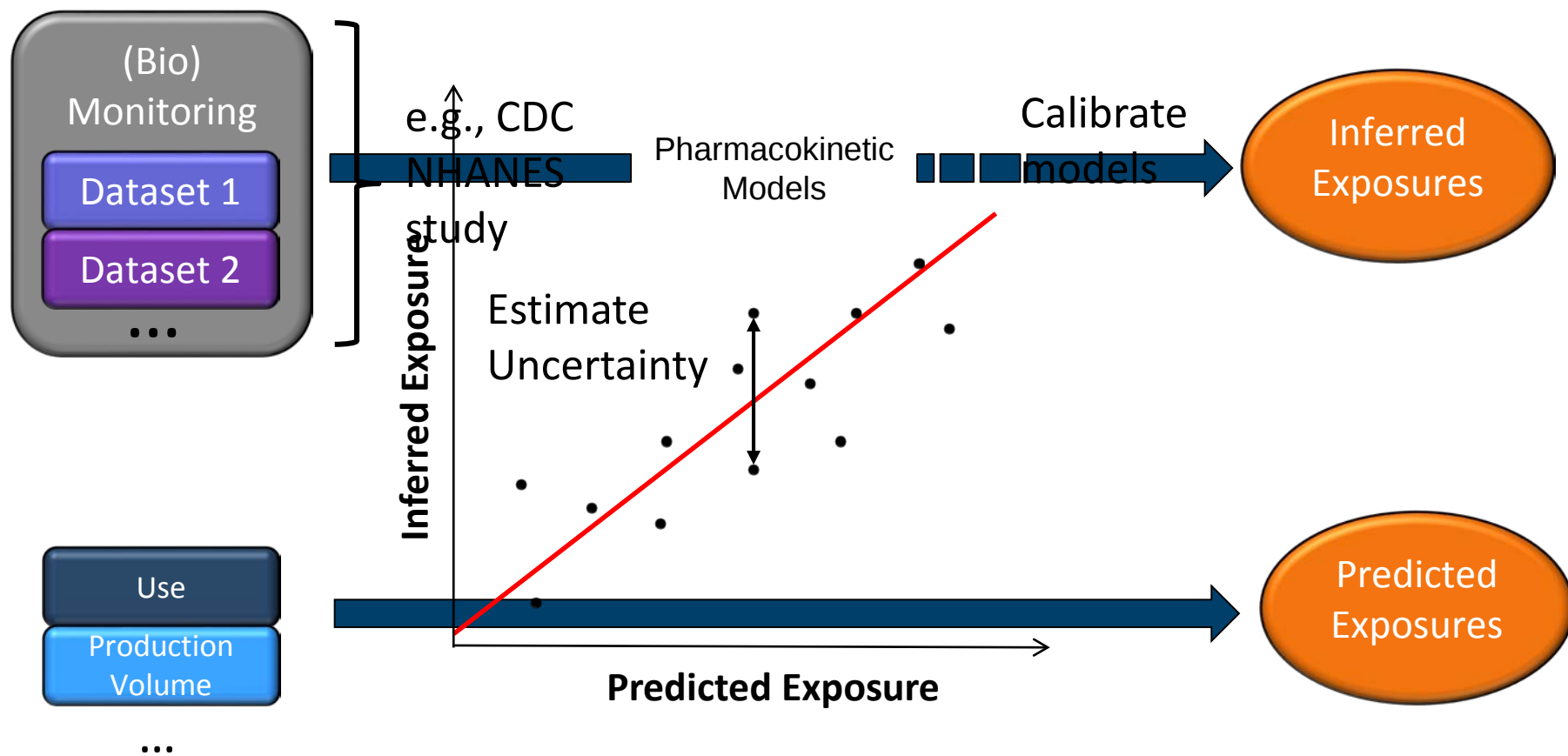
TK & Exposure!



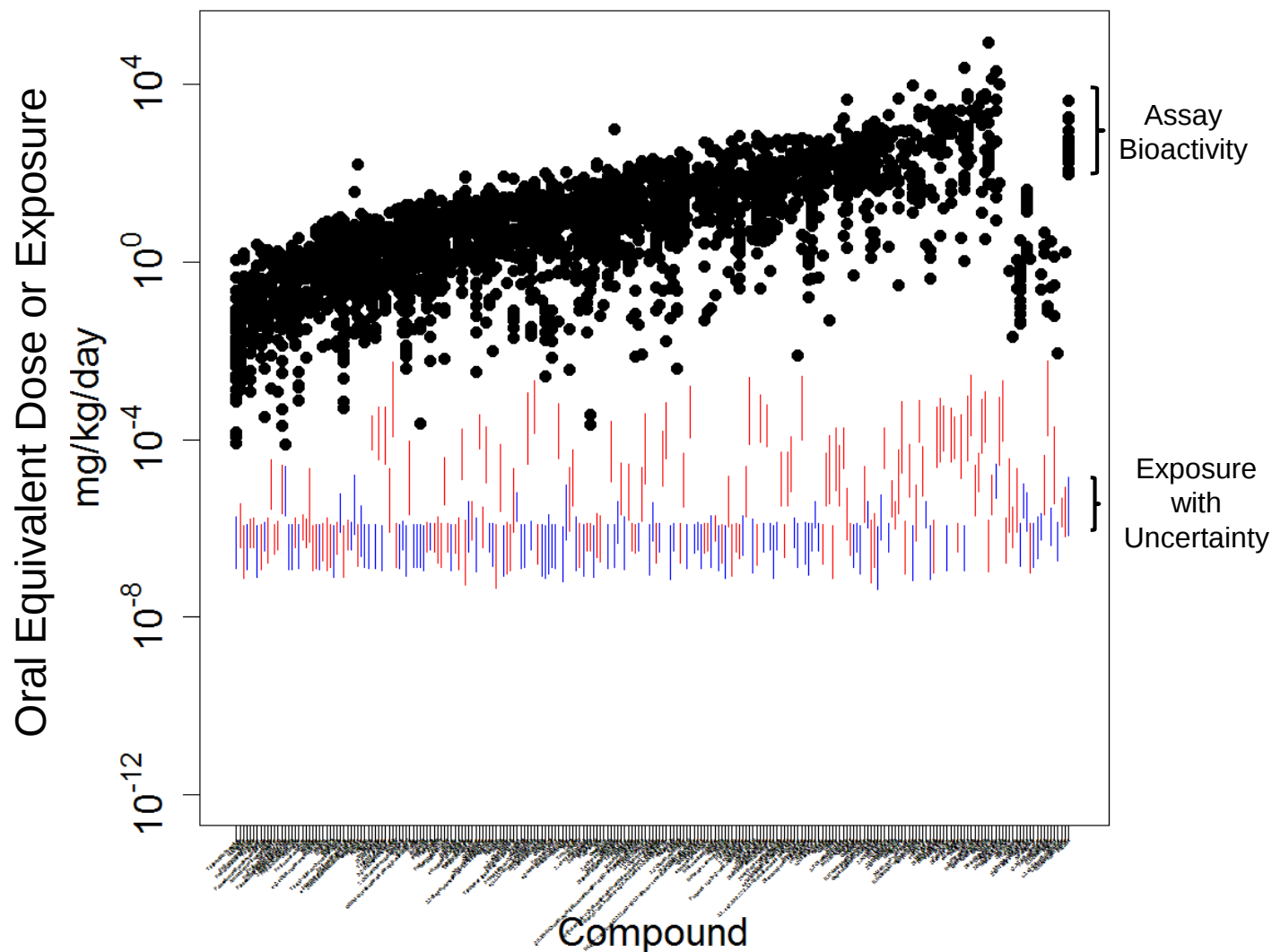




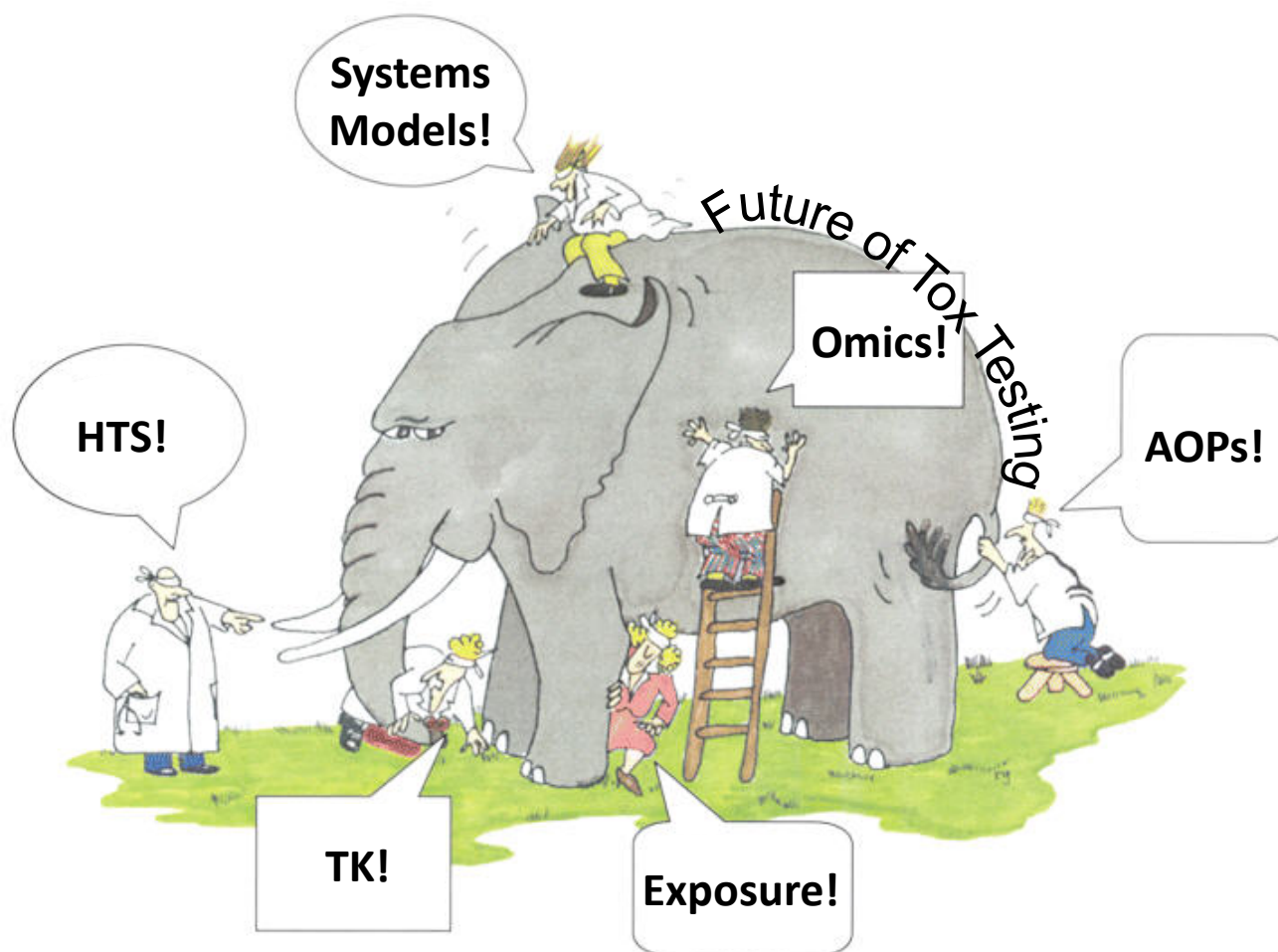
High-Throughput Exposure Models Filling Critical Data Gaps



Activity and Exposure Allow Robust Prioritization of Chemicals



Future of Tox Testing Will Require Integrating HTS with Other Data



Application to Regulatory Decisions

Integrated Bioactivity and Exposure Ranking

*Integrated Bioactivity and Exposure Ranking:
A Computational Approach for the
Prioritization and Screening of Chemicals in
the Endocrine Disruptor Screening Program*

U.S. Environmental Protection Agency
Endocrine Disruptor Screening Program

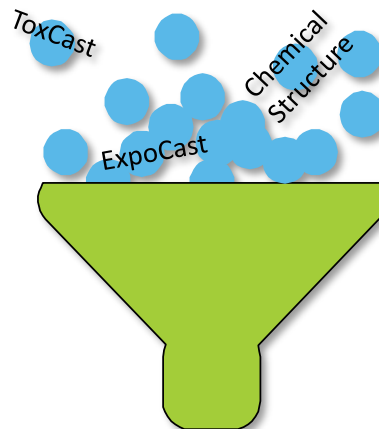
Jointly developed by:

U.S. EPA Office of Chemical Safety and Pollution Prevention (OCSPP)
U.S. EPA Office of Research and Development (ORD)
U.S. EPA Office of Water (OW)

NIH National Toxicology Program Interagency Center for the Evaluation of
Alternative Toxicological Methods (NICEATM)

FIFRA SAP December 2-5, 2014

Prioritization and Screening in EDSP



RapidTox Assessment

 Chemical X SAR/QSAR Estimated Toxicity Value (mg/kg/d) In Vitro Assay Estimated Toxicity Value (mg/kg/d) Estimated Exposure (mg/kg/d)	Physical Chemical Properties			
	MW	MP	pKa	
	BP	VP	LogP	
	Supporting Literature • Lambert et al. Toxicol R Us 88(15):358, 2012 ◦ Summary - This chemical causes toenail dysplasia			

Development of Lower-Tier Assessment
Products for Data Poor Chemicals

Acknowledgements

Tox21 Colleagues:

NTP Crew

FDA Collaborators

NCATS Collaborators

ORD Colleagues:

NERL

NHEERL

NCEA



EPA's National Center for Computational Toxicology