United States Environmental Protection Agency

EPA's CompTox Program – Current and Future Research

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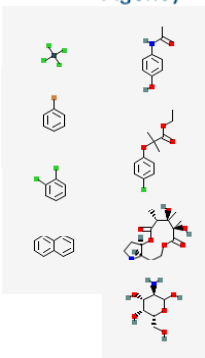
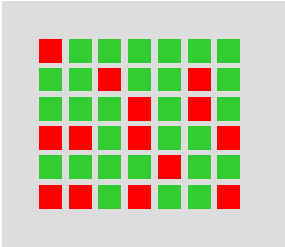
National Center for Computational Toxicology

SAB
May 2012

EPA CompTox Research

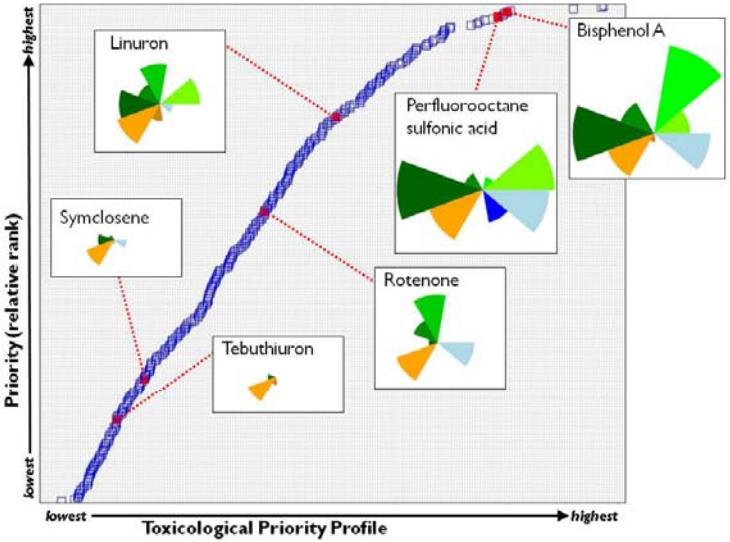


Thousands of chemicals



High throughput biology and chemistry

Bioinformatics/ machine Learning



Predictive toxicology and exposure science

Benefits

-Less expensive
-More chemicals
-Fewer animals
-Solution Oriented

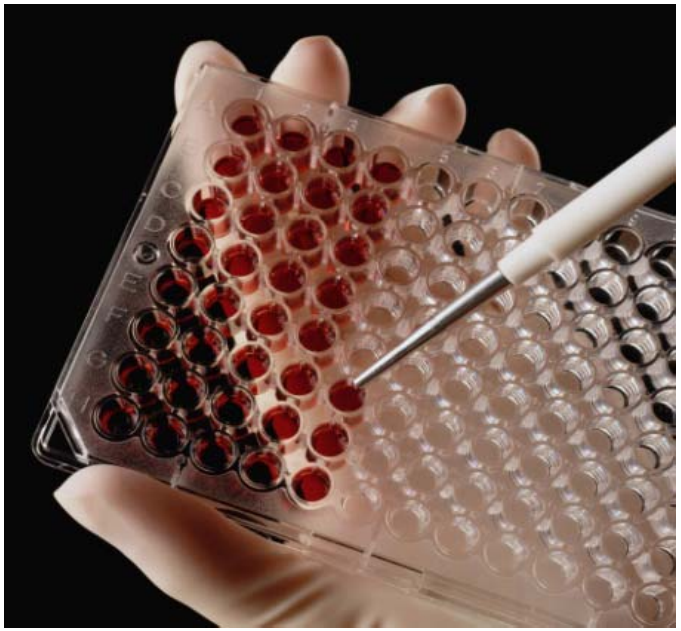
-Innovative
-Multi-disciplinary
-Collaborative
-Transparent

United States Environmental Protection Agency

Focusing on Current and Future Applications of CompTox Tools

- Prioritization of chemicals based on high throughput biological and chemical profiling
- Targeted testing based on outcomes from predictive computational models
- Replacing traditional (in vivo) testing using quantitative Adverse Outcome Pathways

CompTox Research in Chemical Safety for Sustainability (CSS)



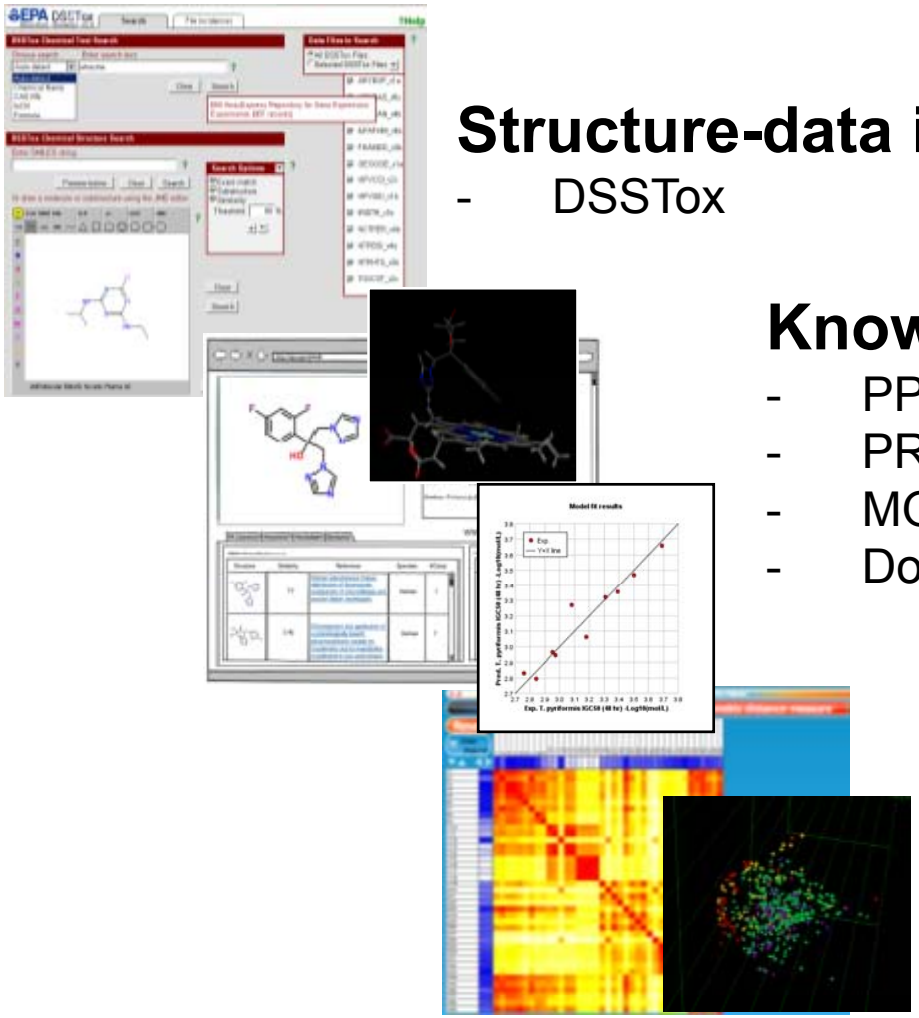
8 Research Themes

- Chemical Inherency → CompTox
- Systems Models → CompTox
- Biomarkers
- Cumulative Risk
- Life Cycle Considerations
- Extrapolation
- Dashboards → CompTox
- Evaluation

CSS Research Theme: Inherent Chemical Properties

- Inherency includes
  - chemical characterization
  - data storage
  - model development and improvement
- Chemical structure-based tools
  - DSSTox, PPC (w/in EFS), MOA profiler, PReParE, DockScreen
  - Analysis of models and chemical domains
- Outputs and linkages
  - Systems (human health & eco)
  - Screening & Prioritization (exposure, effects, toxicity, etc.)
  - Dashboards (data input streams)
- Partners
  - Programs and Regions
  - ORD/NCCT, NERL, NRMRL

Overview of Inherency Tools



Structure-data inventory

- DSSTox

Knowledge base (models)

- PPC within the EFS
- PReParE
- MOA QSAR/profiler
- DockScreen

Chemoinformatics & Analysis

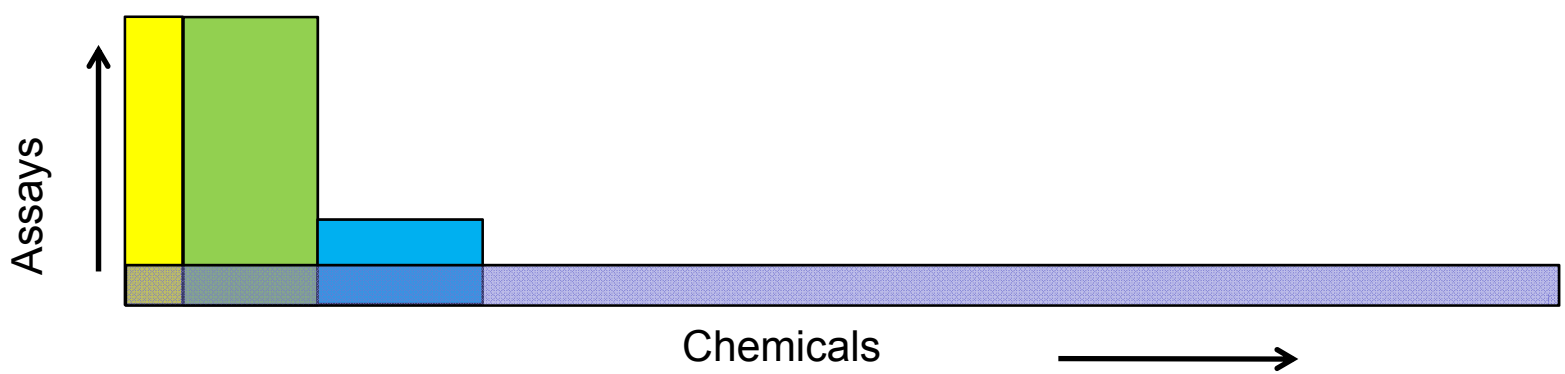
- Identify *similarity* – i.e., nearest neighbor chemicals (surrogates)
- Identify *diversity* – coverage of chemicals
- Model *relevance* – applicability domain

CSS SYSTEMS MODELS

Project	Title	
1	Systems-level approach to adverse outcome pathway (AOP) discovery and application	
2	Systems modeling of specific tissues and multi-organ pathways	⇐ Virtual Liver, Virtual Embryo [NCCT, NCEA, NCER, NERL, NHEERL]
3	Metrics and models that define chemical exposures and internal dose	
4	Systems approaches to assess human and ecological risks	
5	Screening and prioritization for exposure and adverse outcomes	⇐ ToxCast, ExpoCast [NCCT, NERL, NHEERL]
6	An integrated systems approach to assess and predict the toxicity of engineered nanomaterials and their applications	⇐ ToxCast [NCCT, NHEERL]

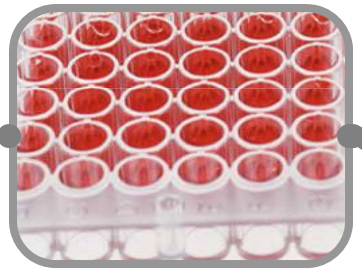
ToxCast: High-Throughput Screening and Prioritization

Set	Chemicals	Assays	Endpts
ToxCast Phase I	293	~600	~1100
ToxCast Phase II	767	~600	~1100
E1K (endocrine)	880	~50	~120
Tox21	8,193	~25	~50

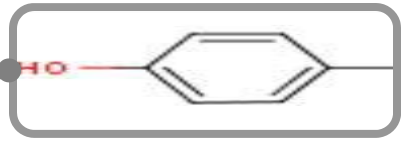


High Throughput Screening 101 (HTS)

Robots

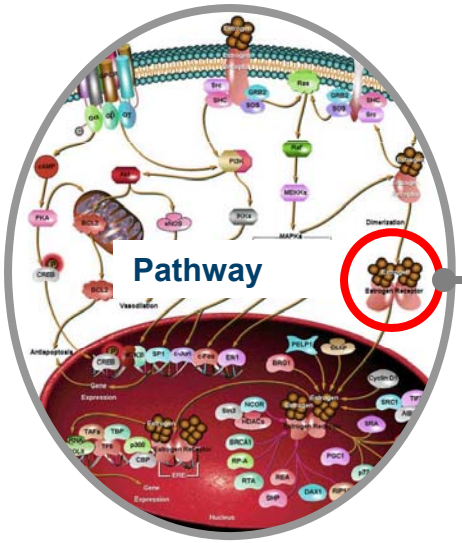


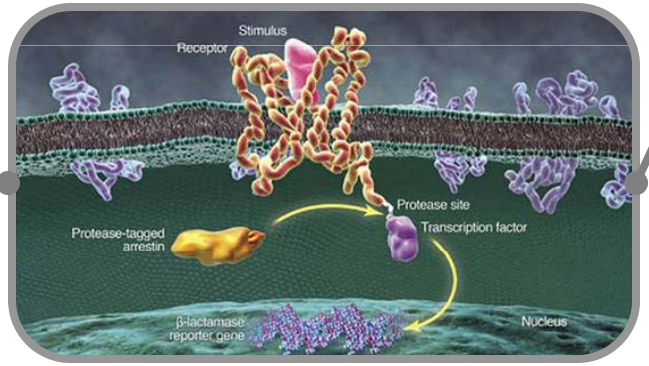
96-, 384-, 1536 Well Plates



Chemical Exposure

Cell Population

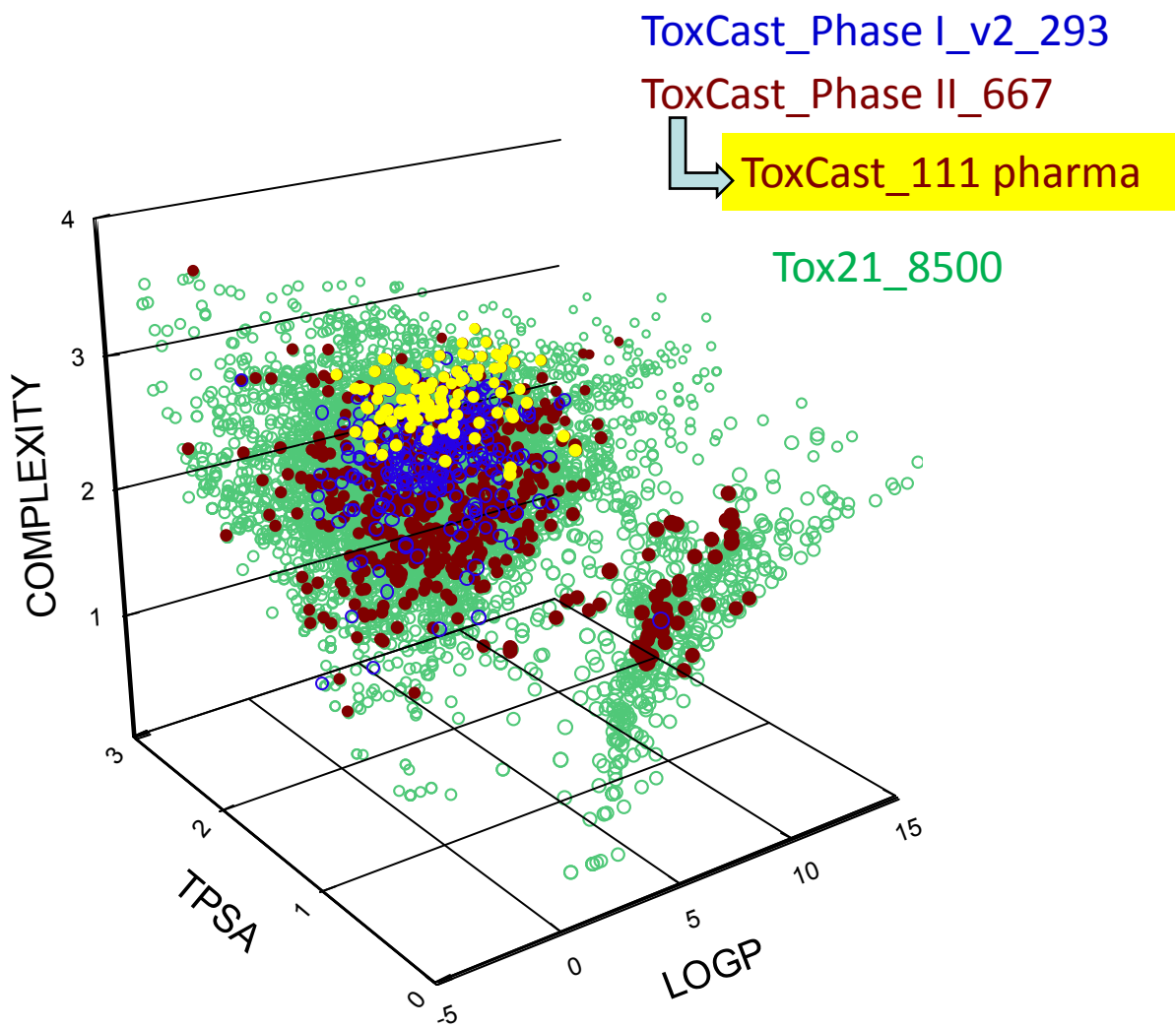




Target Biology (e.g., Estrogen Receptor)

ToxCast Chemical Property Dimension

- LOG P = octanol/water partition coefficient
- TPSA = log (Total Polar Surface Area)
- Complexity = log (complexity based on paths, branching, atoms)



ToxCast HTS Assay Overview (>1100 Assay Endpoints/Readouts)

Assay Source (14)
ACEA
Appredica
Attagene
BioSeek
CellzDirect
NCGC/Tox21
NHEERL MESC
NHEERL NeuroTox
NHEERL Zebrafish
Novascreen
Odyssey Thera

Readout Type
Single
Multiplexed
Multiparametric

Cell Format (4)
Cell line (6)
Primary Cell (3)
Cell-Free
Cell-Based

Organism (9)
Human
Rat
Mouse
Zebrafish
Sheep
wild boar
Rabbit
Cattle
guinea pig

Tissue
Lung Breast
Liver Vascular
Skin Kidney
Cervix Testis
Uterus Brain
Intestinal Spleen
Bladder Ovary
Pancreas Prostate
bone

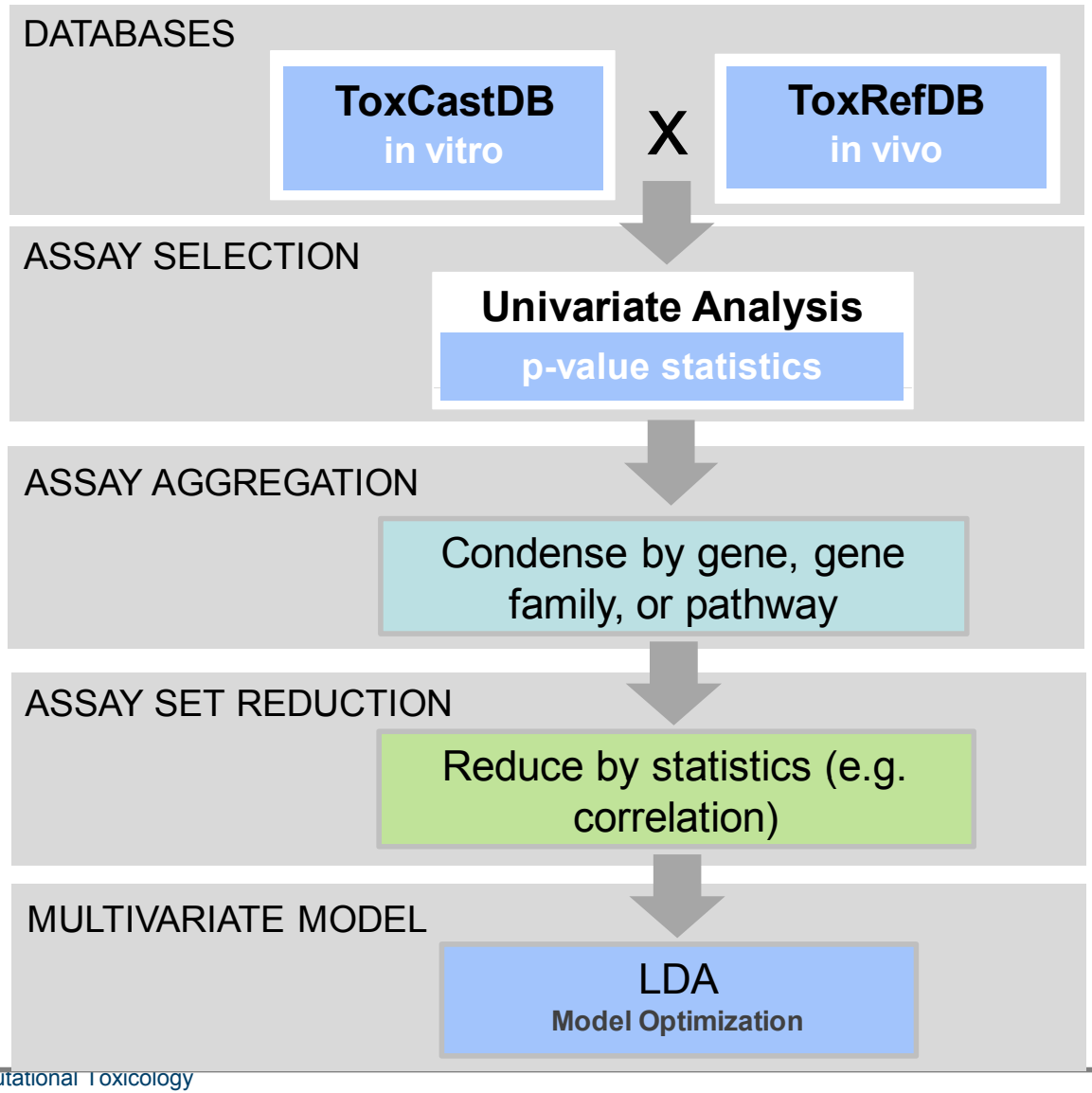
Biological Process Target
Cell Proliferation
cell death
mitochondrial depolarization
protein stabilization
oxidative phosphorylation
regulation of TF activity
regulation of gene expression
receptor activity
receptor binding

Target Family
Response Element
Transporter
Cytokines
Kinase
Nuclear Receptor
CYP
Cholinesterase
Phosphatase
Protease
Metabolism
GPCR
Ion Channel

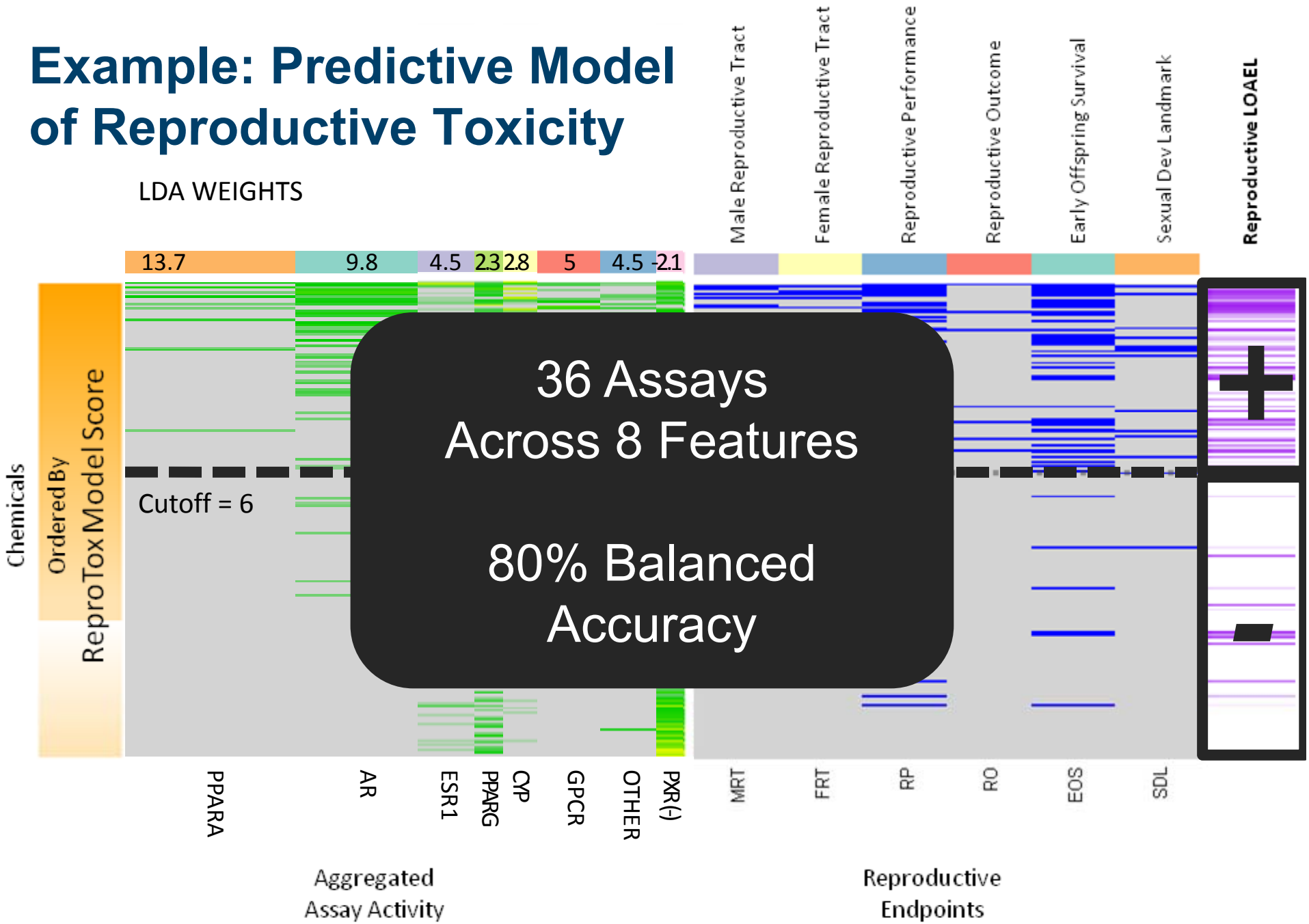
Detection Technology
RT-CES
Fluorescence
ELISA
Alamar Blue Reduction
Microscopy
Reporter gene
Spectrophotometry
Radioactivity
HPLC
TR-FRET
Fluorescence Polarization
Luminescence
Protein-fragment
Complementation

Assay Design Type
viability reporter
morphology reporter
conformation reporter
enzyme reporter
membrane potential reporter
binding reporter
inducible reporter

Predictive Model Development from ToxCast and Other Data



Example: Predictive Model of Reproductive Toxicity



36 Assays
Across 8 Features

80% Balanced
Accuracy

Martin et al Biology of Reproduction 2011

Predictive Toxicity Modeling Based on ToxCast Data

- **Predictive models: endpoints**

  liver tumors: Judson et al. 2010, Env Hlth Persp 118: 485-492
  hepatocarcinogenesis: Shah et al. 2011, PLoS One 6(2): e14584
  cancer: Kleinstreuer et al. 2012, submitted
  rat fertility: Martin et al. 2011, Biol Reprod 85: 327-339
  rat-rabbit prenatal devtox: Sipes et al. 2011, Toxicol Sci 124: 109-127
  zebrafish vs ToxRefDB: Sipes et al. 2011, Birth Defects Res C 93: 256-267

- **Predictive models: pathways**

  endocrine disruption: Reif et al. 2010, Env Hlth Persp 118: 1714-1720
  microdosimetry: Wambaugh and Shah 2010, PLoS Comp Biol 6: e1000756
  mESC differentiation: Chandler et al. 2011, PLoS One 6(6): e18540
  HTP risk assessment: Judson et al. 2011, Chem Res Toxicol 24: 451-462
  angiogenesis: Kleinstreuer et al. 2011, Env Hlth Persp 119: 1596-1603

- **Continuing To Expand & Validate Prediction Models**
- **Generally moving towards more mechanistic/AOP-based models**

ExpoCast: Exposure Science in the 21st Century

Goal: provide a high-throughput analog to ToxCast hazard identification

EPA Case Studies:

TSCA21:
Prioritization of approximately ~500 Toxic Substances Control Act (TSCA) chemicals

EDSP21:
Prioritization of ~2000 Endocrine Disruptors Screening Program (EDSP) chemicals based on endocrine disrupting potential

OW21:
Support future CCL development

Using high-throughput fate and transport models – predict the contribution from industrial use to overall exposure

Developing new models of consumer use

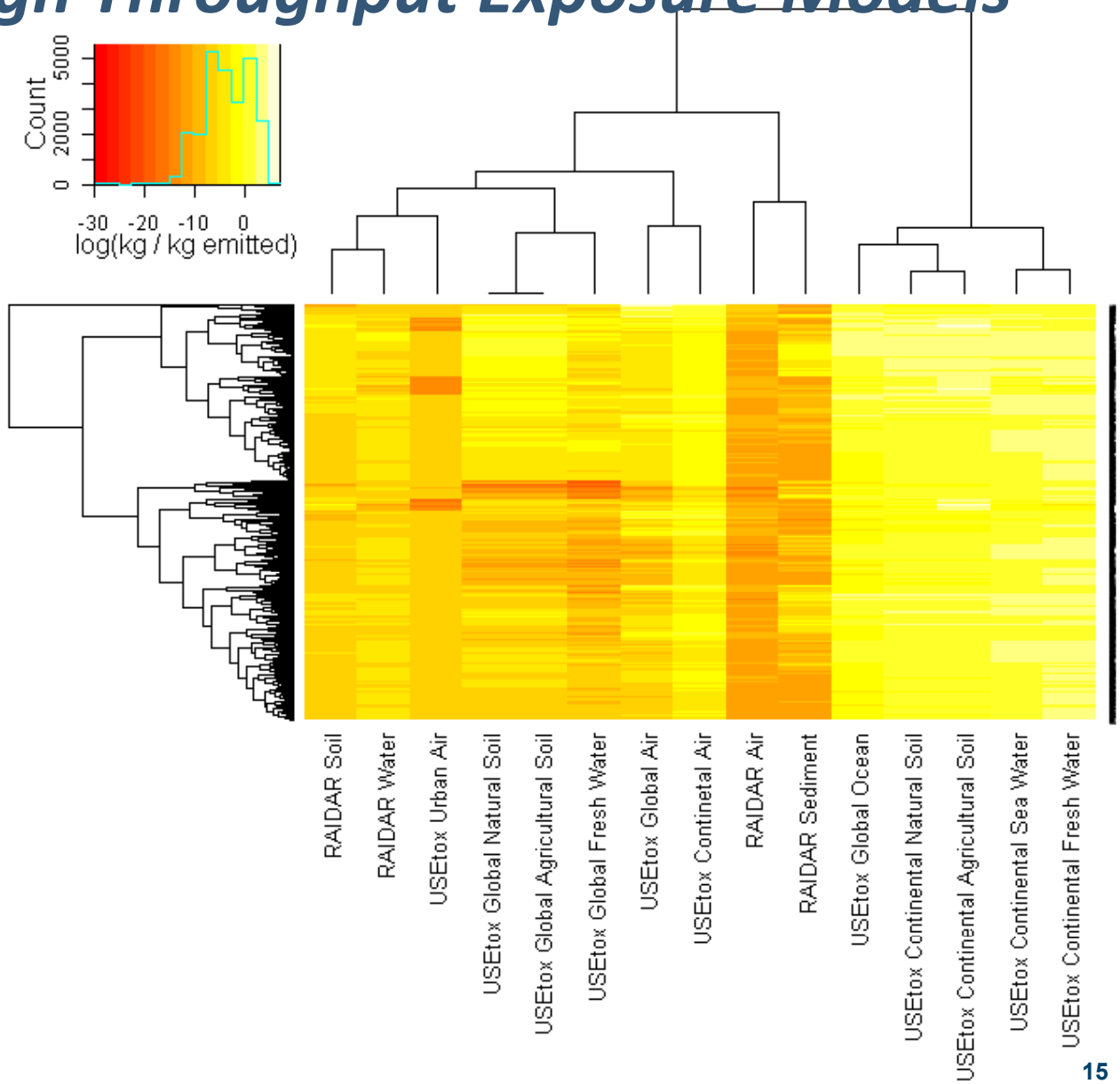
ExpoCast: High Throughput Exposure Models

Exposure-based prioritization challenge identified two models capable of high throughput operation (RAIDAR, USETOX)

Models predict partitioning into environmental media, and describe human interaction with that media

Treat different models like related high-throughput assays

Need to validate with biomonitoring data

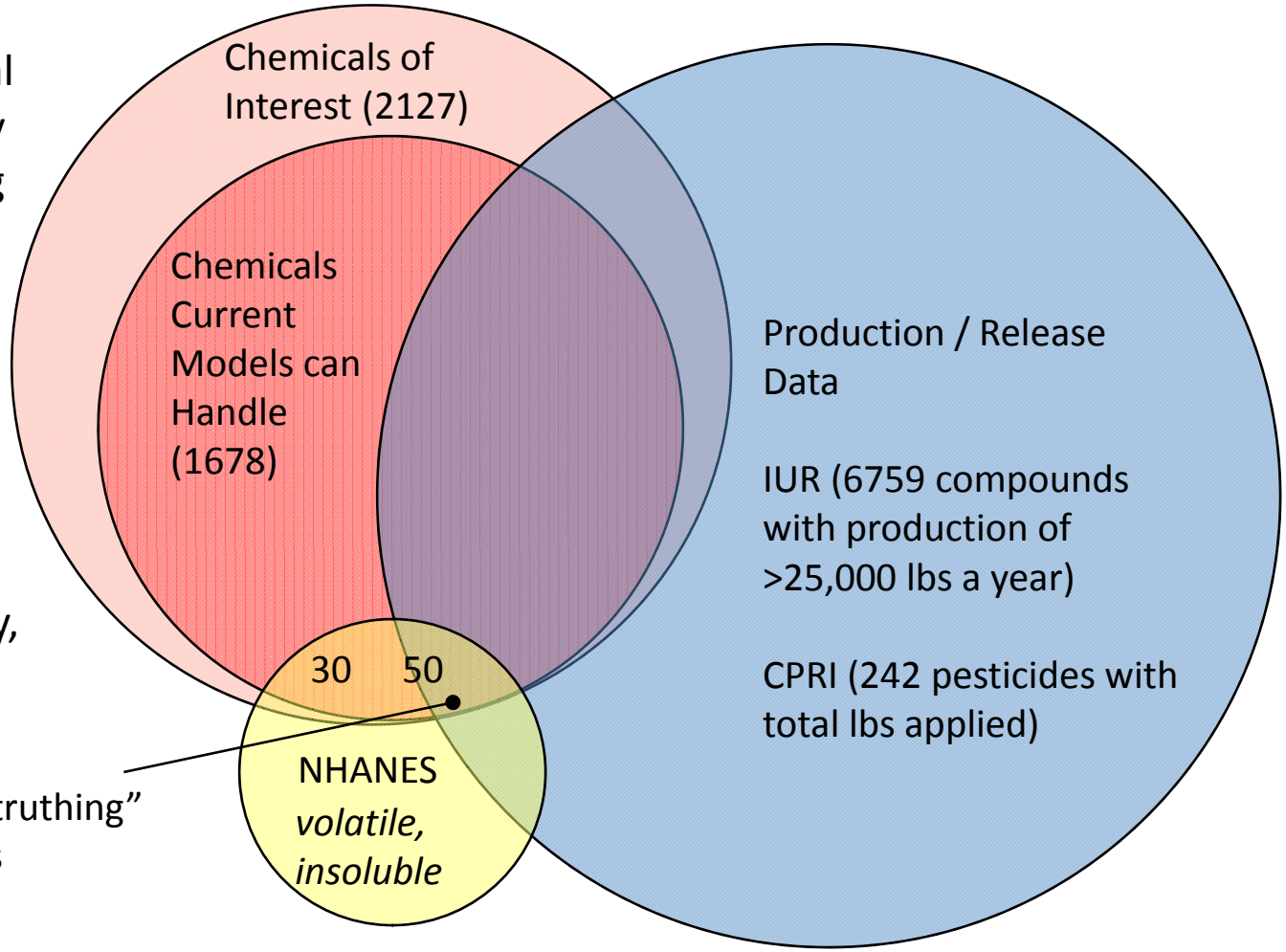


ExpoCast Chemical Domains

CDC reports chemical concentrations every two years for varying demographics (> 6 years in age)

Focusing on U.S. median initially

Capable of adding population variability, but will need consumer use models



CSS Systems Models: Virtual Tissues

Systems modeling is a major CSS research theme

"Use a systems-based research approach, aligned with the National Research Council's vision and strategy for toxicity testing in the 21st century, to advance scientific knowledge and predictive tools to effectively use mechanism-based biological endpoints and data in chemical safety assessments concerned with human health and/or ecosystem sustainability."

Virtual Tissues Predictive models of chemical-induced disruption of normal functions

- Virtual Liver
- Virtual Embryo
- Virtual Endocrine System

Virtual Tissues Goals

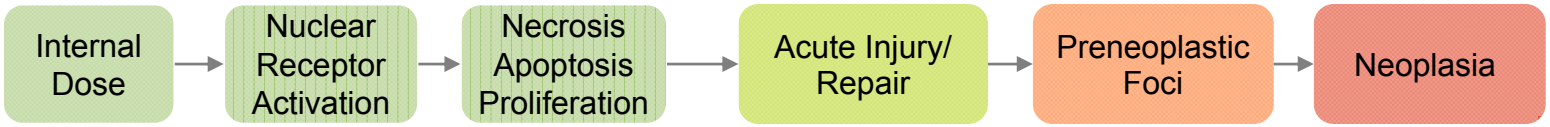
- Elucidate adverse outcome pathways (AOPs) – leverage *in vitro* data
- AOP-driven data collection - toxicokinetics and dynamics
- Quantitative computational predictive models of AOPs

Virtual Liver Goals

- Address research issues in screening, targeted testing and dose-response estimation of hepatic effects
- Produce decision support tools to more effectively
  - Prioritize hepatotoxicants
  - Estimate tissue dosimetry
  - Quantitatively estimate chemical-induced [chronic] liver injury
- Produce experimental models/data to reduce uncertainty
  - Absorption, distribution, metabolism and excretion (ADME)
  - Molecular, cellular and tissue level effects

v-Liver

- Identify key hepatic AOPs of environmental relevance



- Knowledgebase of hepatic AOPs
- Predictive model of dosimetry
  - Microdosimetry in Virtual Lobule (Wambaugh 2010)
  - Experimental data: ToxCast, Hamner, EPA/NERL
- Predictive model of cell phenotypes
  - Signaling cross-talk network model (Jack *et al,* 2011)
  - Experimental data: ToxCast, In-life technologies, EPA/NHEERL, JRC
- Predictive model of tissue-effects
  - Integrated agent-based model
  - Experimental data: ToxCast, EPA/NHEERL, JRC

Virtual Embryo: systems models linking HTS data with adverse outcome pathways

HTS/HCS data and predictive signatures

biological architectures and system dynamics

surrogates for missing or incomplete information

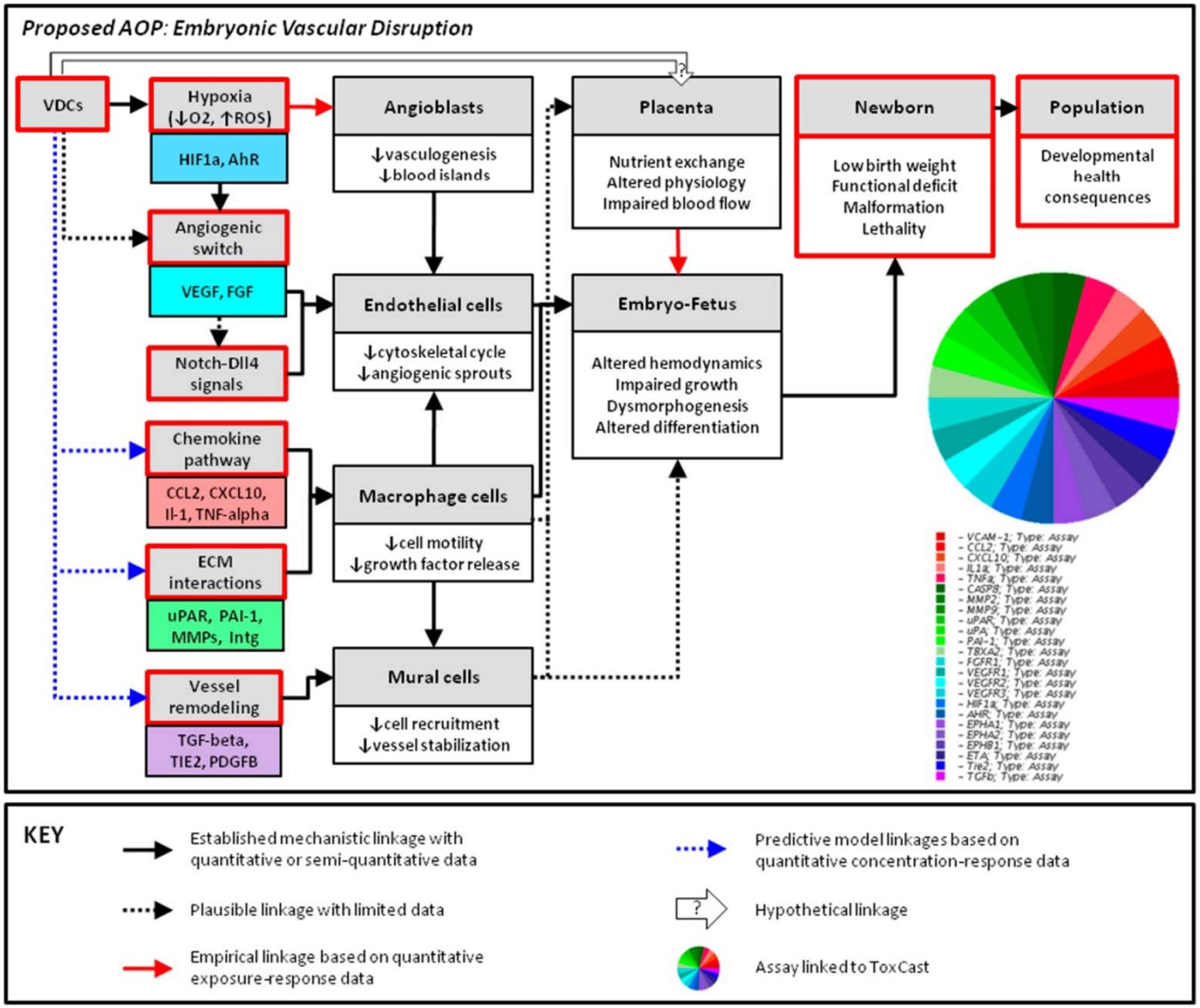
integration of adverse outcome pathways

A computer simulation of normal development (Virtual Embryo) can predict adverse prenatal outcome

v-Embryo™

http://www.epa.gov/ncct/v-Embryo/

V-Embryo Adverse Outcome Pathway (AOP)



SOURCE: Knudsen and Kleinstreuer (2011) Birth Defects Res. C, 93

Dashboards for Decision Support

- Supporting current in-use computational tools and databases
  - ECOTOX, ACToR, ToxRefDB, ToxCastDB, MetaPath, DER Composers

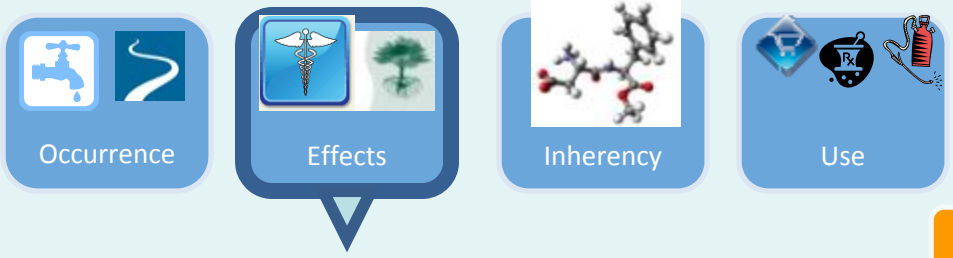
- Developing new systems to support program office decision-support needs
  - Prioritization tools for OSCP, OPPT, OPP, OW, NCEA

Dashboards Key Points

- Encompasses:
  - Computational tools
  - Databases
  - Web sites
- Goal is to make ORD research results readily available to decision-makers
  - EPA Programs and Regions
  - External stakeholders
- Dashboard projects are not stand-alone
  - Integrate outputs from across CSS and ORD research projects

DASHBOARD

DATA SELECTION



HOME

Effects

Health

In vivo

In vitro

Ecological

In vivo

In vitro

OTHER

SELECT

DESELECT

Chemical	E	A	I	U
Atrazine	↑		-	
Bisphenol A	↑	↓	-	-
Triadimefon	-		-	
Imazalil	↑		-	-
Fipronil	-	↓	-	
Propiconazole	-	-	-	-
PFOA	↑	-	-	-
PFOS	↑	-		
DEHP		↓		
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Chemical…500				

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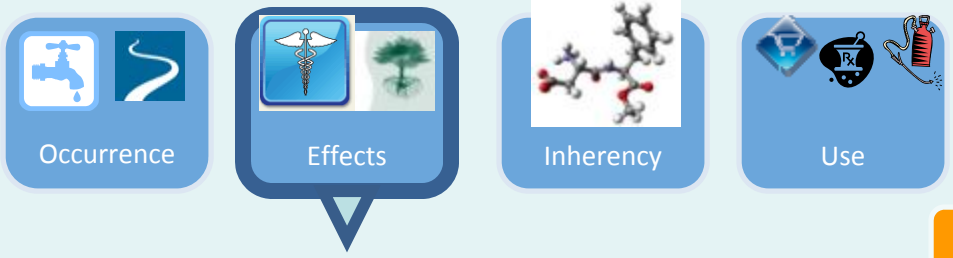
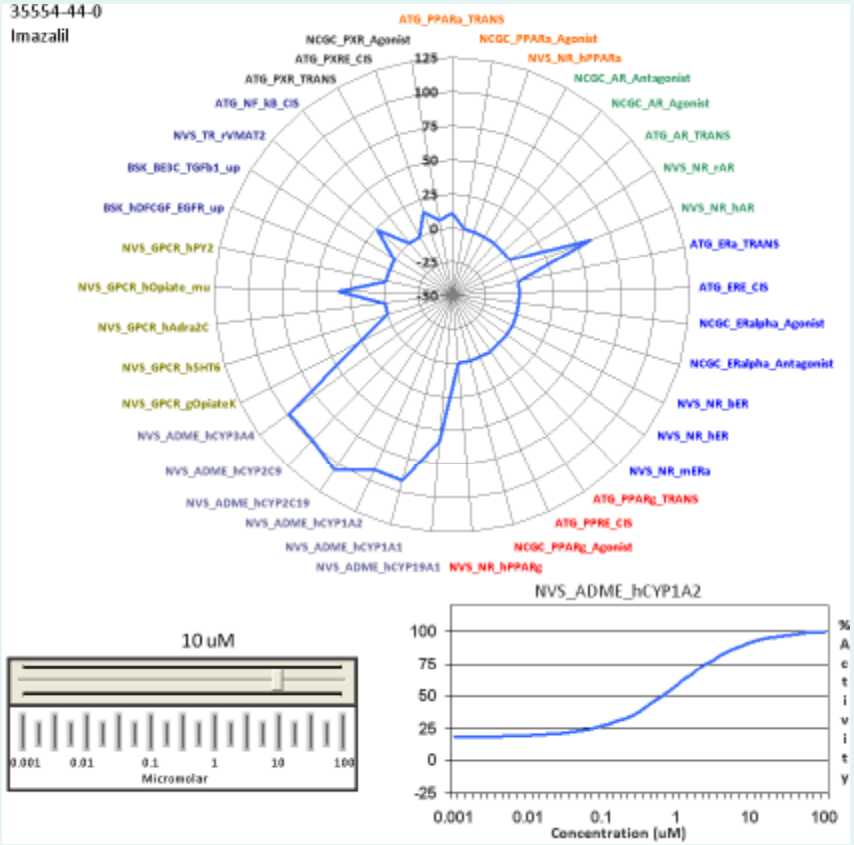
DASHBOARD

CHEMICAL PAGE



HOME



Chemical	E	A	I	U
Atrazine	↑		-	
Bisphenol A	↑	↓	-	-
Triadimefon	-		-	
Imazalil	↑		**-**	**-**
Fipronil	-	↓	-	
Propiconazole	-	-	-	-
PFOA	↑	-	-	-
PFOS	↑	-		
DEHP		↓		
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Chemical…500				

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CSS Dashboards for FY12 / 13

- EDPS21 – Provide tools to prioritize chemicals for EDSP Tier 1 testing
- OW21 – Support prioritization around the CCL process
- TSCA21 –Support prioritization built around OPPT's *TSCA Workplan Chemicals: Methods Document*
- OPP21 – support modeling needs of the pesticides program
- OPP / EFED Uber tool – Supporting ecological risk assessment
- Infrastructure Development
  - Databases and tools to support development of other custom dashboards both inside and external to EPA

Dashboard Summary

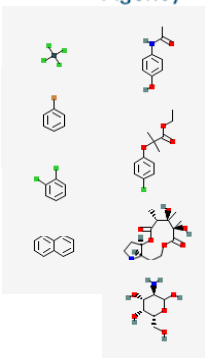
- The Dashboards project's goal is to make ORD science easier to access and use by Programs and Regions

- 2 Main Tracks:
  - Continued support of current, in-use tools
  - Development of custom tools, databases and decision-support systems

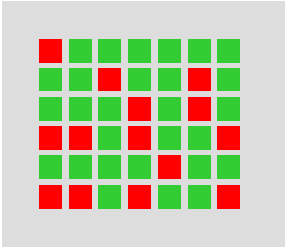
CompTox Communications Strategies

- Media relations
- Fact sheets
- Events
- Social media
- Web
- Communities of Practice
- Asking partners to amplify
- Partner and media database

EPA CompTox Research



Thousands of chemicals



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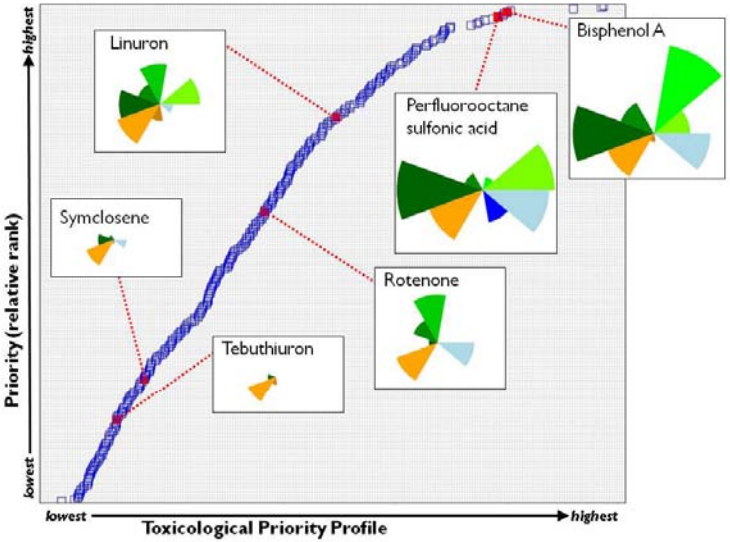

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