

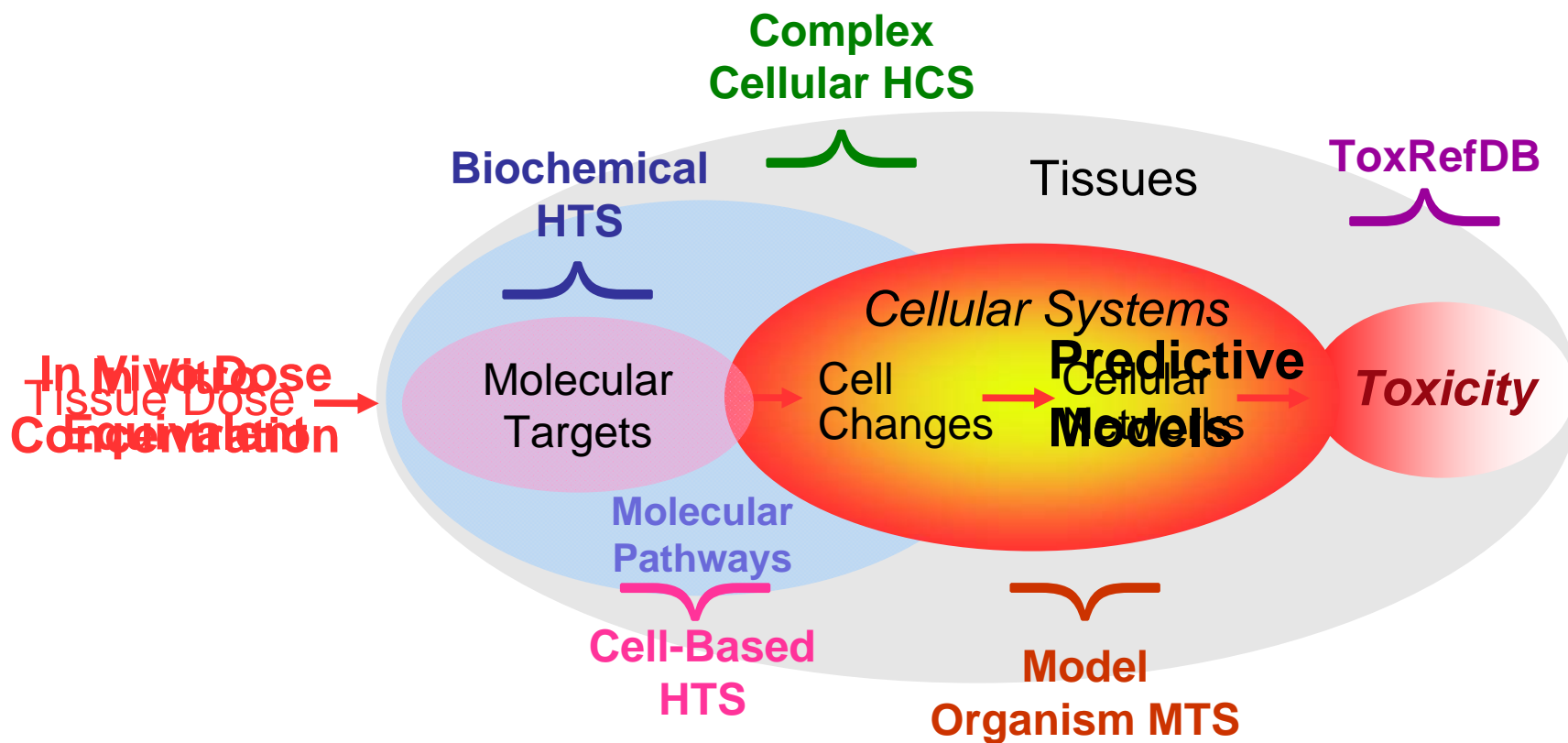
# Overview of the ToxCast™ Research Program: Applications to Predictive Toxicology and Chemical Prioritization

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY



*This work was reviewed by EPA and approved for presentation but does not necessarily reflect official Agency policy.*

# Ultimate Goal of ToxCast: Predicting Human Toxicity



# The ToxCast Program for Prioritizing Toxicity Testing of Environmental Chemicals

## **Key Challenges-**

- **Build chemical library**
- **Control costs**
- **Select assays and pathways**
- **Metabolism**
- **Bioinformatics and modeling**
- **Verify and reduce to practice**



# ToxCast Development Timeline

FY07

FY08

FY09

FY10

FY11

FY12

Proof of Concept: ToxCast Phase I

Verification/Extension: Phase II

Reduce to Practice:  
Phase III

# ToxCast Development

Phase	Number of Chemicals	Chemical Criteria	Purpose	Number of Assays	Cost per Chemical	Target Date
Ia	320	Data Rich (pesticides)	Signature Development	>500	\$20k	FY07-08
Ib	15	Nanomaterials	Pilot	166	\$10K	FY09
IIa	>300	Data Rich Chemicals	Validation	>400	~\$20-25k	FY09
IIb	>100	Known Human Toxicants	Extrapolation	>400	~\$20-25k	FY09
IIc	>300	Expanded Structure and Use Diversity	Extension	>400	~\$20-25k	FY10
IId	>12	Nanomaterials	PMN	>200	~\$15-20K	FY09-10
III	Thousands	Data poor	Prediction and Prioritization	>300	~\$15-20k	FY11-12

January 2009

# ToxCast\_320 Phase I Chemicals

**309 unique structures**

**Replicates for QC**

**8 metabolites**

**291 total pesticide actives**

**273 registered pesticide actives**

**22 pesticide inerts**

**33 antimicrobials**

**56 Tier 1 EDSP**

**23 IUR**

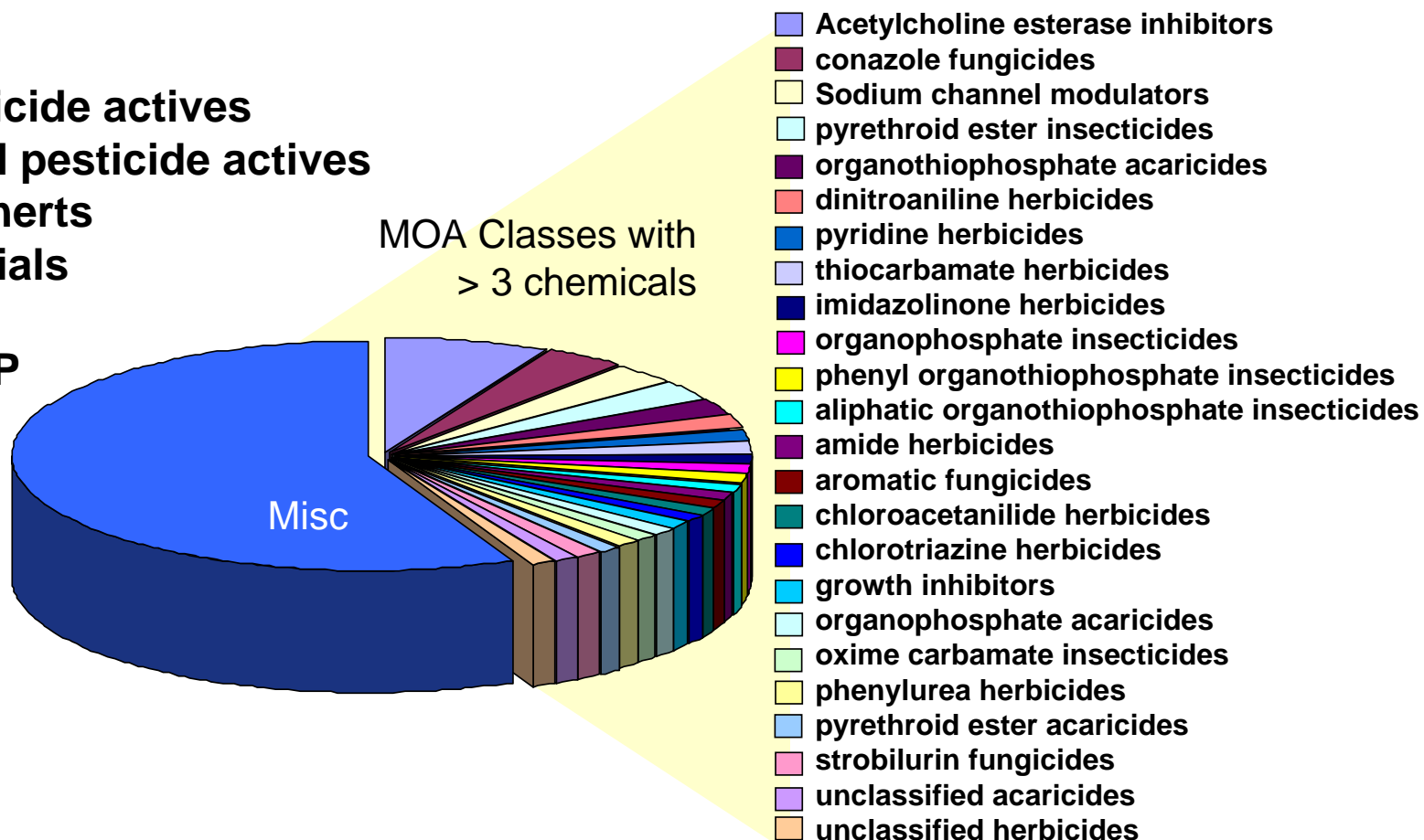
**13 HPV**

**73 OW PCCL**

**11 CCL1**

**10 CCL2**

**25 CCL3**

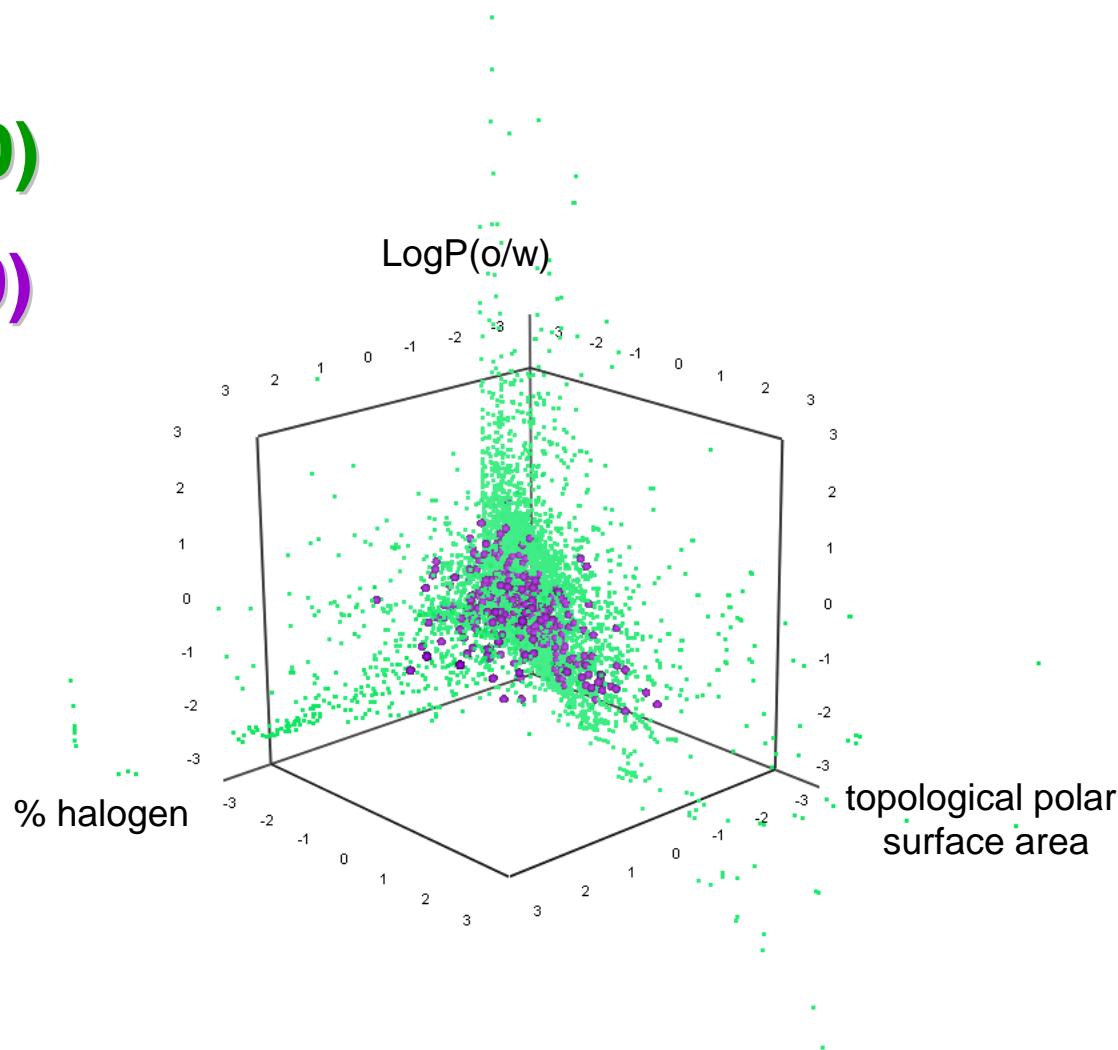


# Chemical Diversity of ToxCast\_320

**ACToR (9000)**

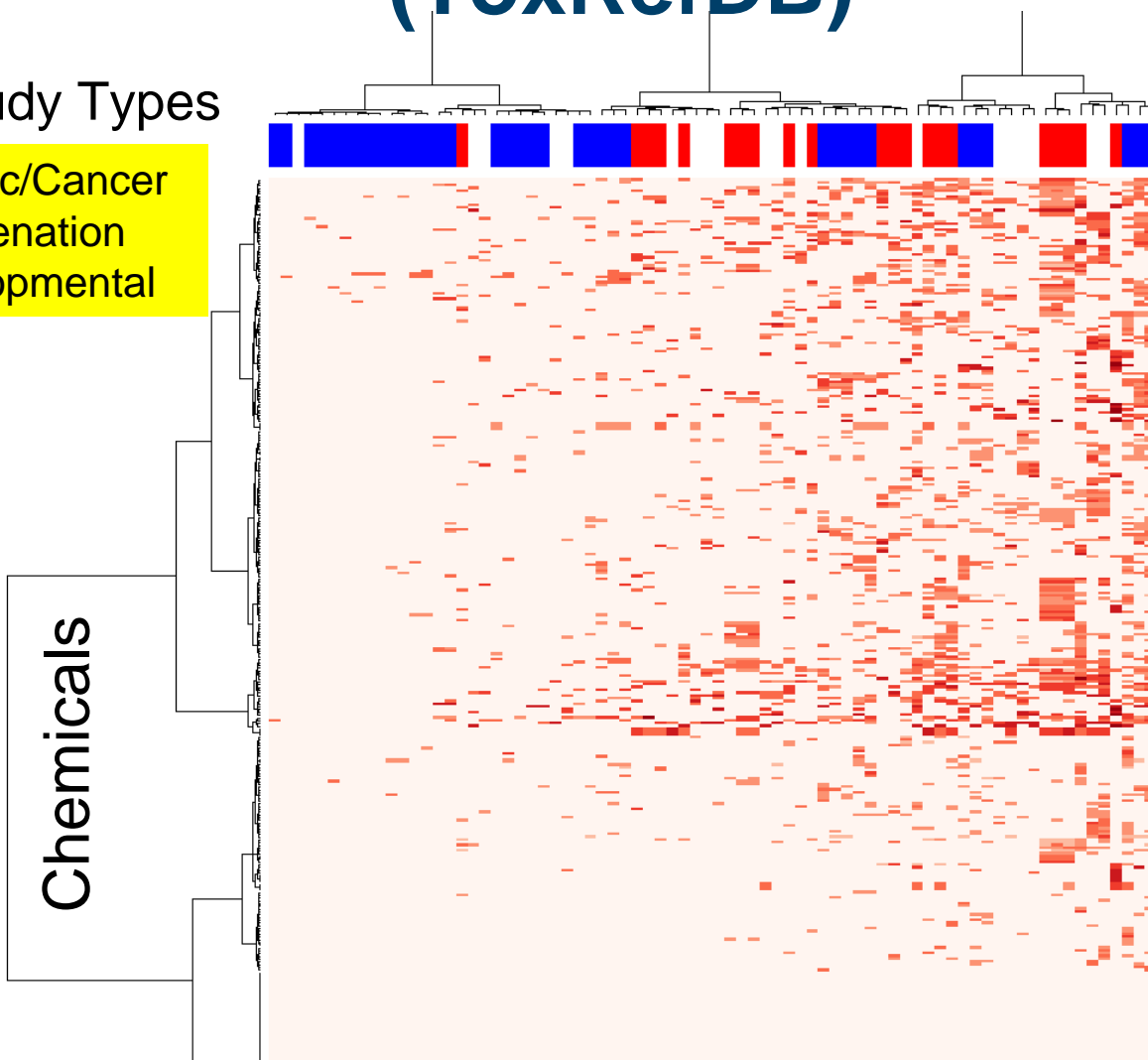
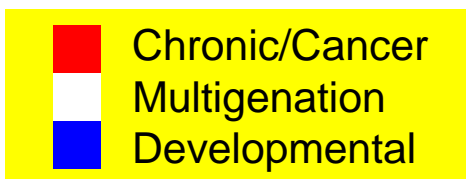
**ToxCast (320)**

- Good representation of compounds across property space
- Few compounds with extreme property values



# Reference Toxicity Database (ToxRefDB)

## In Vivo Study Types





# ToxCast Data Sources

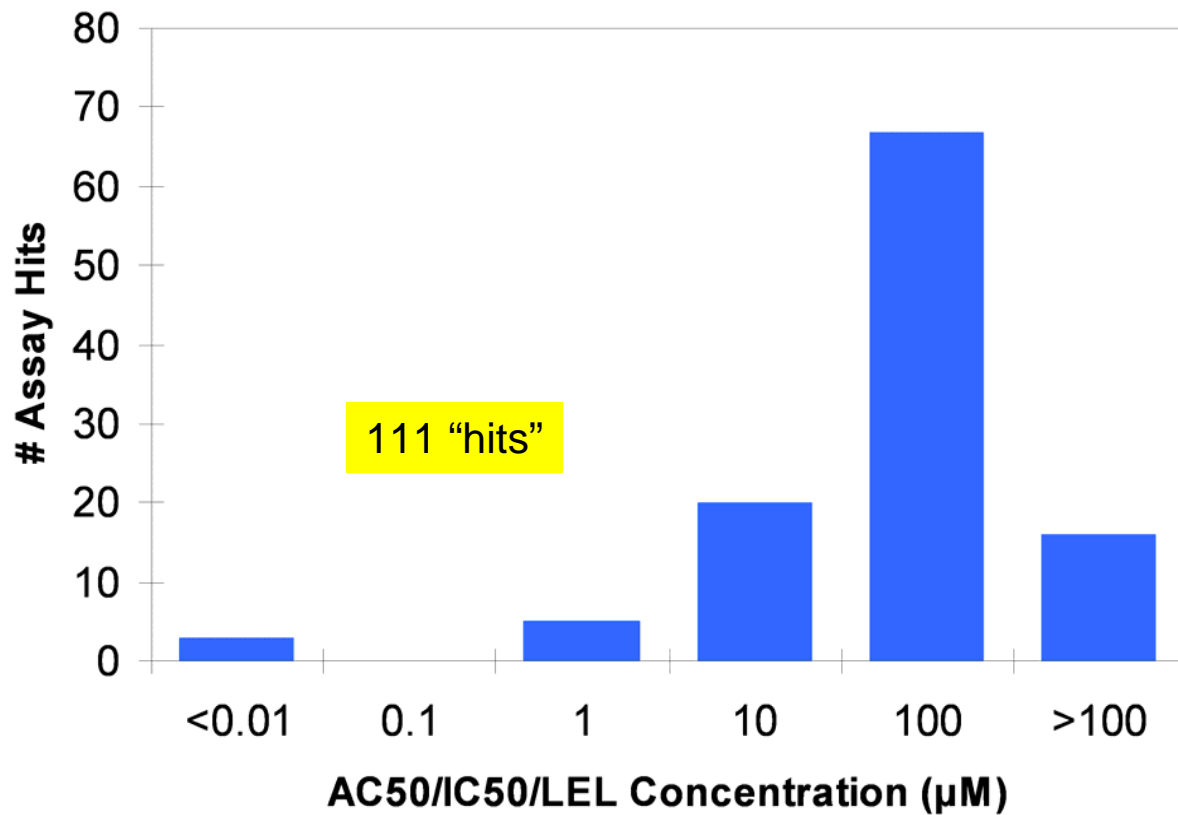


6 contracts, 4 collaborations  
467 assays, 534 endpoints

# ToxCast In vitro data (467 assays)

**Bisphenol A**

- Cell
- Multi
- Hum
- HCS
- qNPA
- XMEs
- Imper
- Geno





# An Example Predictive Model for a Developmental Toxicity

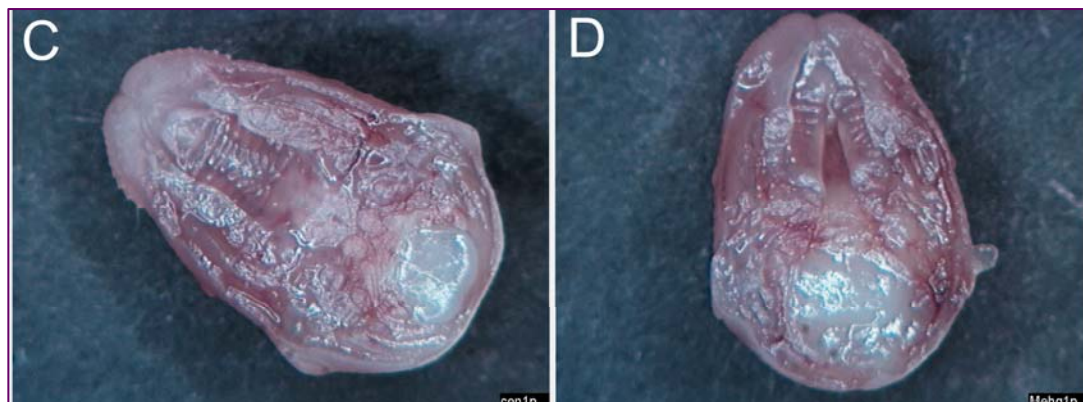
## Cleft Palate

chemicals = 12 \*

assays = 37

relative risk (avg) = 6.24

pathways ( $\geq 5$  hits) = 13



PubMed co-occurrences (April 14, 2009)

<b>PATHWAY</b>	<b>SIGNAL</b>	<b>cleft palate</b>	<b>palatal development</b>
AhR	<i>hypoxia?</i>	23	16
GPCR	cAMP	25	32
GR	glucocorticoids	187	61
RAR/RXR	retinoids	189	83
Wnt	Wnt	18	22

\* Cymoxanil, Cyproconazole, Dichlobenil, Tri-allate, Propiconazole, Spiroxamine, Triadimefon, Triclopyr, Fluazinam, Flusilazole, Mancozeb, Dibutyl phthalate

# Predicting Toxicity From Dose to Outcome

