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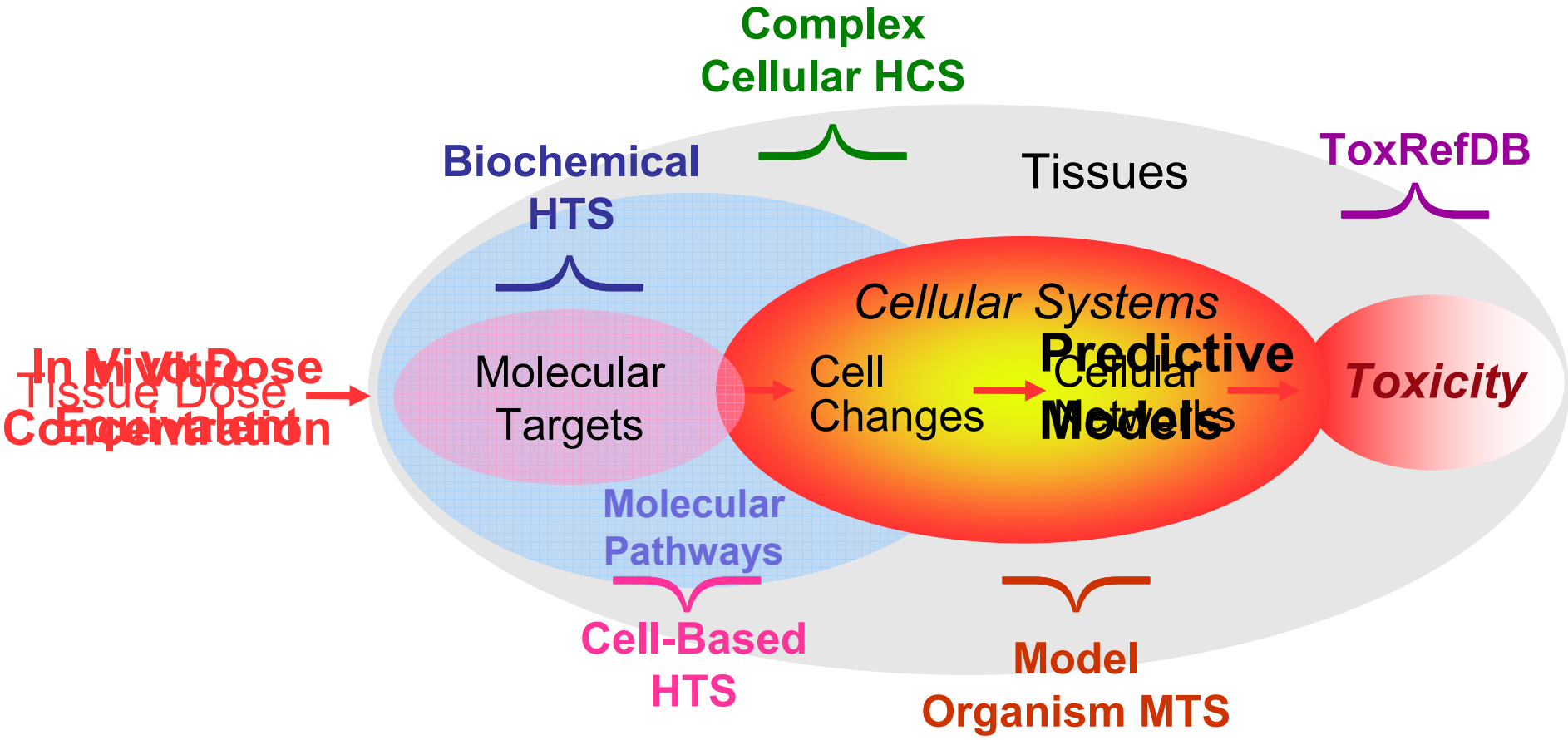
Overview of the ToxCast™ Research Program: Applications to Predictive Toxicology and Chemical Prioritization

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

Office of Research and Development
National Center for Computational Toxicology

May 14, 2009

Ultimate Goal of ToxCast: Predicting Human Toxicity



TOXICOLOGICAL SCIENCES 95(1), 5–12 (2007)

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

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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

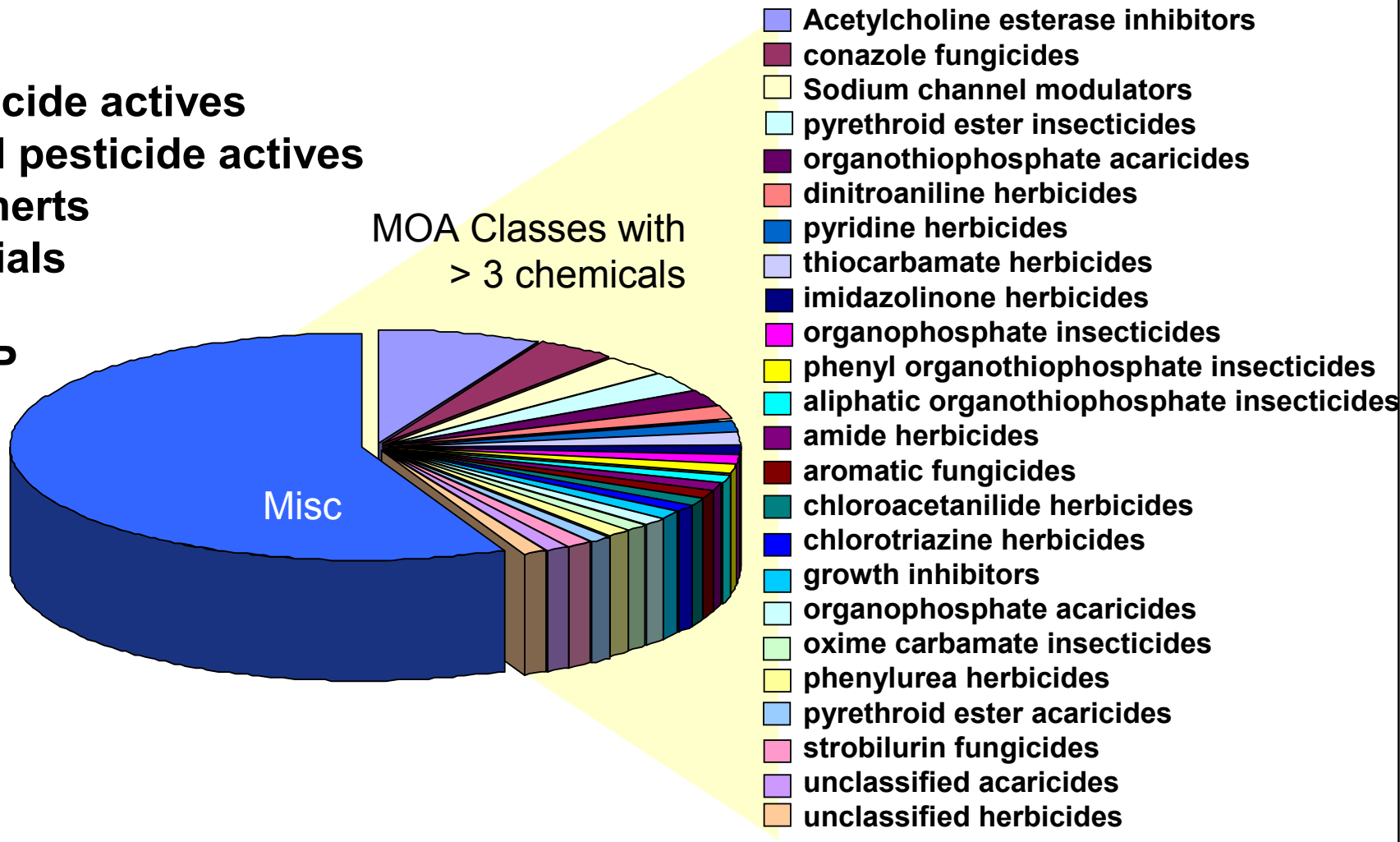
309 unique structures
Replicates for QC
8 metabolites

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

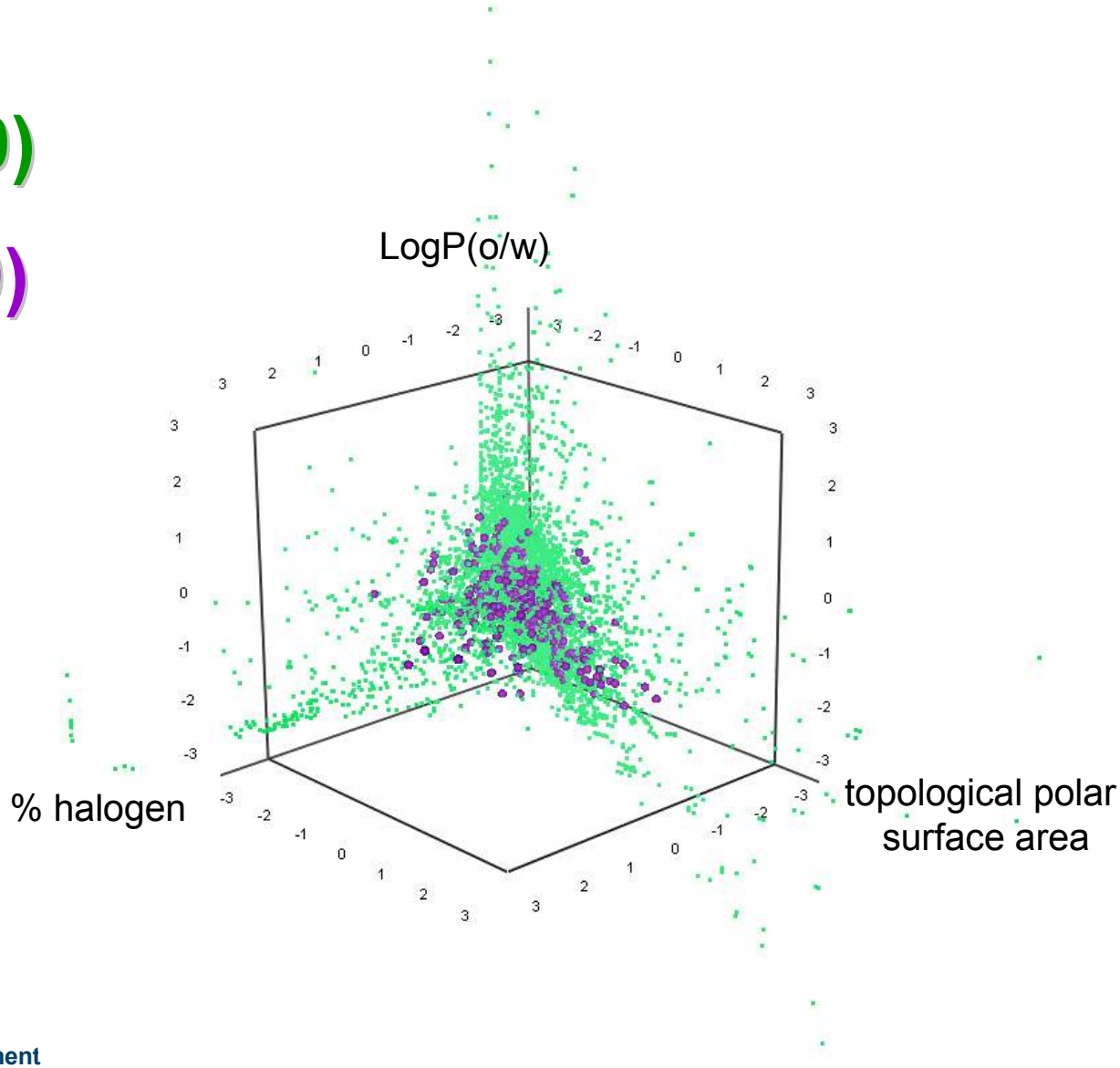


Chemical Diversity of ToxCast_320

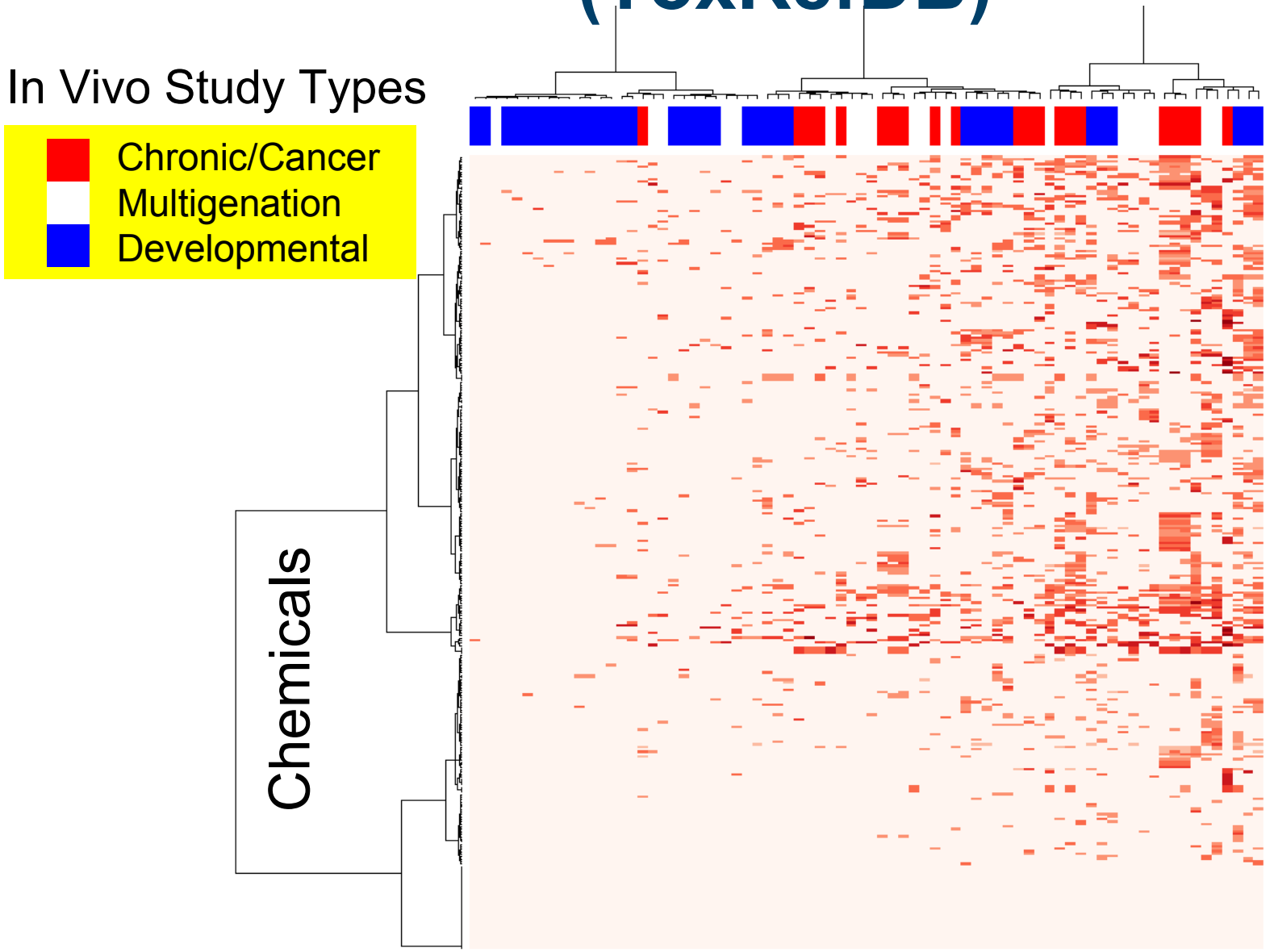
ACToR (9000)

ToxCast (320)

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



Reference Toxicity Database (ToxRefDB)



ToxCast Data Sources

Compound Focus, Inc.
a subsidiary of BioFocus DPI
A Galápagos Company

CELLUMEN

attagene
The Home of TFomics™

CellzDirect™
invitrogen corporation

NOVASCREEN
a Caliper Life Sciences company

BioSeek

L'ORÉAL

SOLIDUS

ACEA
Biosciences, Inc.

gentronix

NCGC

Tox21

National Toxicology Program
U.S. Department of Health and Human Services

6 contracts, 4 collaborations
467 assays, 534 endpoints

ToxCast In vitro data (467 assays)

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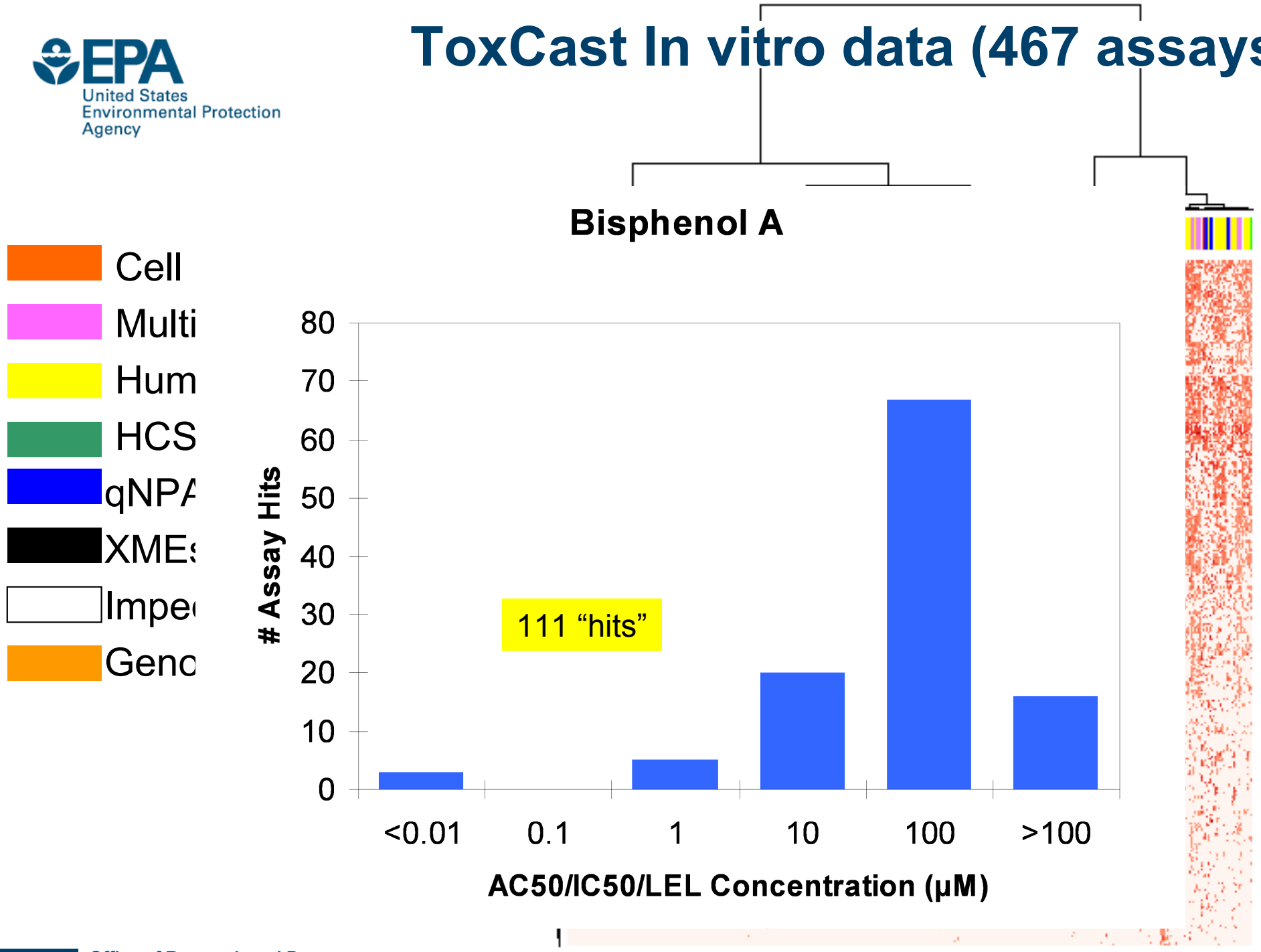

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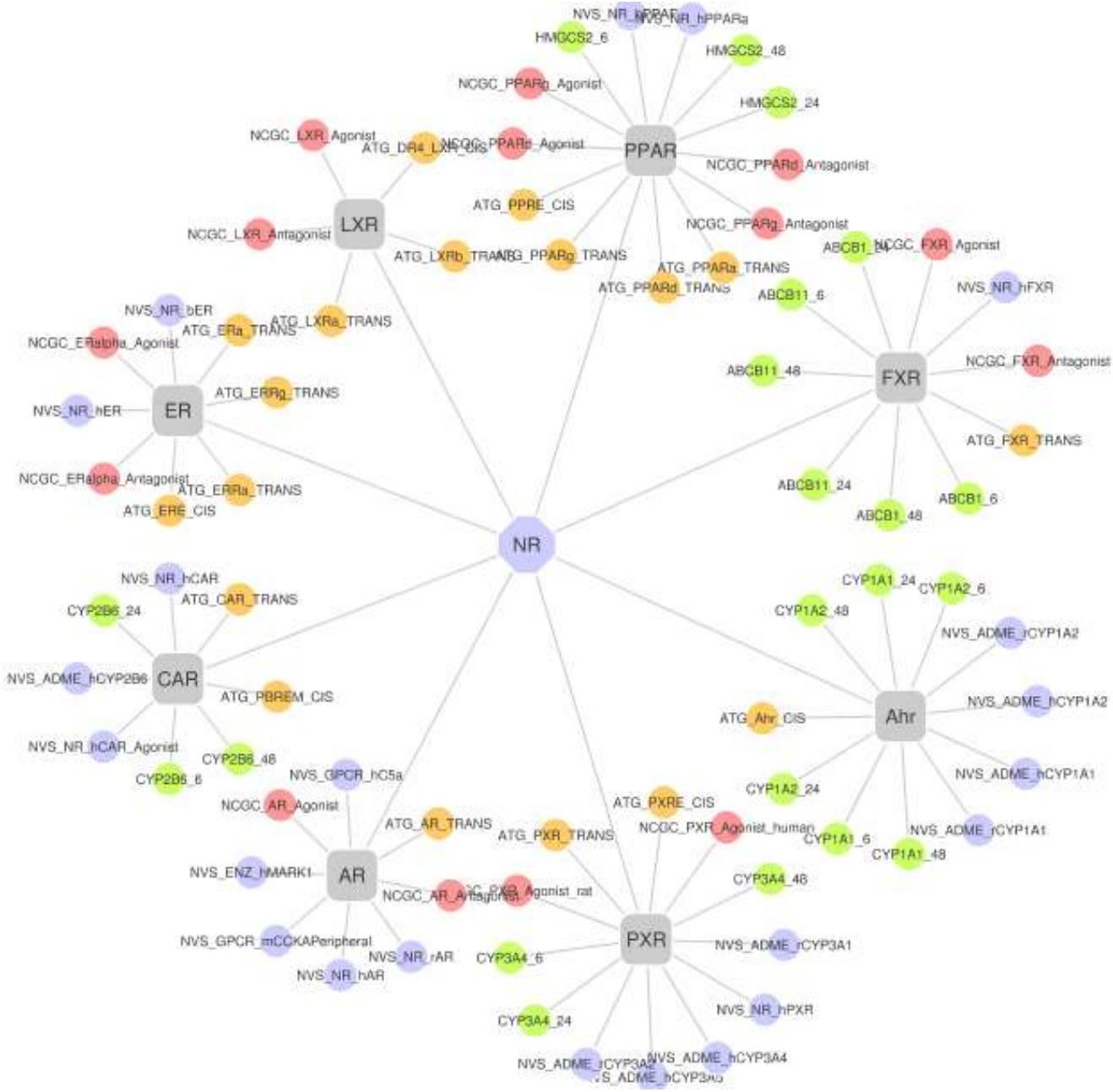
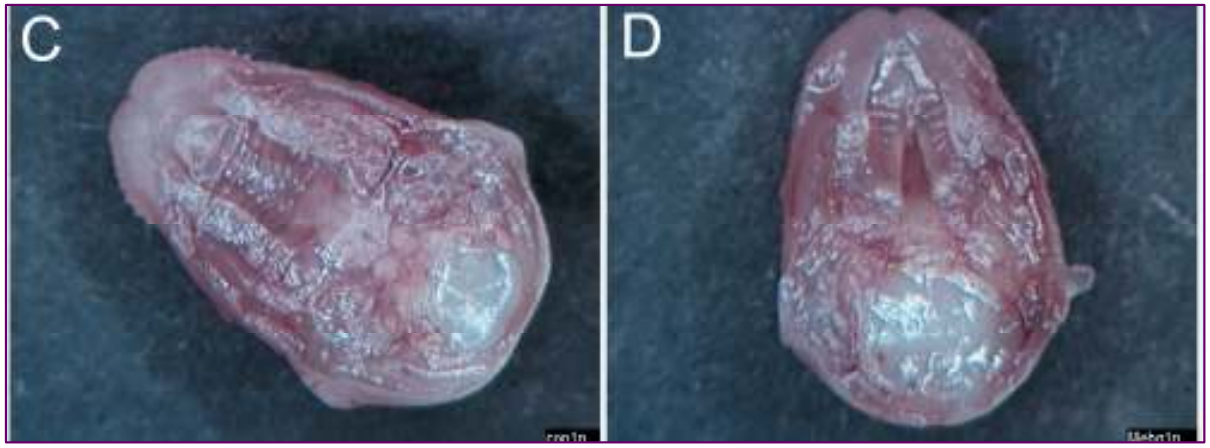
Multiple Assays per Endpoint



An Example Predictive Model for a Developmental Toxicity

Cleft Palate

chemicals = 12 *
assays = 37
relative risk (avg) = 6.24
pathways (≥5 hits) = 13



PubMed co-occurrences (April 14, 2009)

PATHWAY	SIGNAL	cleft palate	palatal development
AhR	*hypoxia?*	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

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Predicting Toxicity From Dose to Outcome