

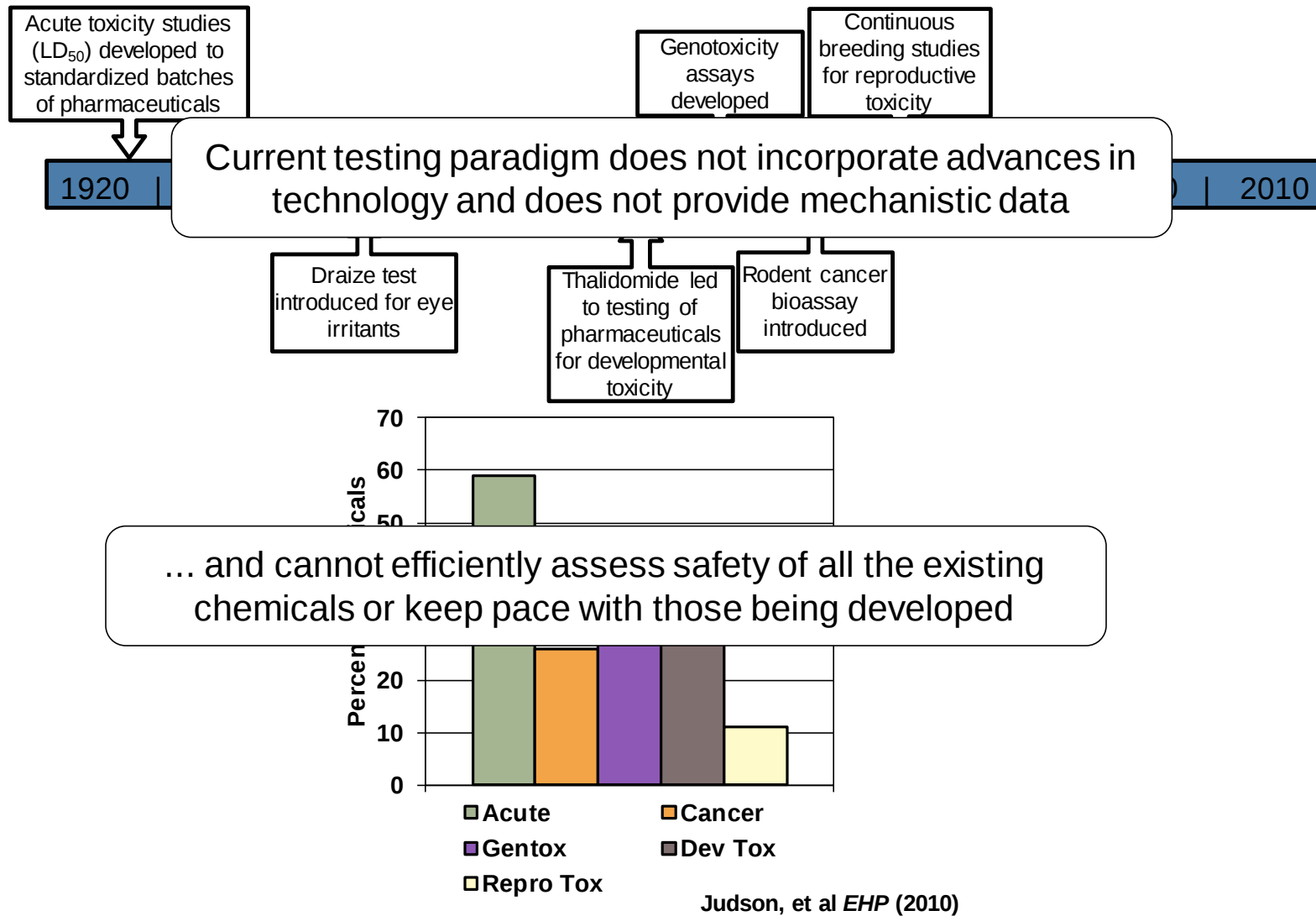
The U.S. EPA ToxCast Program: Moving from Data Generation to Application



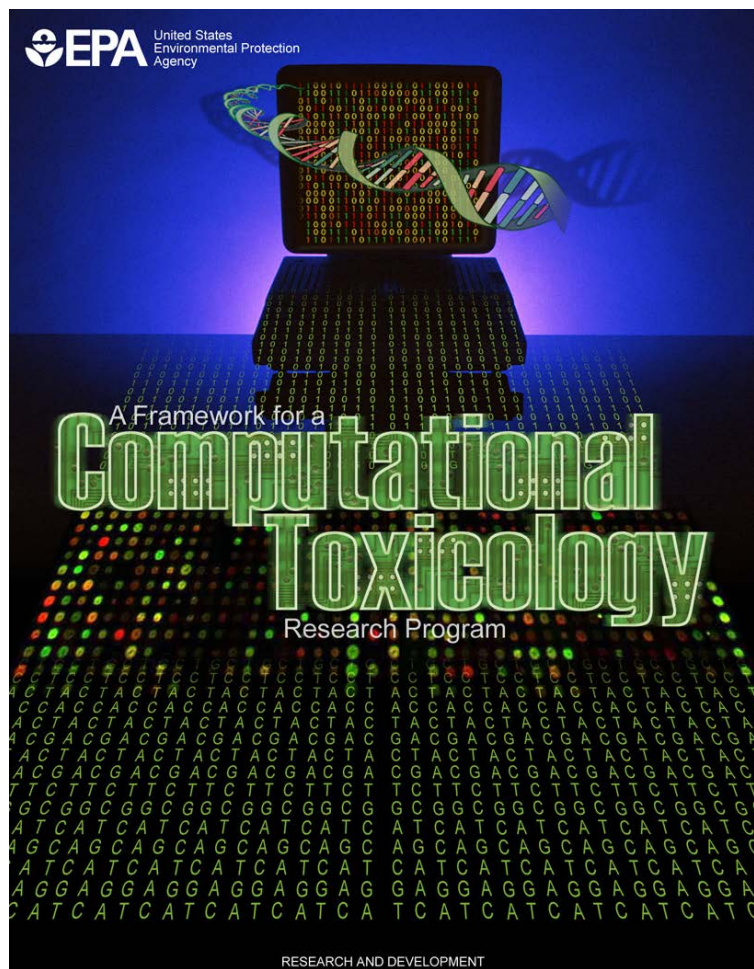
Society of Toxicology Annual Meeting
March 23, 2015

Rusty Thomas
Director
National Center for Computational Toxicology

Current System for Chemical Testing is Antiquated and Inefficient



EPA Formed the CompTox Center to Address this Challenge



Strategic Plan for CompTox Research Program
(November, 2003)



Celebratory Opening of NCCT
(March 1, 2005)

The Effort was Expanded with the Formation of Tox21

MEMORANDUM OF UNDERSTANDING

ON

High Throughput Screening, Toxicity Pathway Profiling,
and Biological Interpretation of Findings



MOU Signed February, 2008; Revised July, 2010

XI. APPROVAL

National Toxicology Program


Linda S. Birnbaum, Ph.D., DABT, ATS
Director
National Institute of Environmental Health Sciences
National Institutes of Health

5-25-10
Date

NIH Chemical Genomics Center


Eric D. Green, M.D., Ph.D.
Director
National Human Genome Research Institute
National Institutes of Health

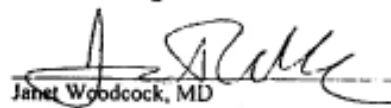
6/3/10
Date

U.S. Environmental Protection Agency


Paul J. Anastas, Ph.D.
Assistant Administrator
Office of Research and Development

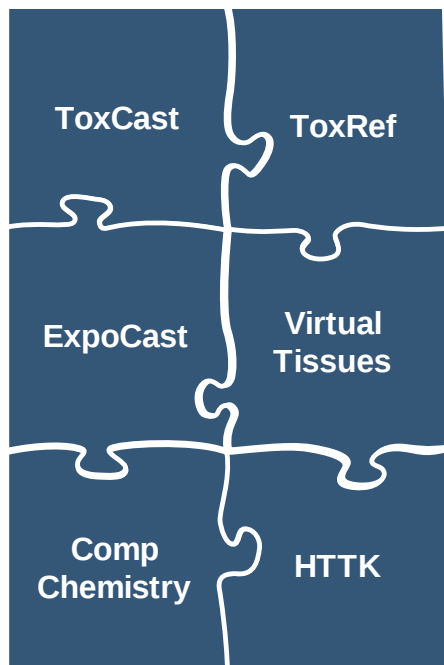
4 June 2010
Date

Food and Drug Administration


Janet Woodcock, MD
Director
Center for Drug Evaluation and Research

5/24/10
Date

Recent Highlights from a Decade of Progress



- High-throughput *in vitro* screening of ~2,000 chemicals across ~700 assay endpoints representing over 327 genes and 293 pathways
- High quality, curated chemical structure database of 22,000 molecules
- Legacy *in vivo* data from 5,891 animal toxicology studies on ~1,110 unique chemicals
- Exposure estimates for over 7,000 chemicals based on production volume and chemical use
- A database of chemical-product categories (CPCat) that maps over 45,000 chemicals to ~8,000 product uses or functions
- Steady-state IVIVE models for hundreds of chemicals based on high-throughput *in vitro* assays
- AOPs and computational models for embryonic vascular disruption, cleft palate, hypospadias, and limb (digit) defects

At the Beginning of Regulatory Application

Prioritization of the EDSP Universe of Chemicals

Prioritization of the Endocrine Disruptor Screening Program Universe of Chemicals for an Estrogen Receptor Adverse Outcome Pathway Using Computational Toxicology Tools

**U.S. Environmental Protection Agency
Endocrine Disruptor Screening Program**

Jointly developed by:

Office of Chemical Safety and Pollution Prevention (OCSPP)
Office of Science Coordination and Policy (OSCP)
Office of Pesticide Programs (OPP)
Office of Pollution Prevention and Toxics (OPPT)

Office of Water (OW)
Washington, DC 20460

Office of Research and Development (ORD)
National Environmental and Effects Health Research Laboratory (NEEHRL)
Mid-Continent Ecology Division (MED), Duluth, MN 55804
Toxicity Assessment Division (TAD), RTP, NC 27111

National Center for Computational Toxicology (NCCT)
Research Triangle Park, NC 27709

December 2012

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)

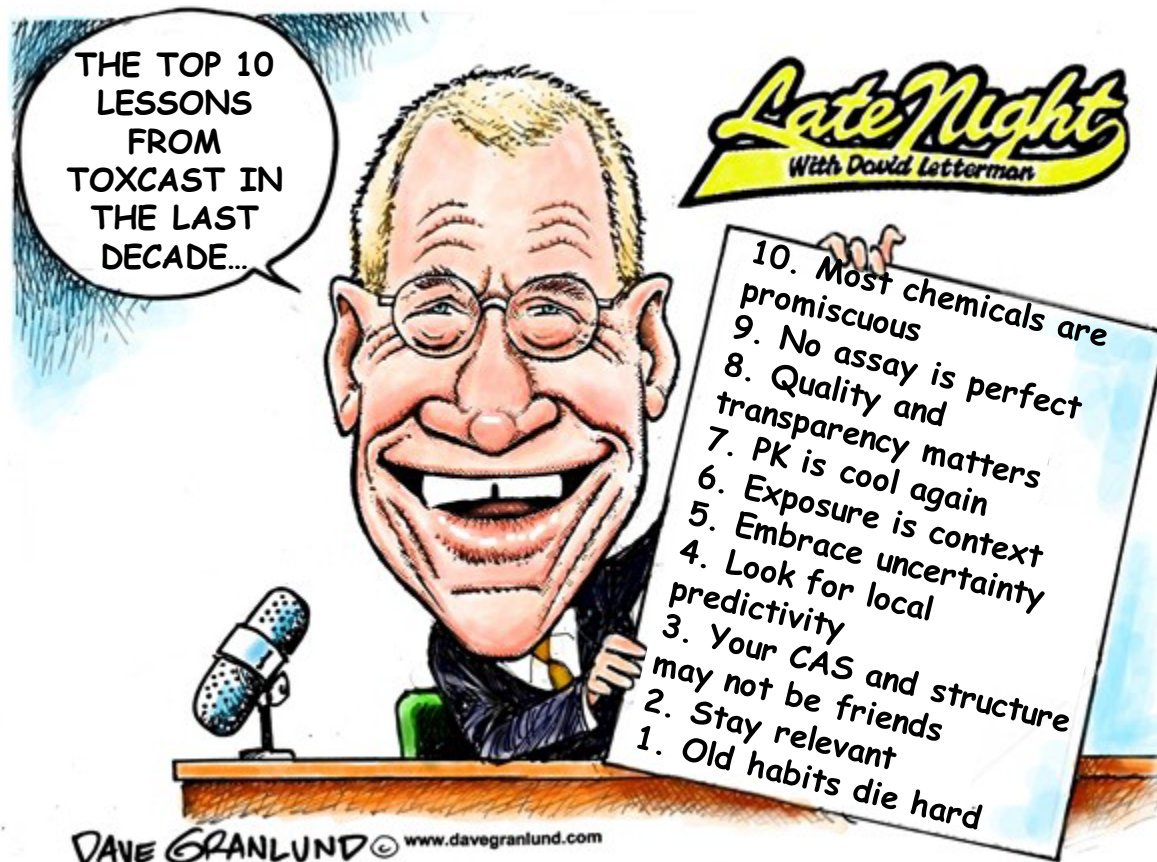
FIFRA SAP December 2-5, 2014

Exposure SAP White Paper

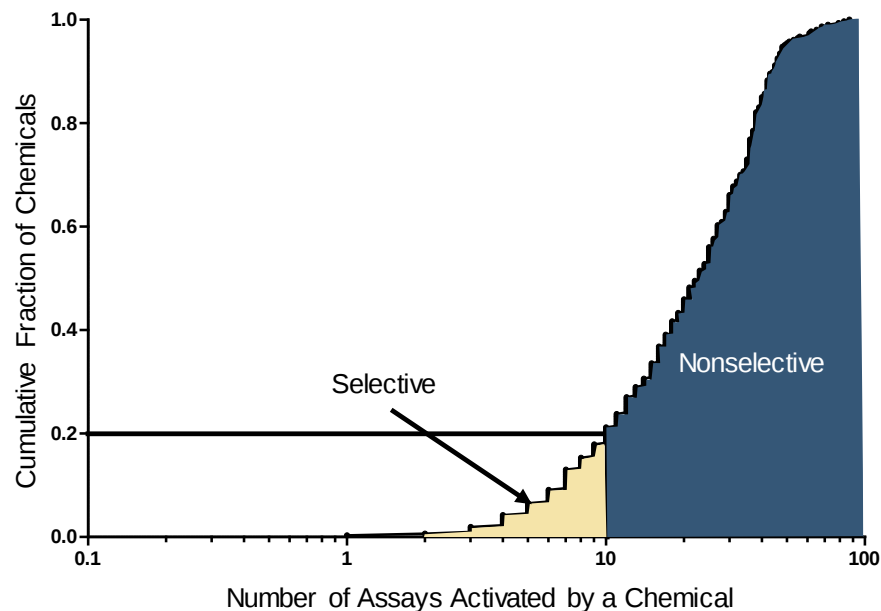
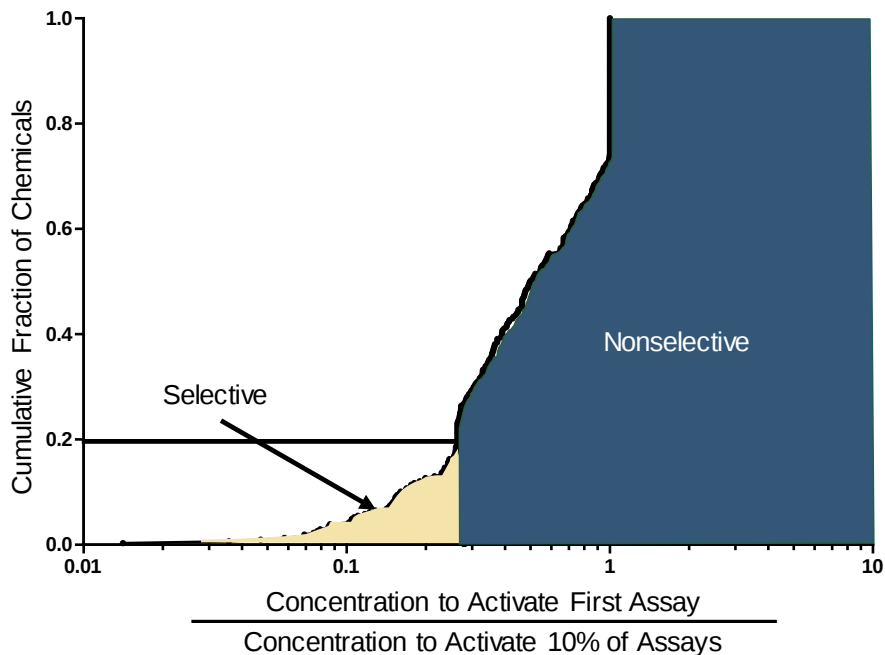
New High-throughput Methods to Estimate Chemical Exposure

Scientific Advisory Panel Meeting, July 2014

Top 10 Lessons Learned

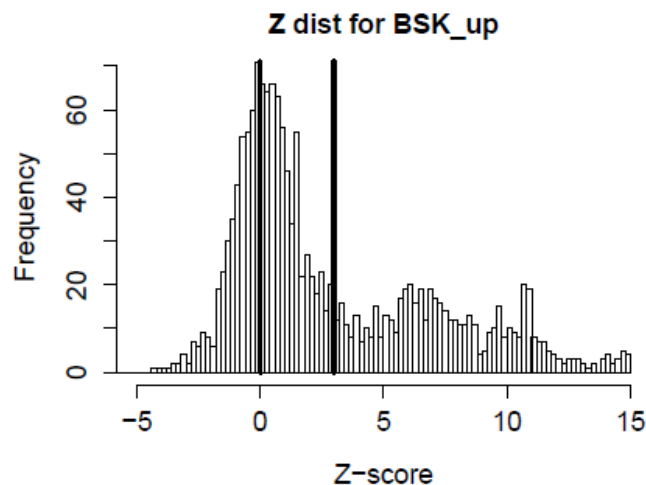
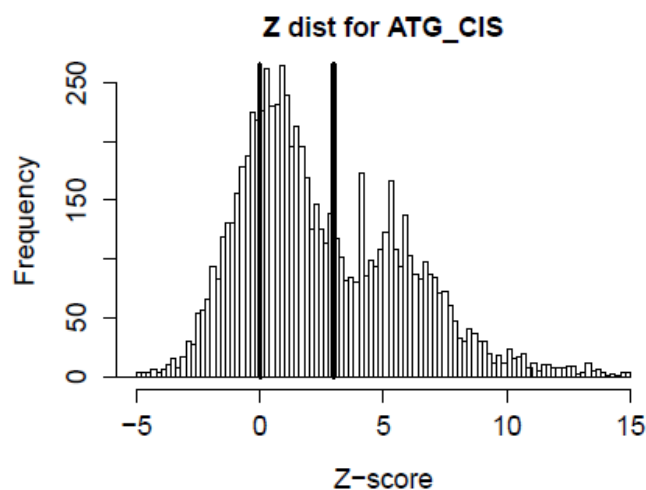
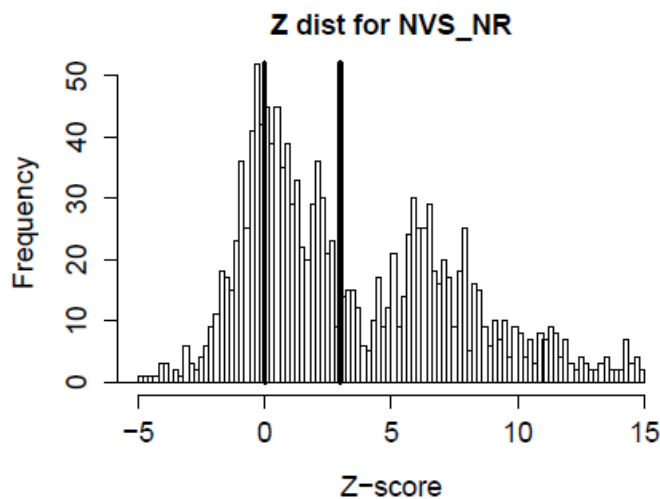
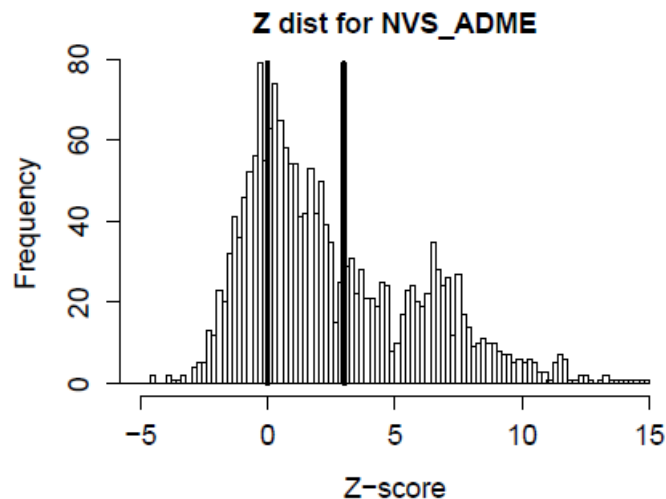


Lesson #10: Most Chemicals are Promiscuous



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

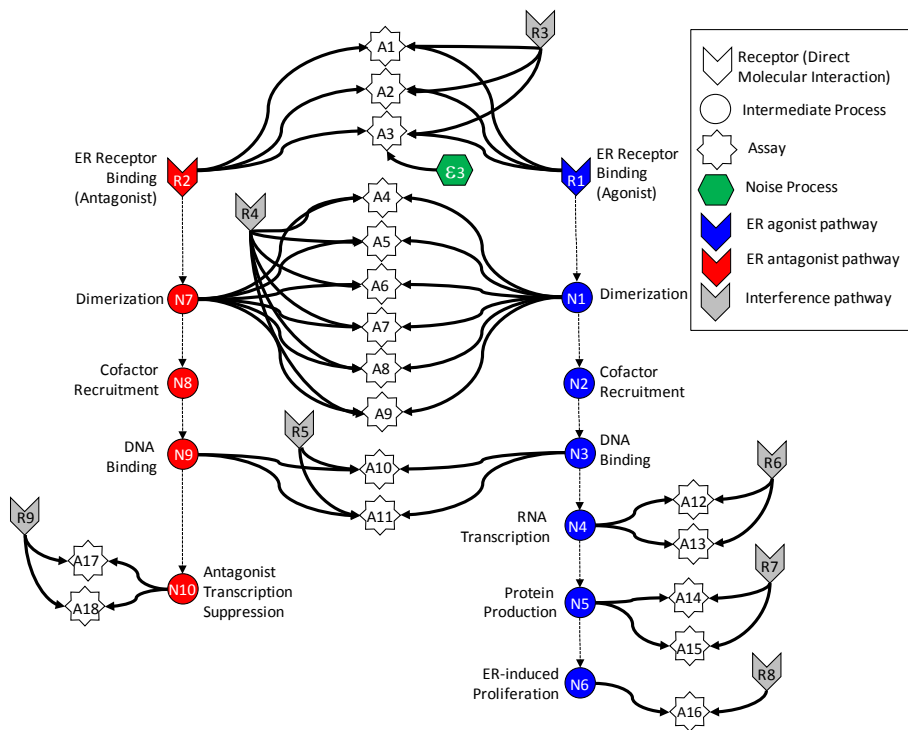
Non-Selectivity Frequently Occurs at Cytotoxic Concentrations



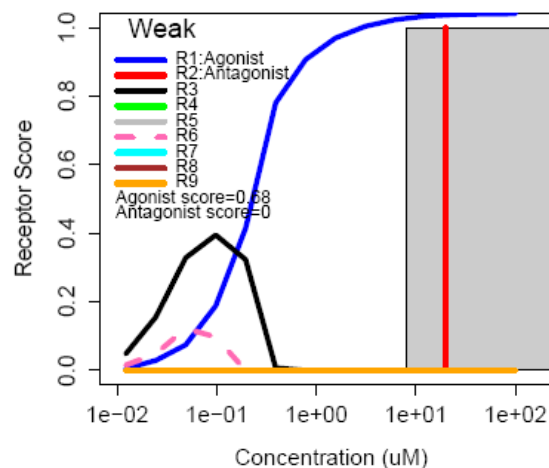
Z-score = #SD from Cytotox Region

Lesson #9: No Assay is Perfect (Search for Consensus)

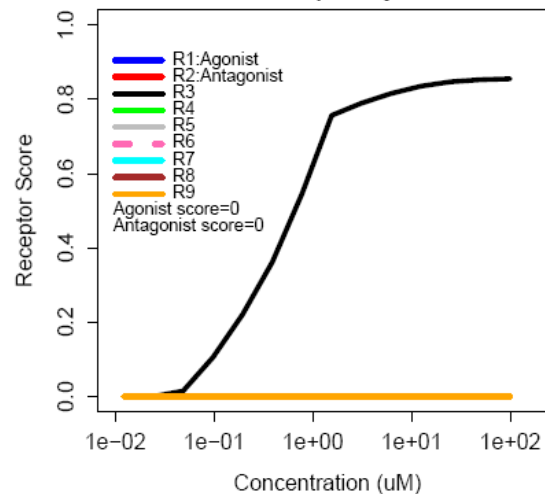
18 *In Vitro* Assays Measure ER-Related Activity



80-05-7 : Bisphenol A

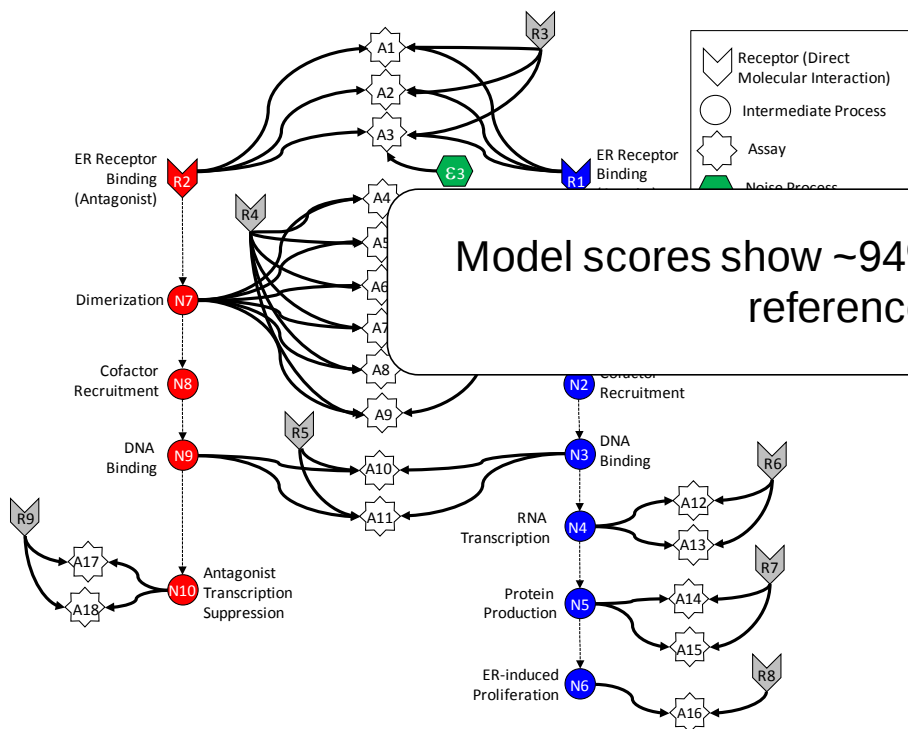


10016-20-3 : alpha-Cyclodextrin

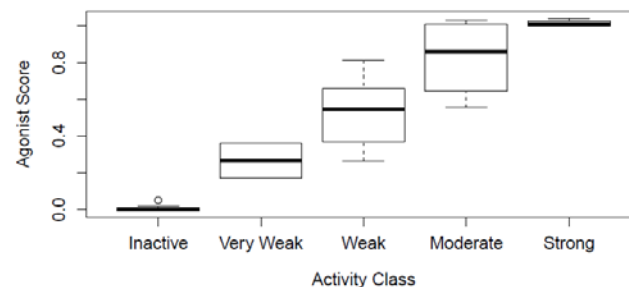
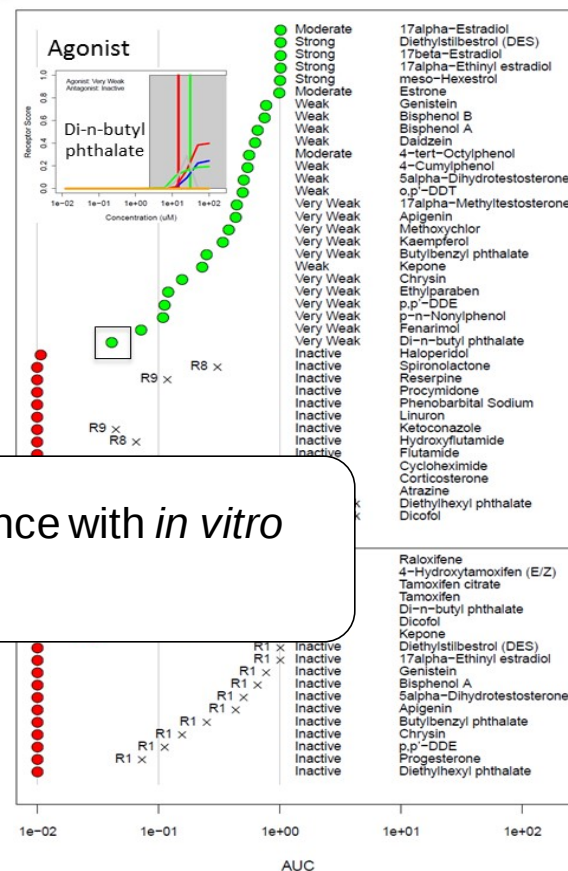


Lesson #9: No Assay is Perfect (Search for Consensus)

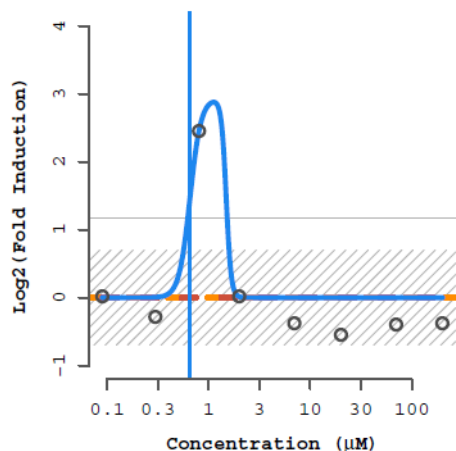
18 *In Vitro* Assays Measure ER-Related Activity



Model scores show ~94% concordance with *in vitro* reference chemicals



Lesson #8: Quality and Transparency Matters



ASSAY: ARID117 (ATQ_Era_TRANS)

NAME: Thioglycolic acid
CHID: 26141 CASRN: 68-11-1
SPID(S): TX007664
L4ID: 420385

HILL MODEL (in red):
tp ga gw
val: 3.1e-11 -2.15 0.416
sd: NaN NaN NaN

GAIN-LOSS MODEL (in blue):
tp ga gw la lw
val: 2.93 -0.184 8 0.173 18
sd: 3.56 0.334 9.48 5.82 814

	CNST	HILL	GNLS
AIC:	20.14	26.14	17.79
PROB:	0.23	0.01	0.76
RMSE:	0.92	0.92	0.32

MAX_MEAN: 2.45 MAX_MED: 2.45 BMAD: 0.233

COFF: 1.17 HIT-CALL: 1 FITC: 50 ACTP: 0.77

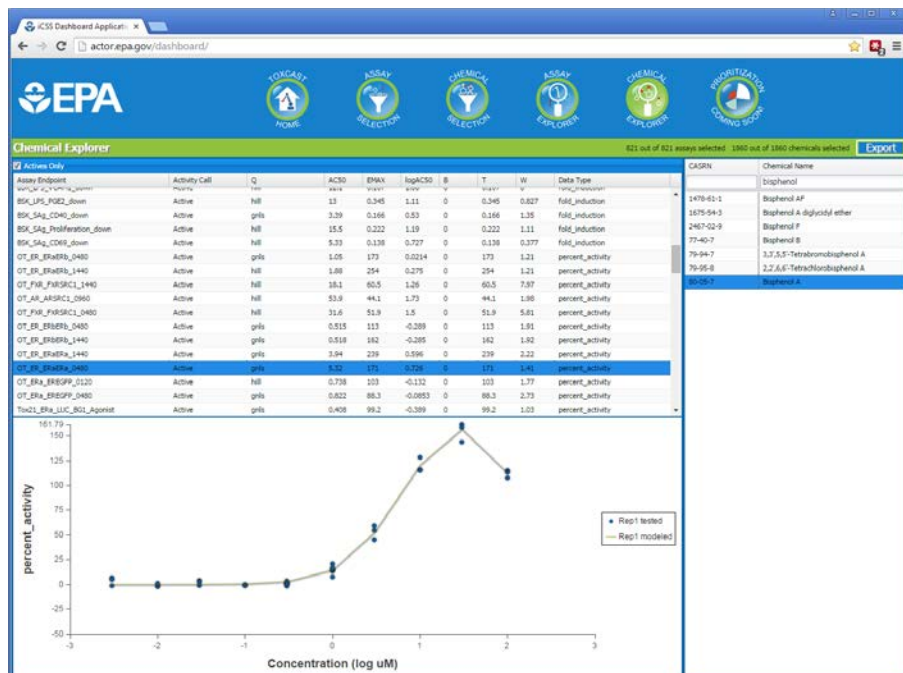
FLAGS:

Only one conc above baseline, active
Borderline active

- Public release of Tox21 and ToxCast data on PubChem and EPA web site (raw and processed data)
- ToxCast data analysis pipeline has been completely revamped
 - More rigorous statistically and robust to outliers
 - Data quality flags to indicate concerns with chemical purity and identity, noisy data, systematic assay errors, and activity in range of cytotoxicity
- Tox21 and ToxCast chemical libraries undergoing analytical QC and results will be publicly released
- Release of ToxCast “Owner’s Manual”
 - Chemical Procurement and QC
 - Data Analysis
 - Assay Characteristics and Performance
- External audit on ToxCast data and data analysis pipeline
- Multiple webinars and workshops to educate stakeholders on high-throughput screening data analysis and interpretation

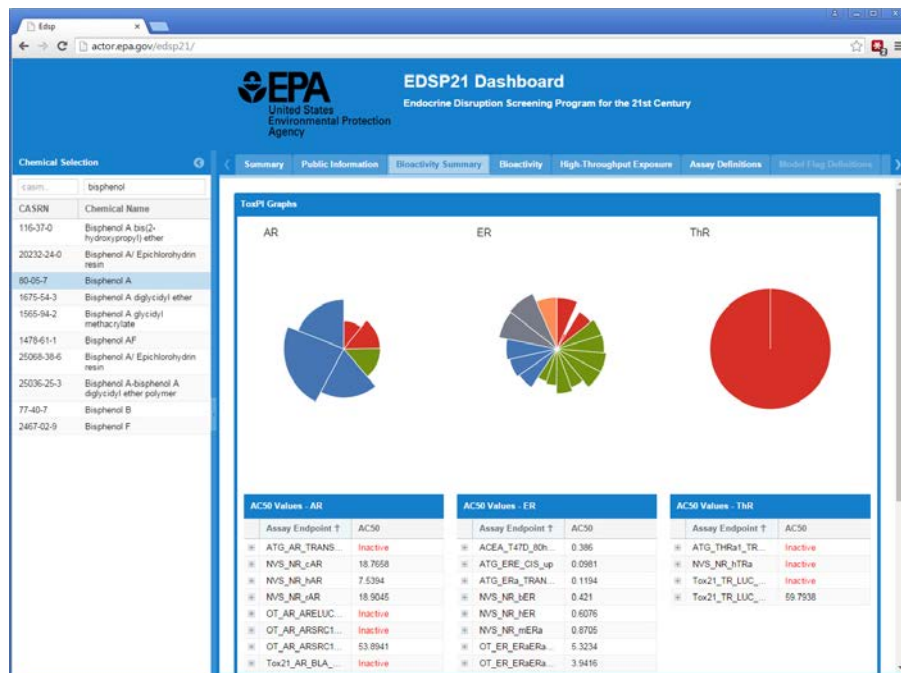
Lesson #8: Quality and Transparency Matters

icSS Dashboard



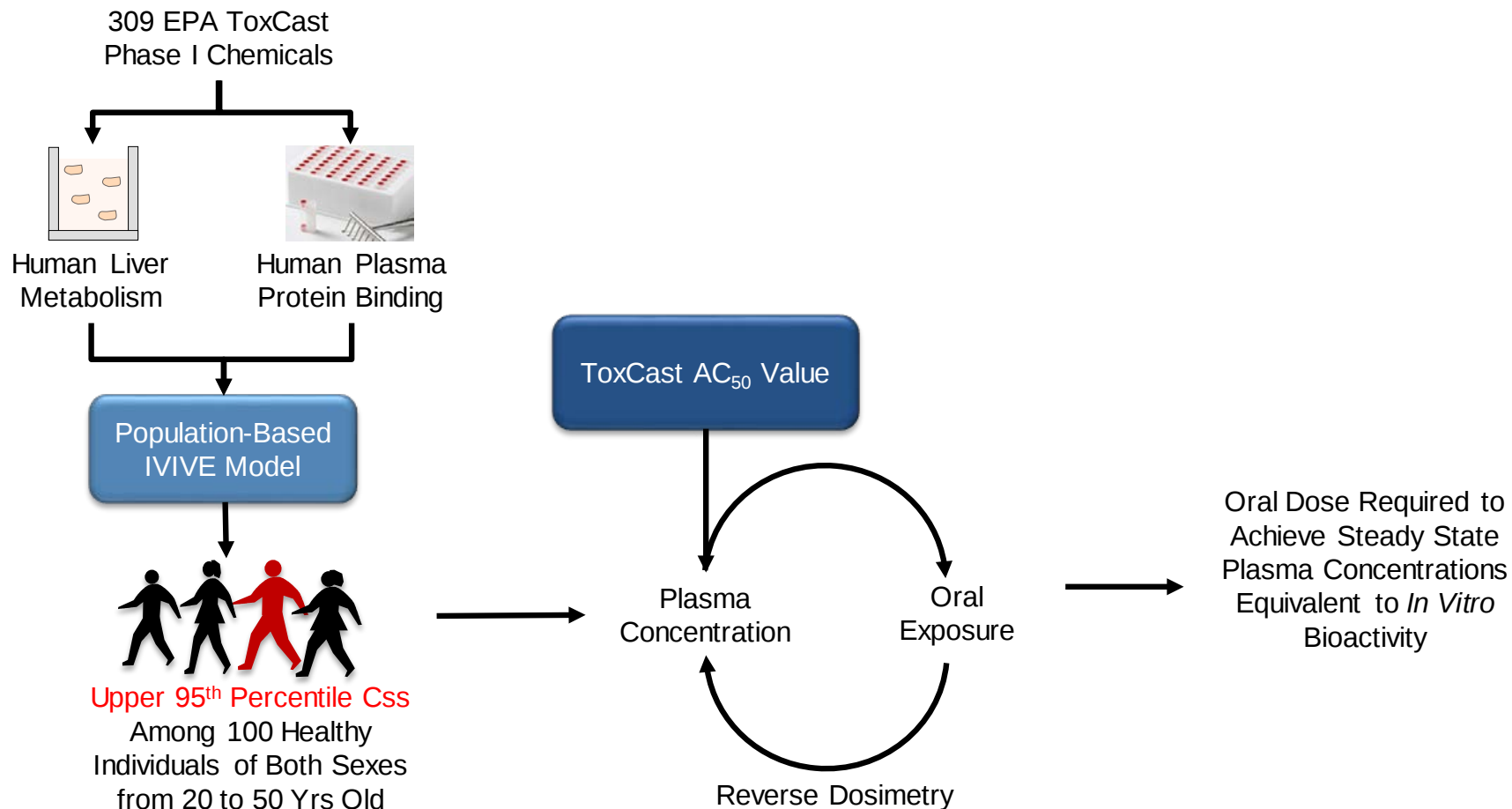
<http://actor.epa.gov/dashboard/>

EDSP21 Dashboard

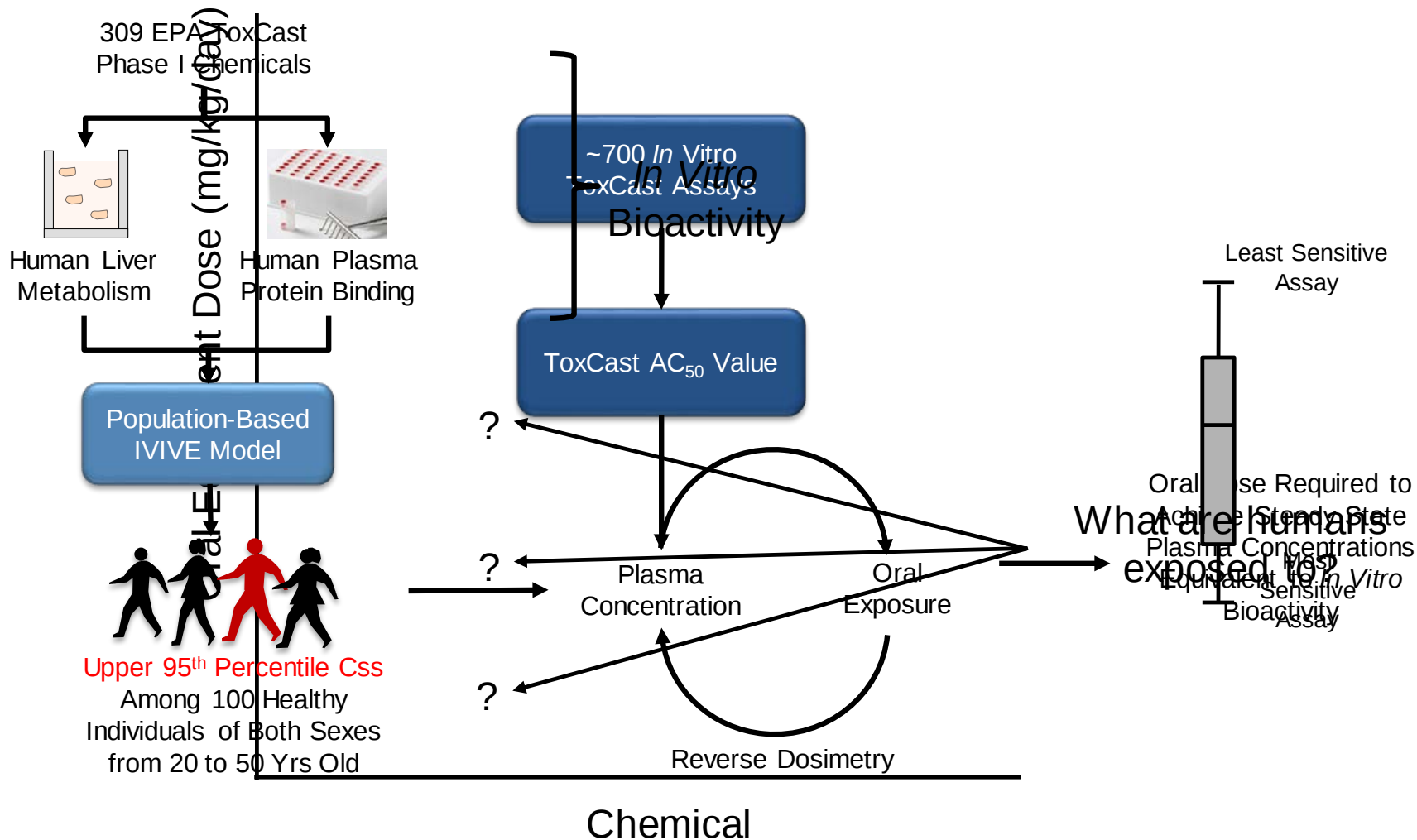


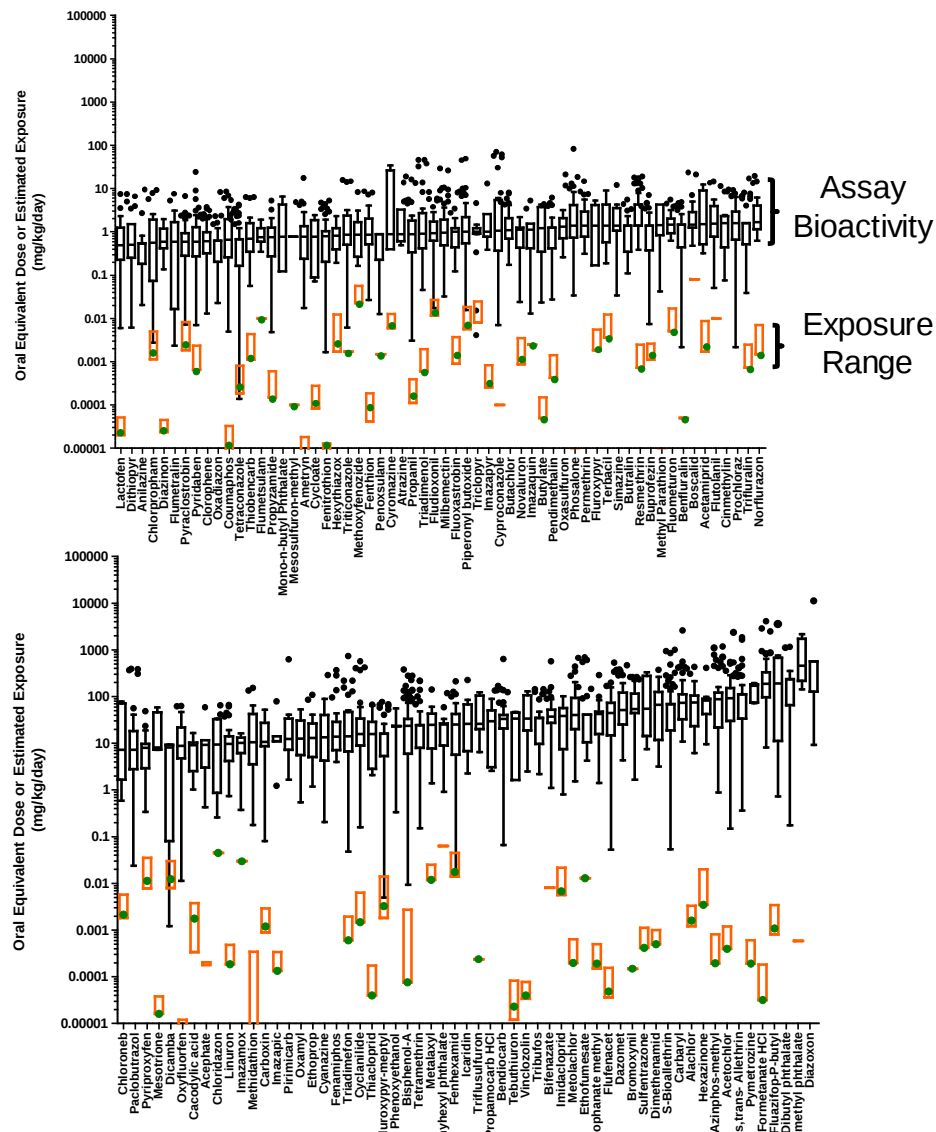
<http://actor.epa.gov/edsp21/>

Lesson #7: PK is Cool Again

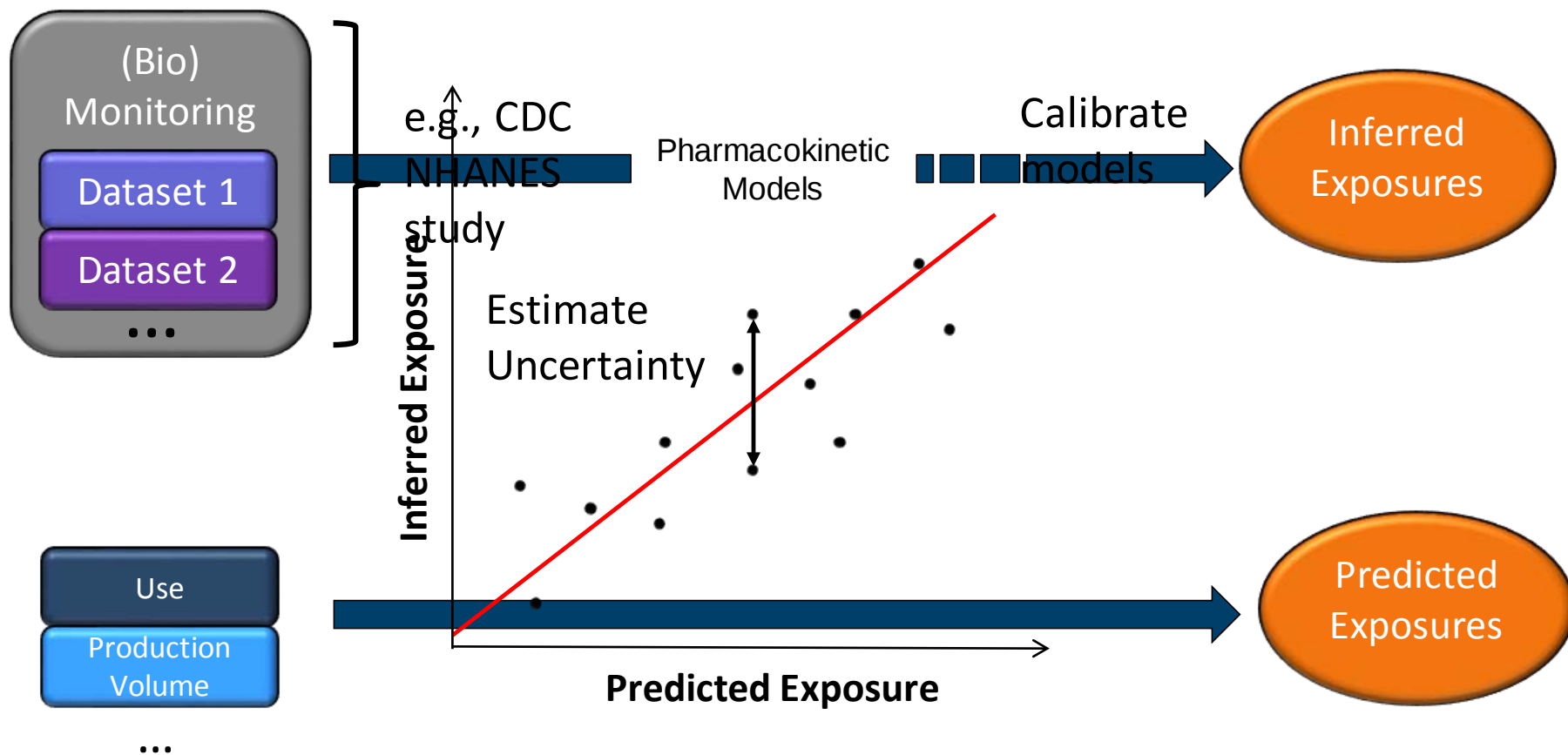


Lesson #6: Exposure is Context





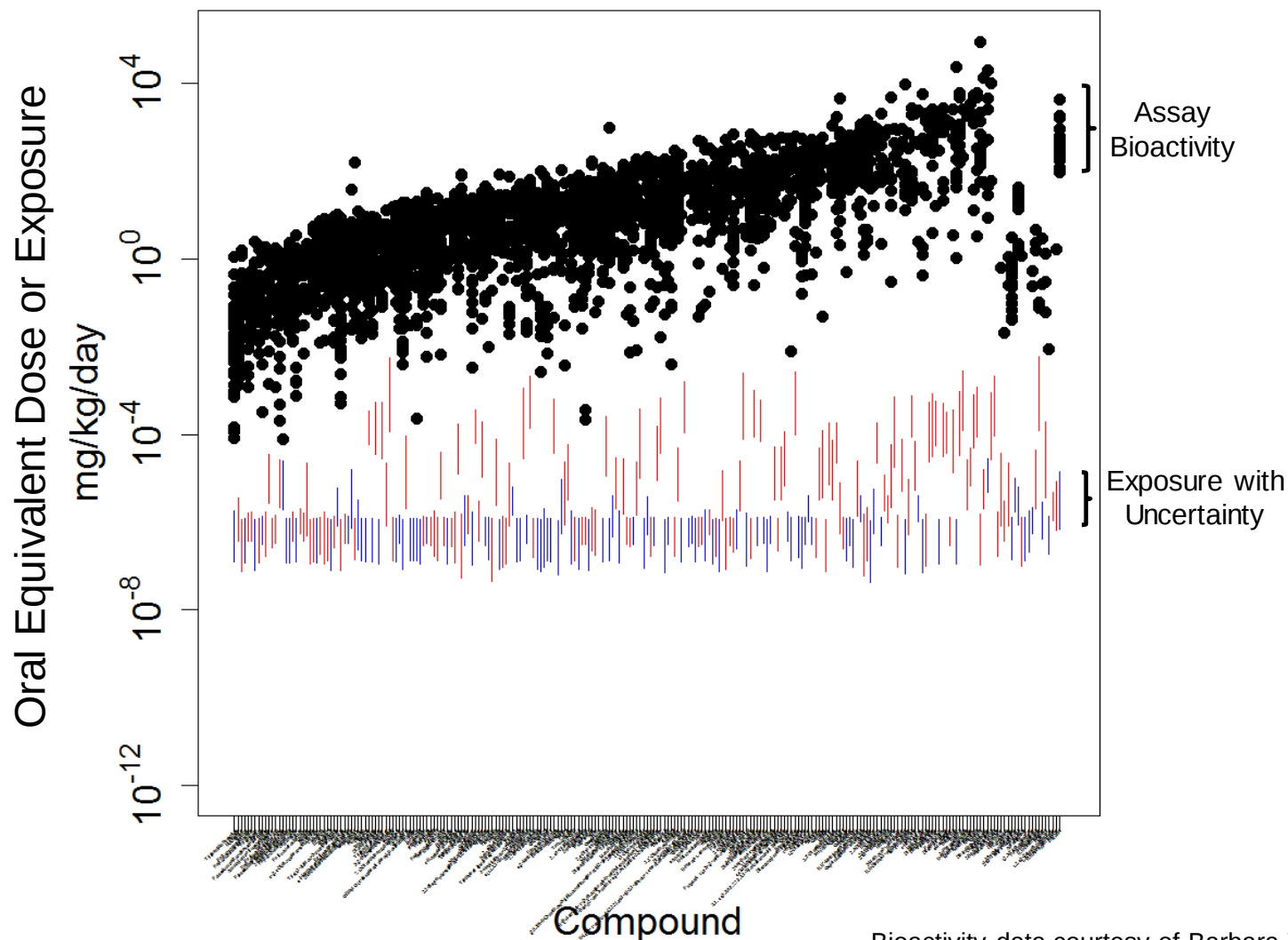
Lesson 5: Embrace Uncertainty



*See talk by J. Wambaugh Thursday morning, Abstract #2445

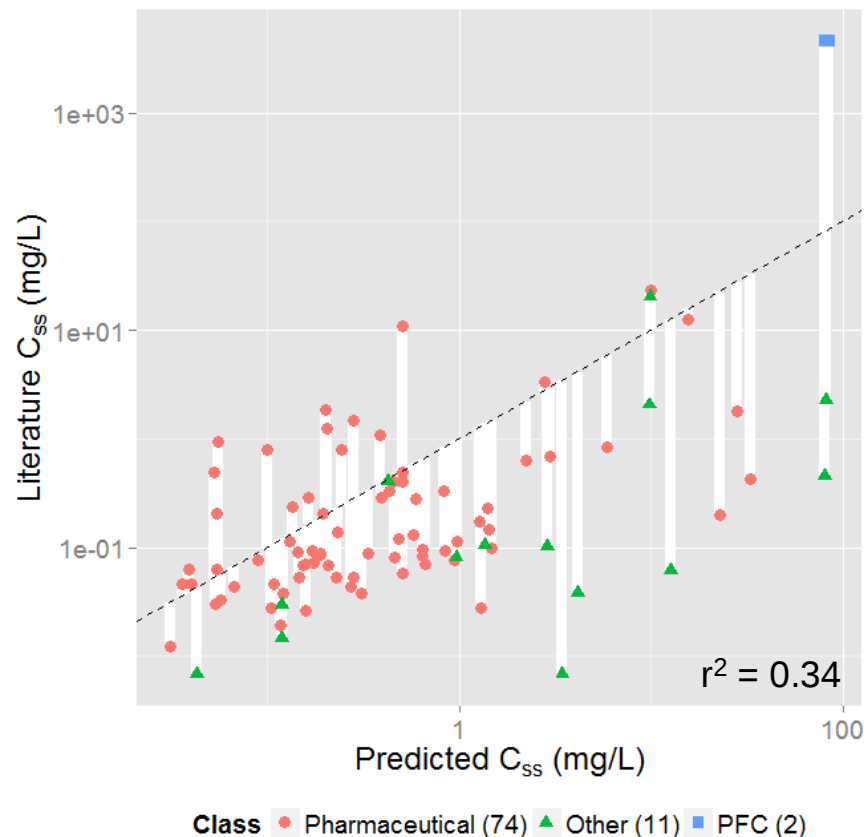
Wambaugh et al., *Environ Sci Technol.*, 2014

Lesson 5: Embrace Uncertainty

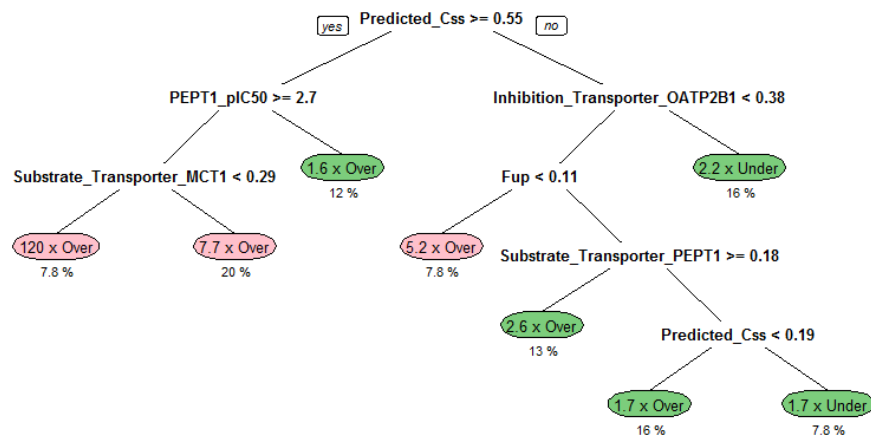


Bioactivity data courtesy of Barbara Wetmore

Lesson 4: Look for Local Predictivity



Recursive Partition Tree on Residuals



*Transporter substrate predicted with QSAR (Sedykh et al, 2013)

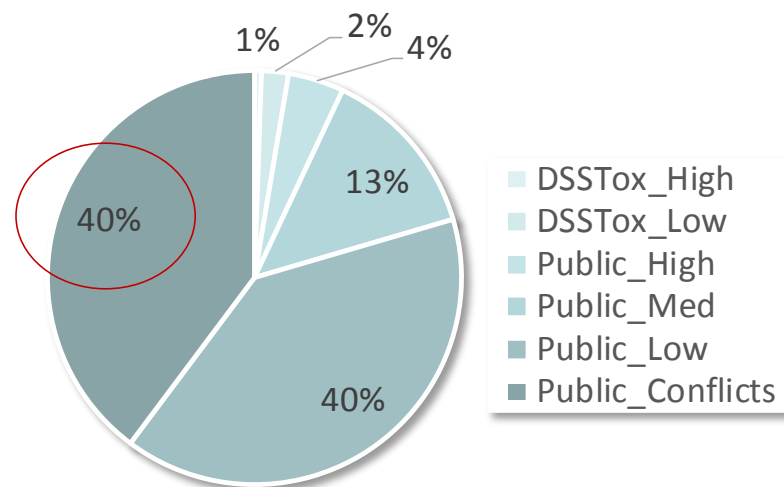
Lesson #3: Your CAS and Structure May Not Be Friends

DSSTox Database

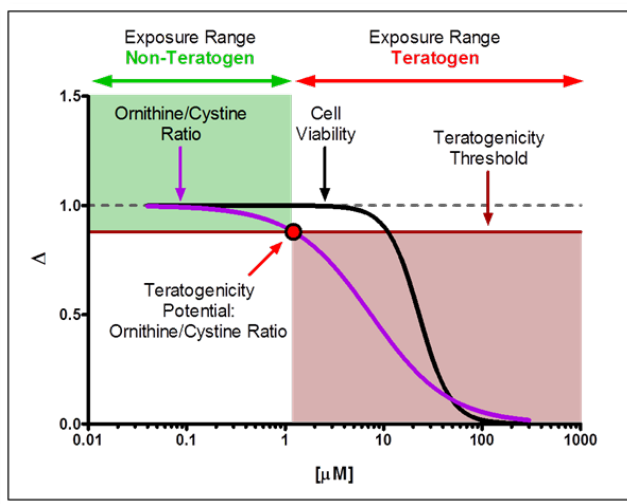
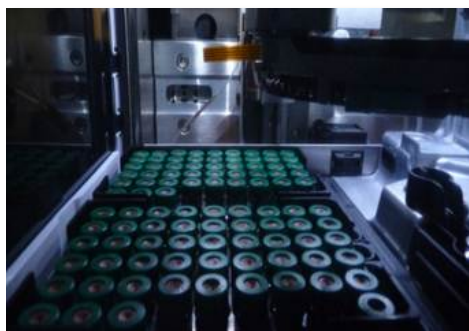
The screenshot shows the DSSTox website with a sidebar menu on the left containing links like Home, About DSSTox, Work in Progress, Frequent Questions, Structure Data Files, Central Field Definition Table, Apps, Tools & More, DSSTox Community, Site Map, Glossary of Terms, Help, and DSSTox Publications. The main content area is titled 'National Center for Computational Toxicology (NCCT)' and 'DSSTox'. It describes the 'Distributed Structure-Searchable Toxicity (DSSTox) Database Network' as a project of EPA's National Center for Computational Toxicology. A diagram illustrates the process: 'Chemical Structures' + 'Toxicity Data' leads to 'DSSTox SDF Files', which are then 'Standardized', 'Documented', 'Structure-Searchable', and 'Application-independent'. Below this, there are links to 'DSSTox Data Files: Details' and a list of specific data files with their dates.

(~22,000 curated chemical structures)

Quality of CAS-Structure Mappings



Lesson #2: Stay Relevant



- Undifferentiated human embryonic stem cells (H9 cells) treated for 72 hours
- Conditioned media from the final 24h treatment period was analyzed by LC-MS-based metabolomics to determine ornithine/cystine (o/c) ratio
- Teratogenicity defined by the o/c ratio ≤ 0.88
- Concurrent cell viability measured
- Rapid screen of 1066 ToxCast chemicals produced 15-16% actives

Source: Stemina (2014) Standard Protocol for the in vitro DevTox quickPredict Assay.

Platform	ref	k	TP	FP	FN	TN	sens	spec	BA	PPV	NPV
devTOX	Cytotoxicity by itself only had an estimated predictive accuracy of 30-40% using a subset of ToxCast chemicals									0.94	0.75
devTOXqP										1.00	0.60
devTOXqP	ToxCast	32	15	0	7	10	0.68	1.00	0.84	1.00	0.58

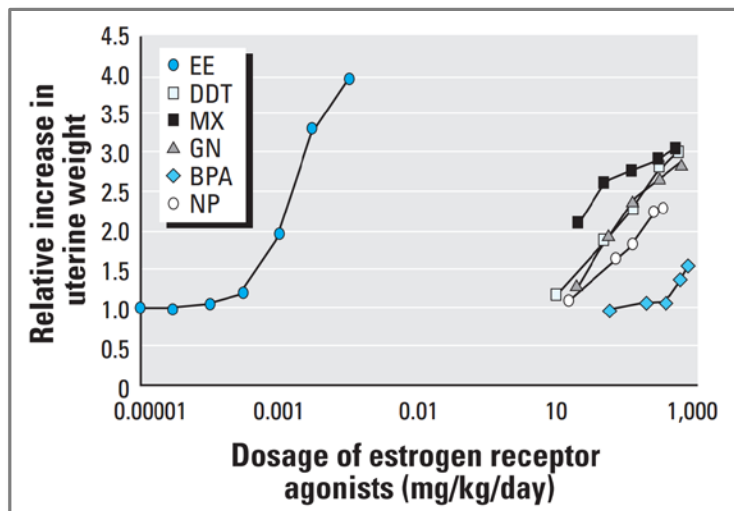
[1] West et al. (2010) Tox Appl Pharm 247: 18-27.

[2] Kleinstreuer et al. (2011) Tox Appl Pharm 257: 111-121.

[3] Palmer et al. (2013) Birth Defects Res B 98: 343-363.

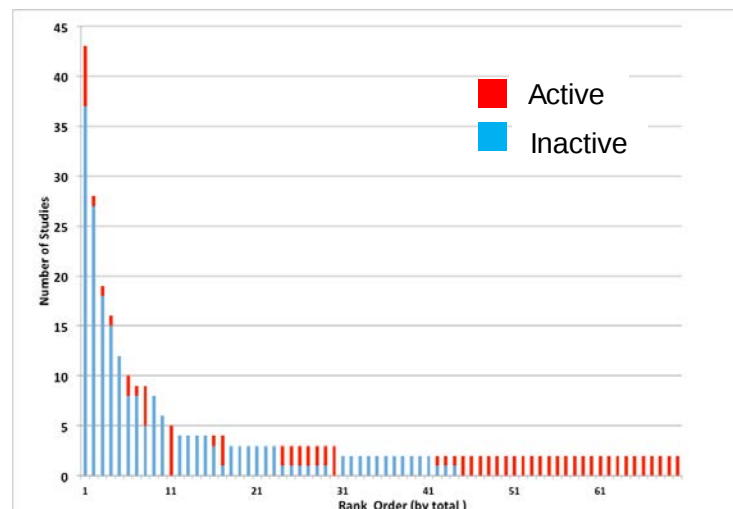
Lesson #1: Old Habits Die Hard

Original OECD TG 440 Validation



Owens and Koëter, *Environ Health Perspect*, 2003

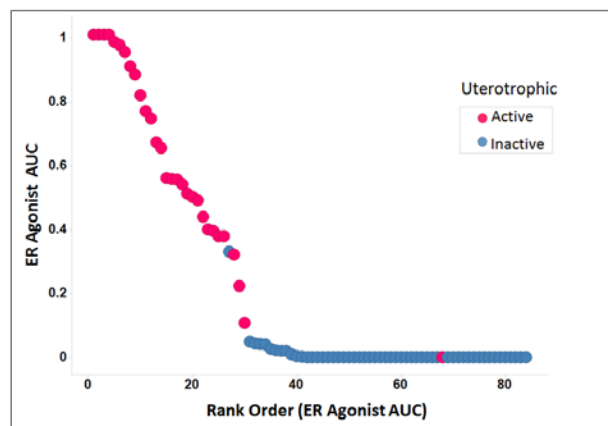
Concordance of *In Vivo* Uterotrophic Studies



Graph courtesy of Warren Casey

Predictive Performance of *In Vitro* Assays for *In Vivo* Uterotrophic Studies

True Positive	30
True Negative	54
False Positive	1
False Negative	1
Accuracy	0.97
Sensitivity	0.97
Specificity	0.98



Acknowledgements

Tox21 Colleagues:

NTP Crew

FDA Collaborators

NCATS Collaborators



EPA's National Center for Computational Toxicology

Visit EPA's Exhibit Booth #2133

EPA's Demo Sessions

- CPCat- Chemical and Product Categories Database
- iCSS Dashboard
- ToxCast Data Download Page
- AOP Wiki
- EDSP21 Dashboard
- More!

Booth Materials

- Project and Program Factsheets
- Information on Funding, Grants, and Employment Opportunities

Meet the Directors Sessions

- EPA Lab, Center and Office Directors
- Informal- 1 Hour Sessions

epa.gov/research/sot

For full calendar of events and materials