Incorporating New Technologies into Toxicity Testing and Risk Assessment:

Moving from 21st Century Vision to a Data-Driven Framework

May 22, 2012

ARA Workshop

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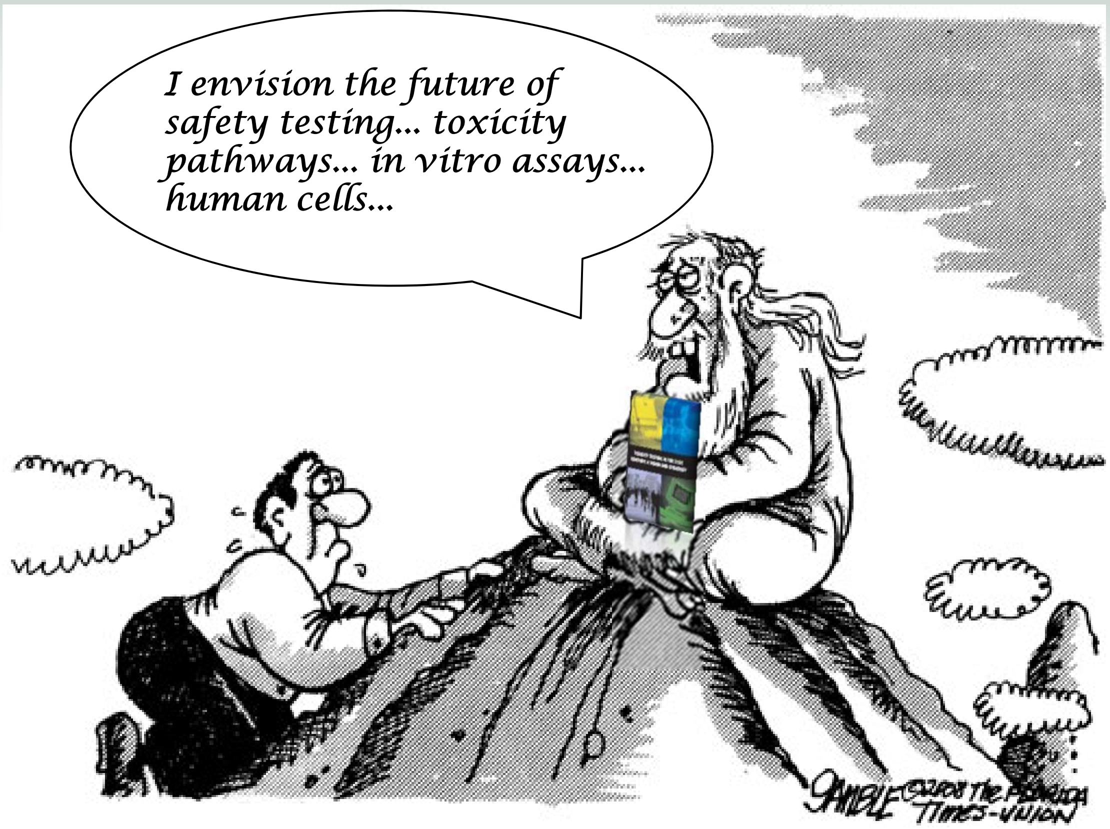
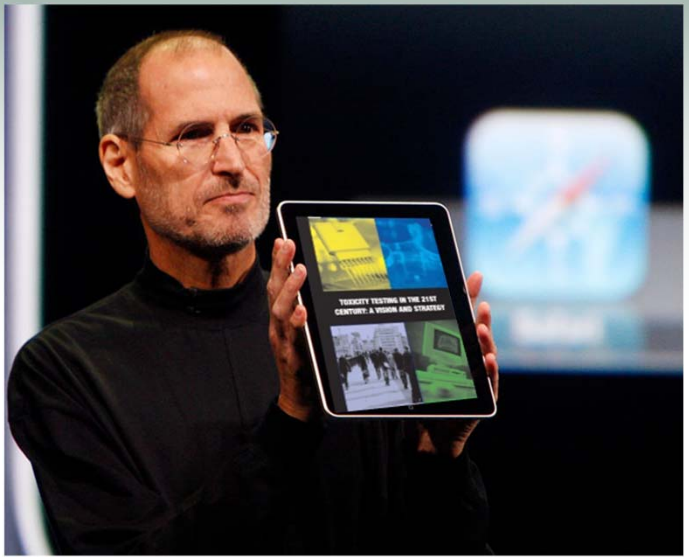
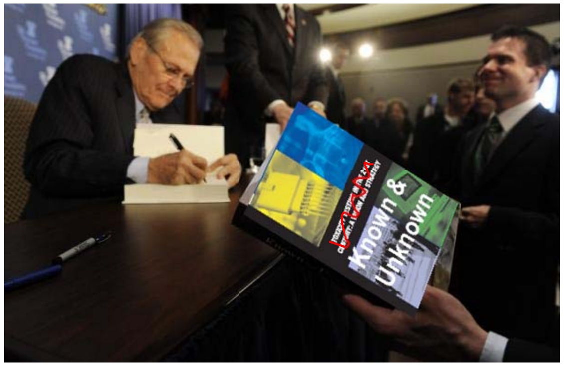
The Hamner Institutes for Health Sciences

In 2007 A Vision Was Bestowed on the Toxicology Community



The NRC Vision Went Viral



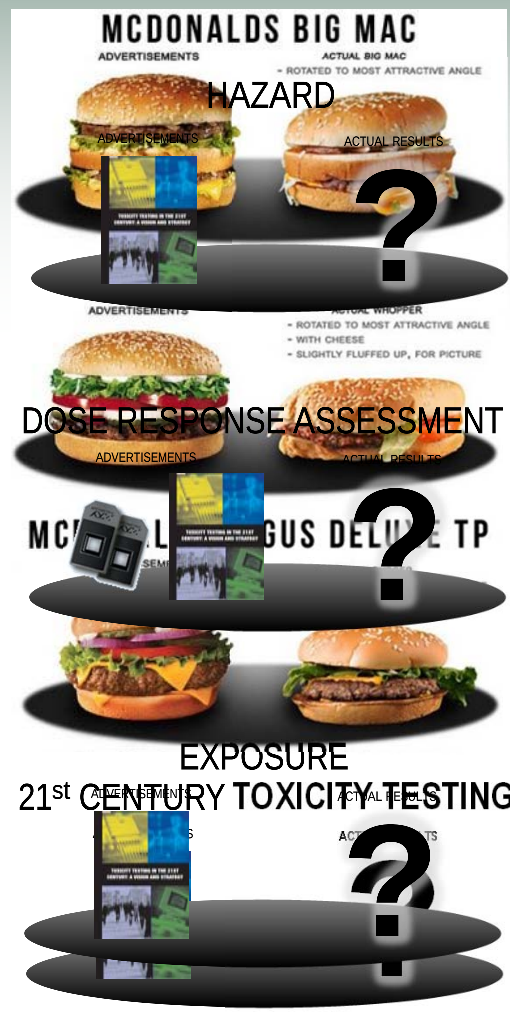


Now Everyone has a Vision...

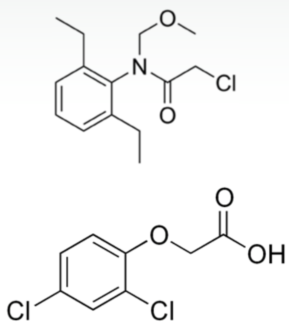
But, It is Time to Transition From Vision to Reality

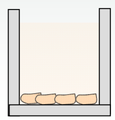
But, is it Time to Transition From Vision to Reality

Evaluating the Role of New Technologies in a Data-Driven Tox and Risk Assessment Framework

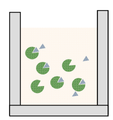


Initial Concept for ToxCast

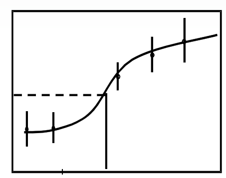


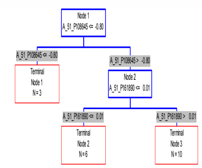


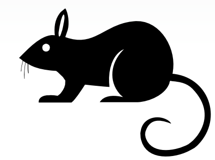
~200 Cellular Assays



~300 Biochemical Assays







In Vivo Endpoints

309 Phase I Chemicals (Pesticides/HPV)

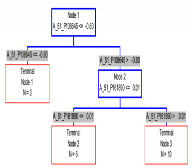
***In Vitro* High Throughput Screens**

Activity of the Chemical Based on Concentration in the Well

Predictive Combinations of Assays

***In Vivo* Hazard Prediction and Prioritization**

Currently Published Work on Predictive Toxicity Signatures



Signature Development

BIOLOGY OF REPRODUCTION **85**, 327–339 (2011)
Published online before print 12 May 2011.
DOI 10.1095/biolreprod.111.090977

Predictive Model of Rat Reproductive Toxicity from ToxCast High Throughput Screening[1]

Matthew T. Martin,[2] Thomas B. Knudsen, David M. Reif, Keith A. Houck, Richard S. Judson, Robert J. Kavlock, and David J. Dix

National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina

- Reproductive toxicity signature
- 74% Balanced Accuracy
- **Pre-filtered assays and lumped subset into into 6 classes based on genes and functional grouping**
- **Only study with external validation set**

***In Vitro* Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast Project**

Richard S. Judson, Keith A. Houck, Robert J. Kavlock, Thomas B. Knudsen, Matthew T. Martin, Holly M. Mortensen, David M. Reif, Daniel M. Rotroff, Imran Shah, Ann M. Richard, and David J. Dix

National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA

- Rat liver tumor signature
- No formal classification statistical analysis (cross-validation)

TOXICOLOGICAL SCIENCES **124(1)**, 109–127 (2011)
doi:10.1093/toxsci/kfr220
Advance Access publication August 26, 2011

Predictive Models of Prenatal Developmental Toxicity from ToxCast High-Throughput Screening Data

Nisha S. Sipes,*,[1] Matthew T. Martin,* David M. Reif,* Nicole C. Kleinstreuer,* Richard S. Judson,* Amar V. Singh,† Kelly J. Chandler,‡ David J. Dix,* Robert J. Kavlock,* and Thomas B. Knudsen*

**National Center for Computational Toxicology, Office of Research & Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711; †Lockheed Martin, Research Triangle Park, North Carolina 27711; and ‡National Health and Environmental Effects Research Laboratory, Office of Research & Development, U. S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711*

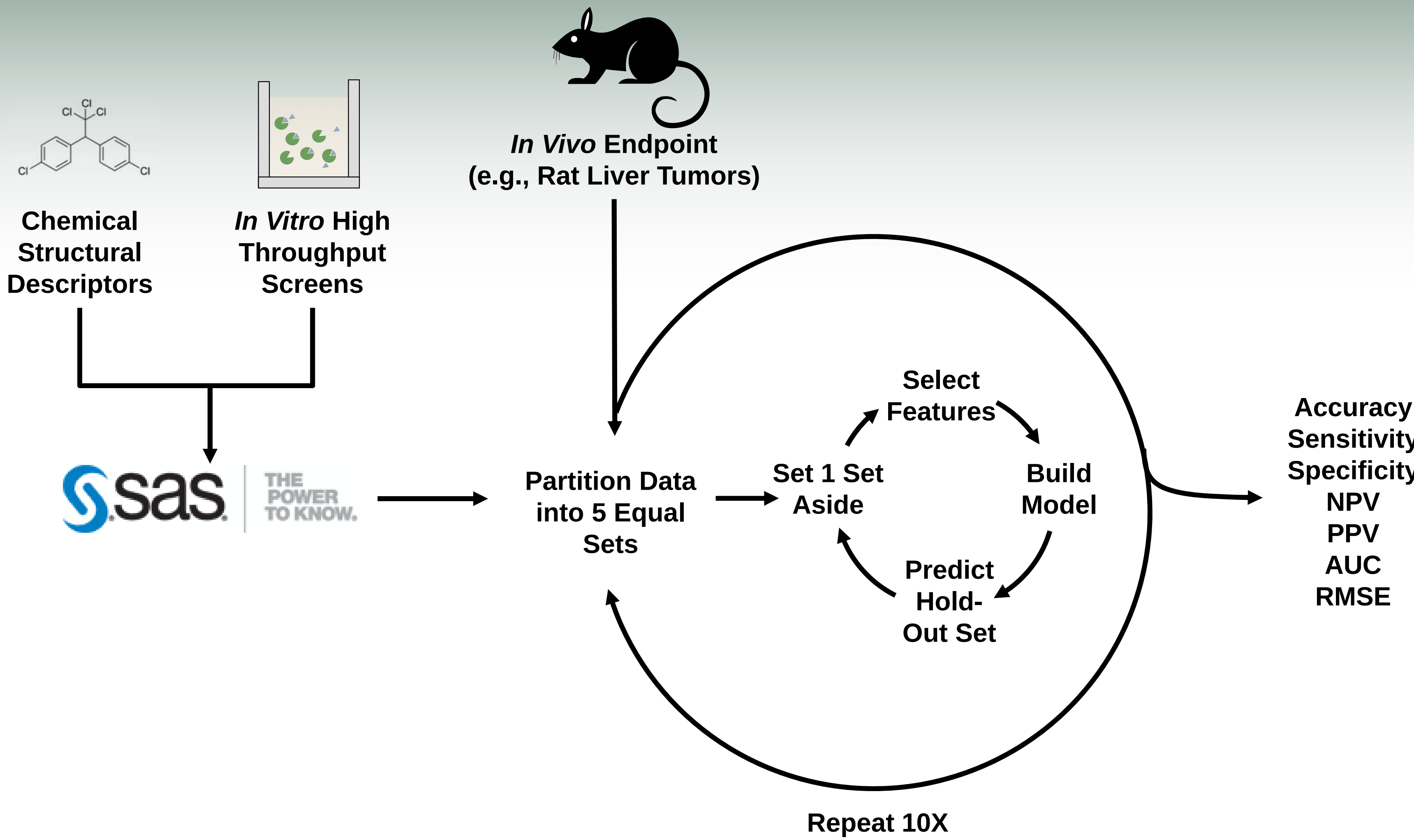
- Developmental toxicity signature
- 71% Balanced Accuracy
- **Pre-filtered assays and aggregated assays based on genes and GO categories**

Environmental Impact on Vascular Development Predicted by High Throughput Screening

Nicole C. Kleinstreuer[1], Richard S. Judson[1], David M. Reif[1], Nisha S. Sipes[1], Amar V. Singh[2], Kelly J. Chandler[1,3], Rob DeWoskin[4], David J. Dix[1], Robert J. Kavlock[1] and Thomas B. Knudsen[1]

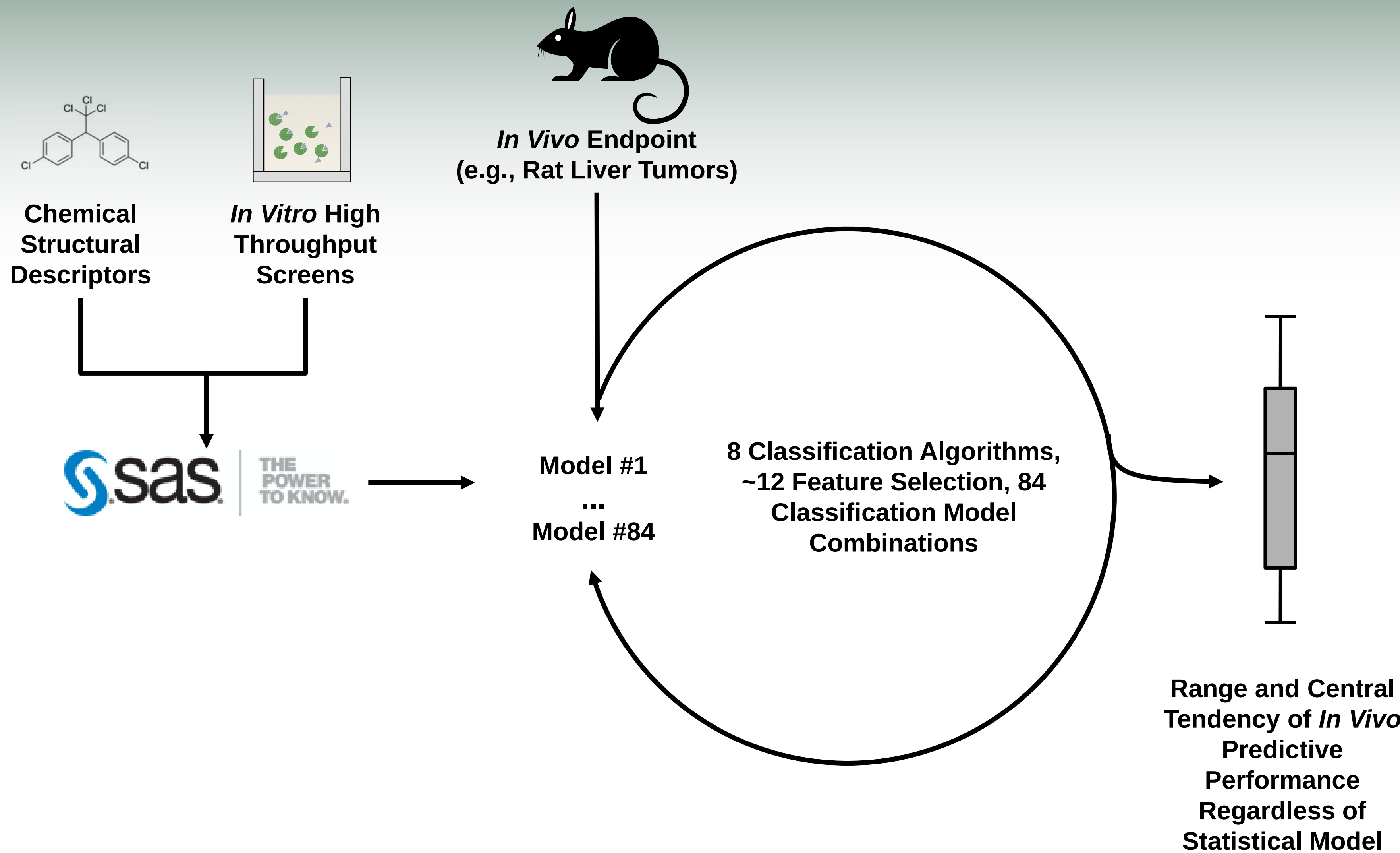
- Vascular development signature
- 80% Accuracy

Project Design



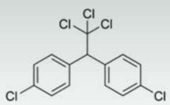
Thomas *et al., Tox Sci., In Press*

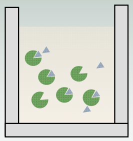
Project Design

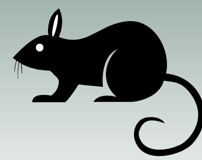


Thomas *et al.*, *Tox Sci.*, *In Press*

Project Design







60 *In Vivo* Endpoints

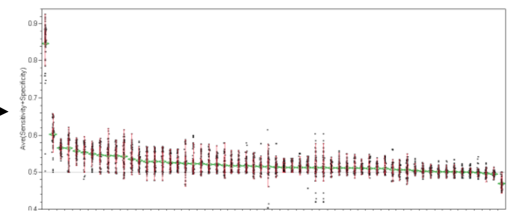
Chemical Structural Descriptors

***In Vitro* High Throughput Screens**

Model #1

...

Model #84



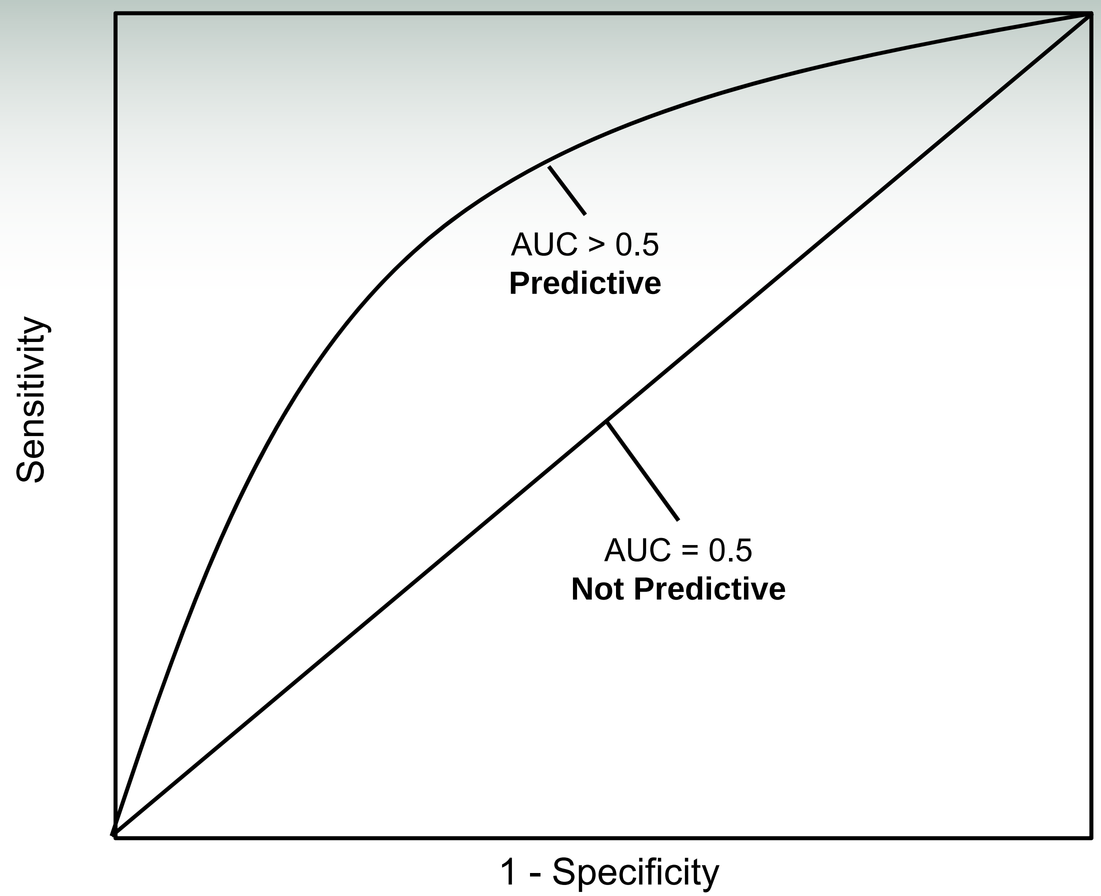
Broad-based Evaluation of *In Vitro*-to-*In Vivo* Predictive Performance

Thomas *et al.*, *Tox Sci.*, *In Press*

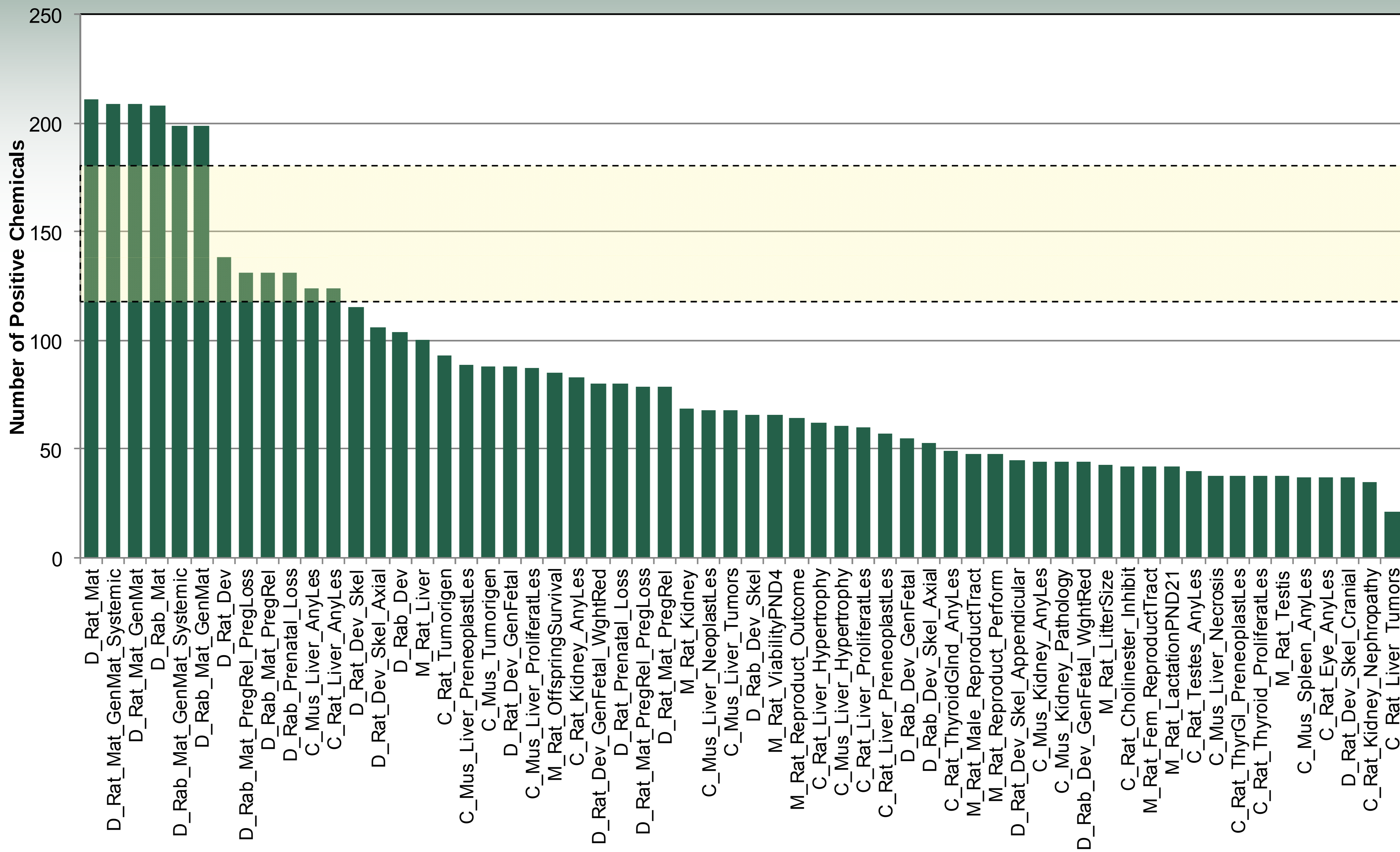
Getting on the Same Page for Statistics

		In Vivo Animal Response: Positive	*In Vivo* Animal Response: Negative	
Prediction Based on *In Vitro* Assays or Chemical Structure	Positive	TP	FP	PPV = TP / (TP + FP)
	Negative	FN	TN	NPV = TN / (FN + TN)
		Sensitivity = TP / (TP + FN)	Specificity = TN / (FP + TN)	

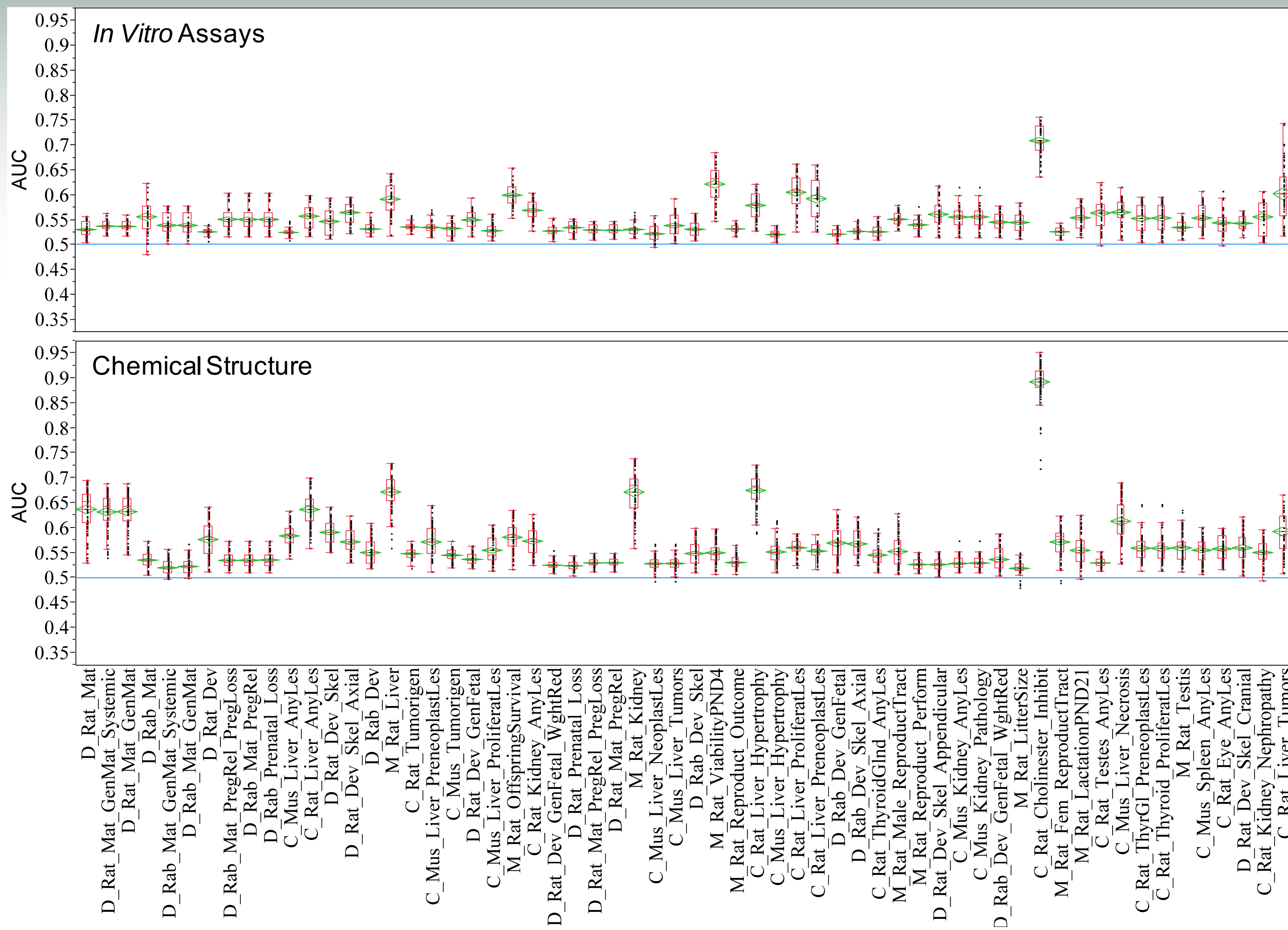
Getting on the Same Page for Statistics



Prevalence of Positive Chemicals Among Endpoints is an Issue

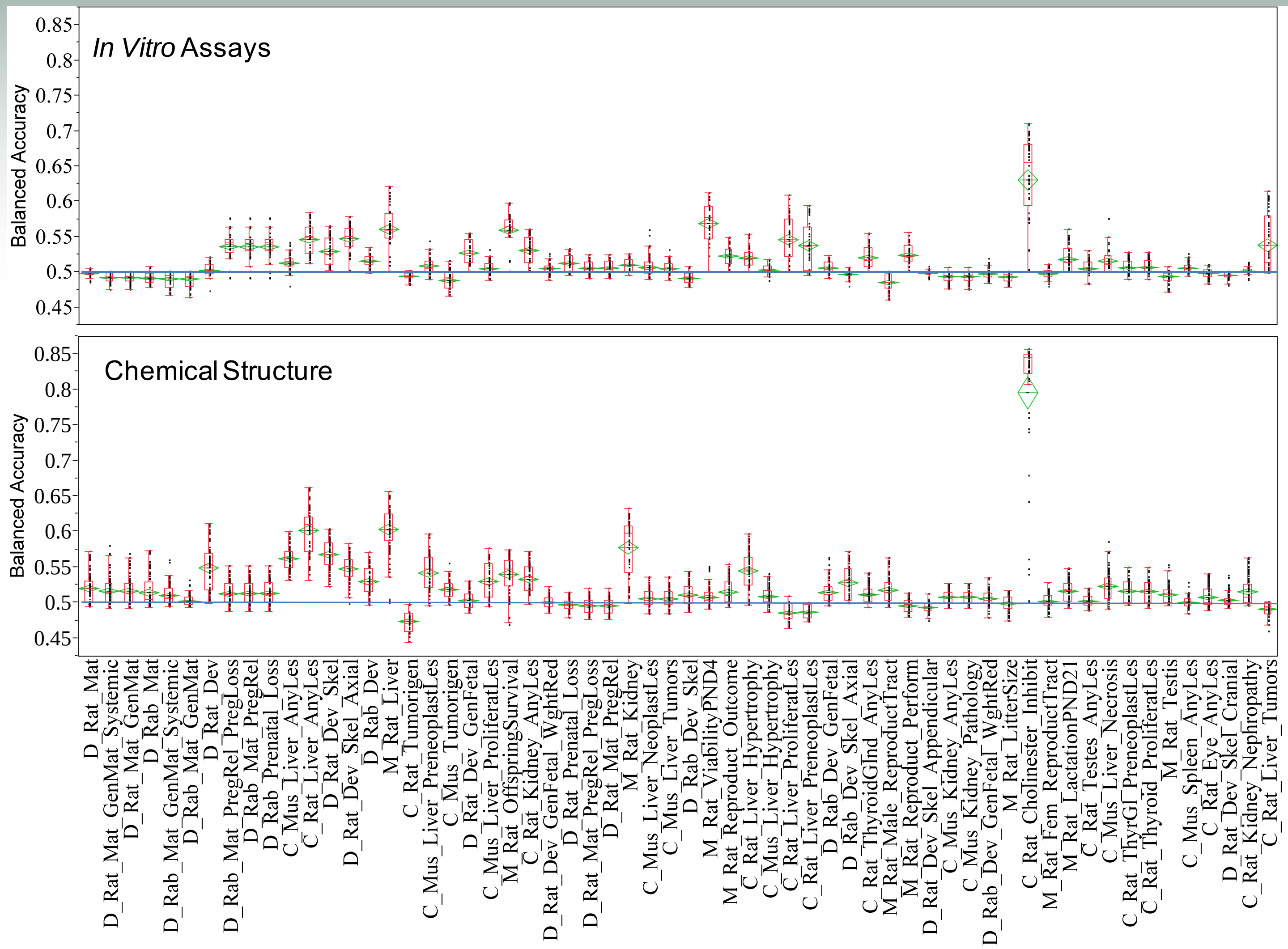


AUC of the ROC Curve of *In Vitro* Assays for Predicting *In Vivo* Toxicity



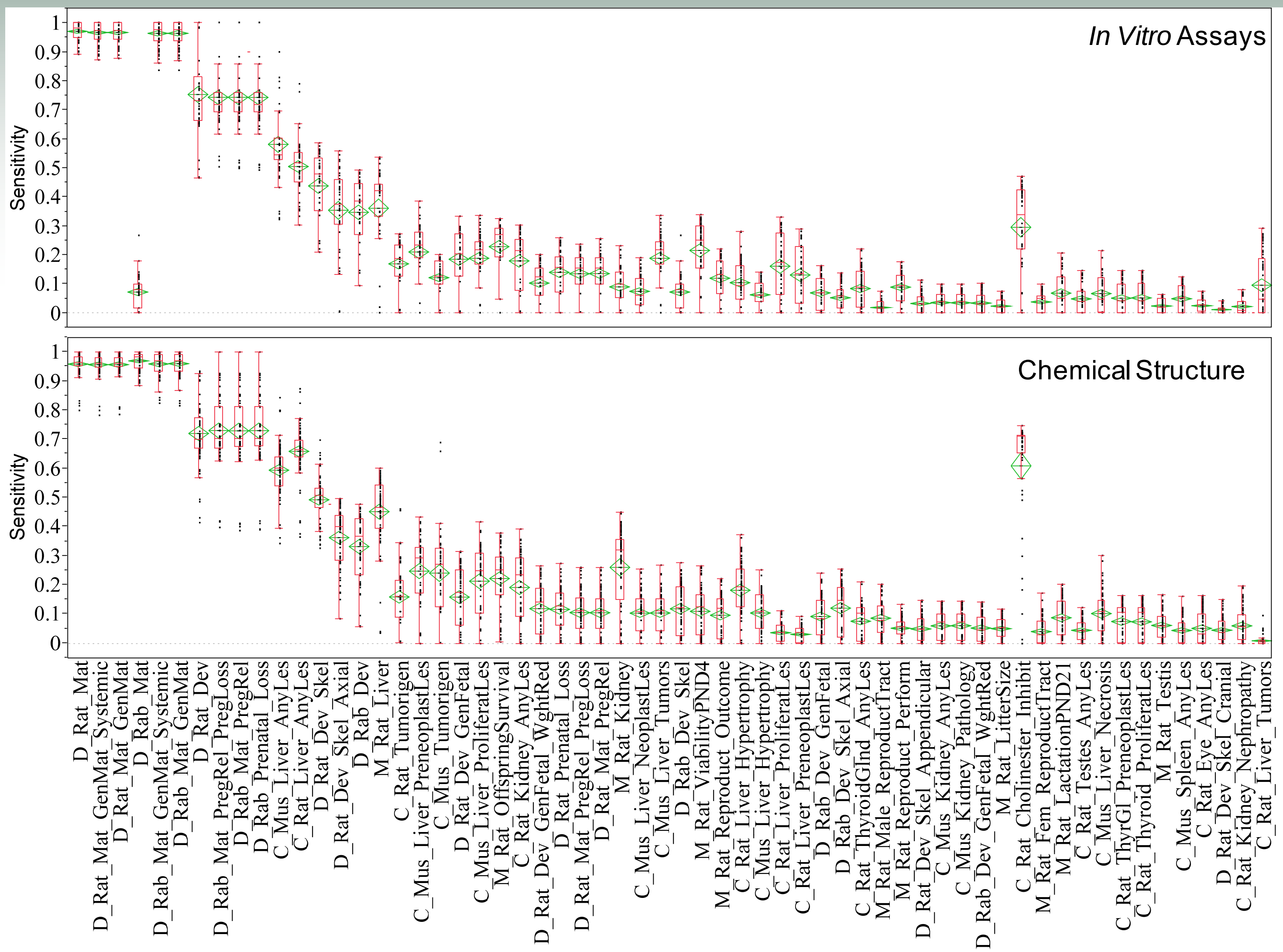
Thomas *et al.*, *Tox Sci.*, *In Press*

Balanced Accuracy of *In Vitro* Assays for Predicting *In Vivo* Toxicity

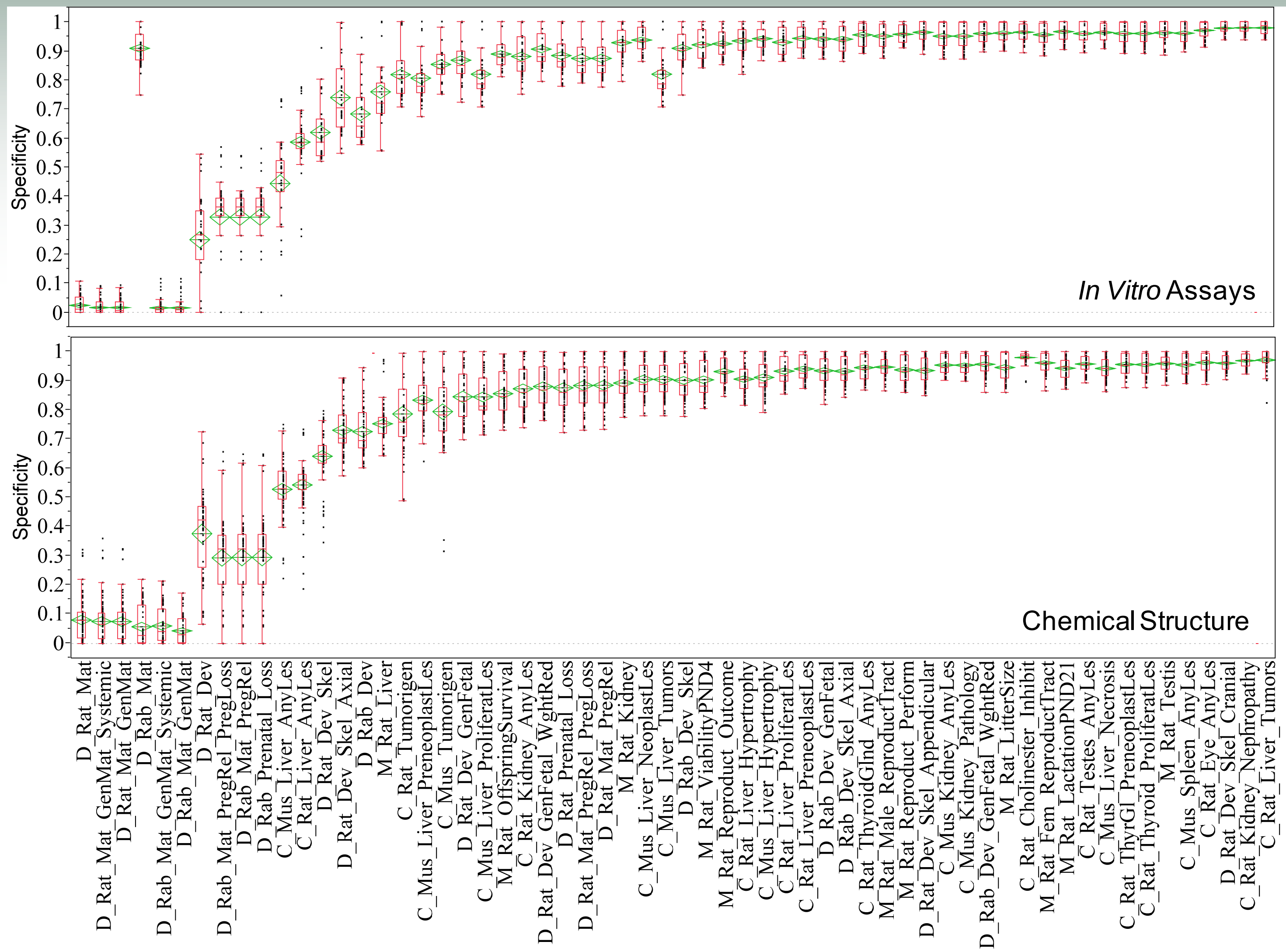


Thomas *et al.*, *Tox Sci.*, *In Press*

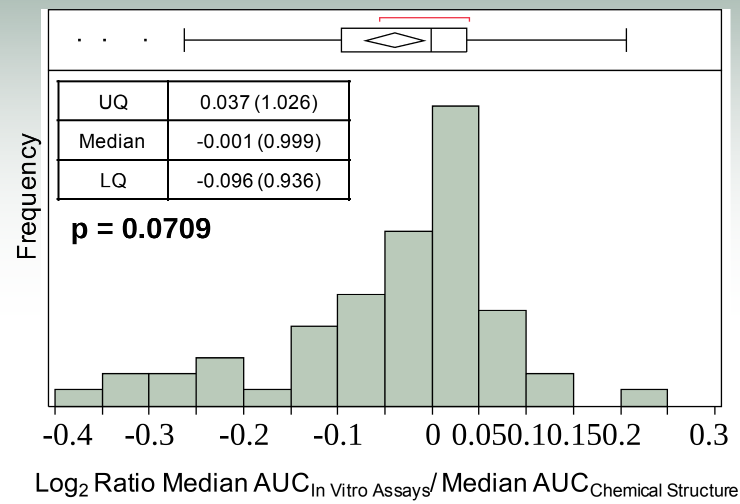
Sensitivity of *In Vitro* Assays for Predicting *In Vivo* Toxicity

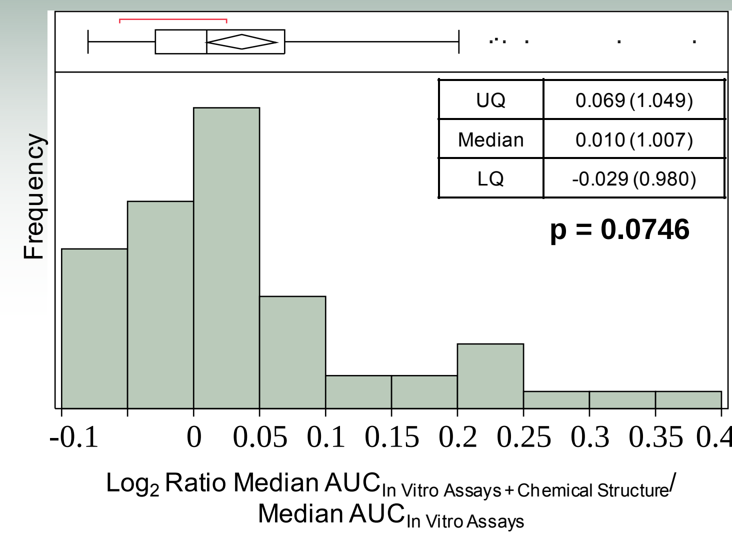


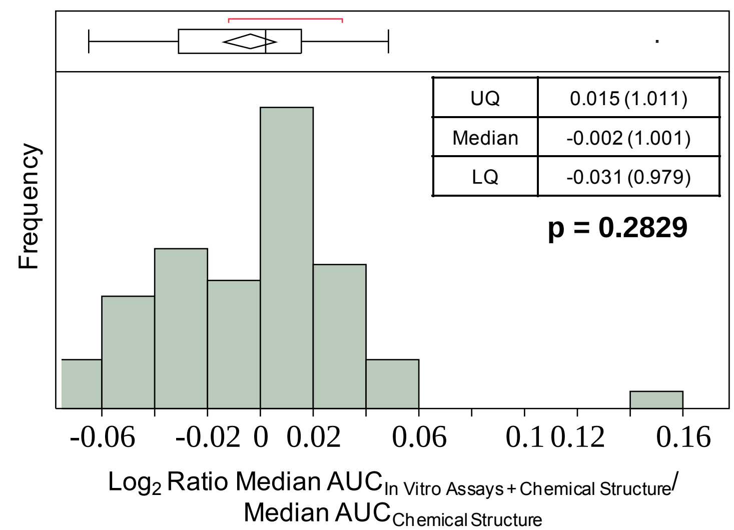
Specificity of *In Vitro* Assays for Predicting *In Vivo* Toxicity



In Vitro Assays Predict *In Vivo* Hazard No Better Than Chemical Structure

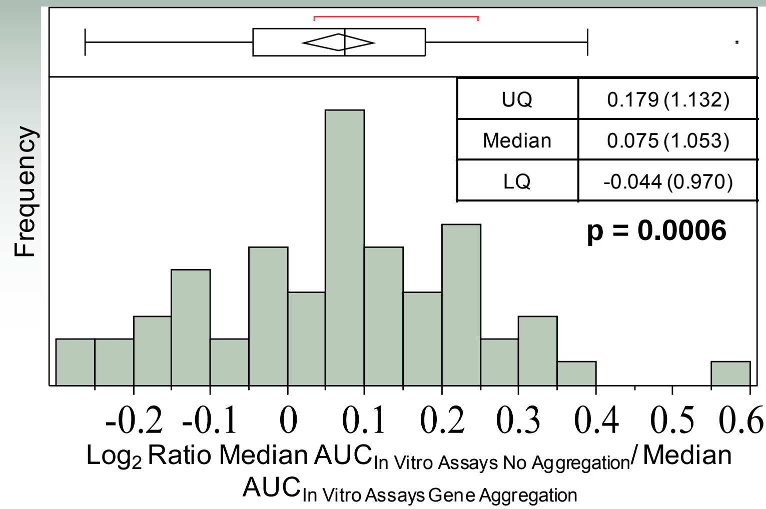


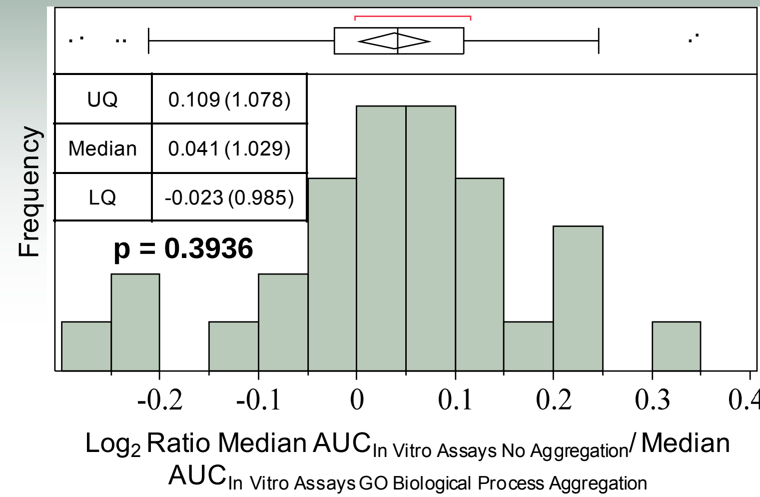


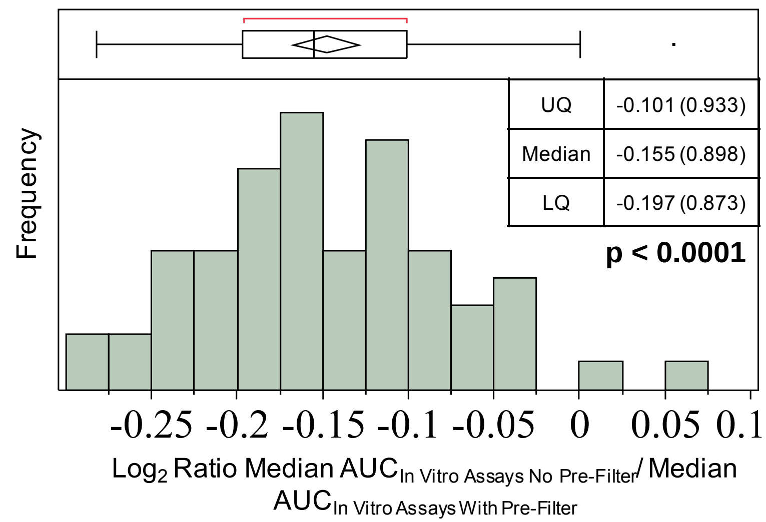


Thomas *et al.*, *Tox Sci.*, *In Press*

In Vitro Assay Aggregation Shows Little Benefit While Pre-Filtering Biases Performance

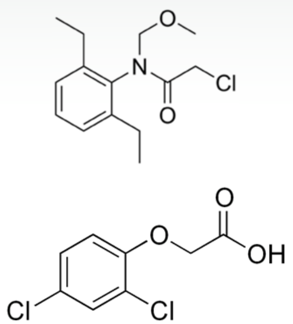


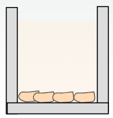




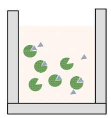
Thomas *et al., Tox Sci., In Press*

ToxCast Revisited

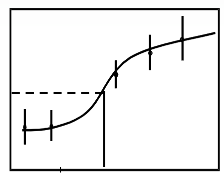


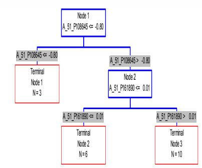


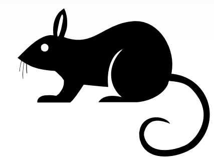
~200 Cellular Assays



~300 Biochemical Assays







In Vivo Endpoints

309 Phase I Chemicals (Pesticides/HPV)

***In Vitro* High Throughput Screens**

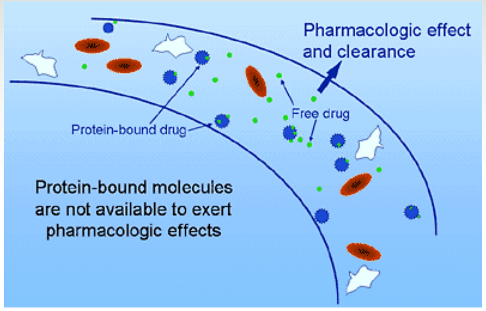
Activity of the Chemical Based on Concentration in the Well

Predictive Combinations of Assays

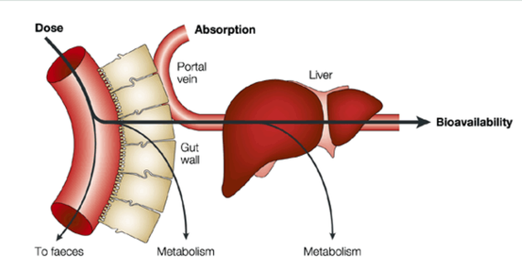
***In Vivo* Hazard Prediction and Prioritization**

Nominal Concentrations Can Misrepresent *In Vivo* Doses

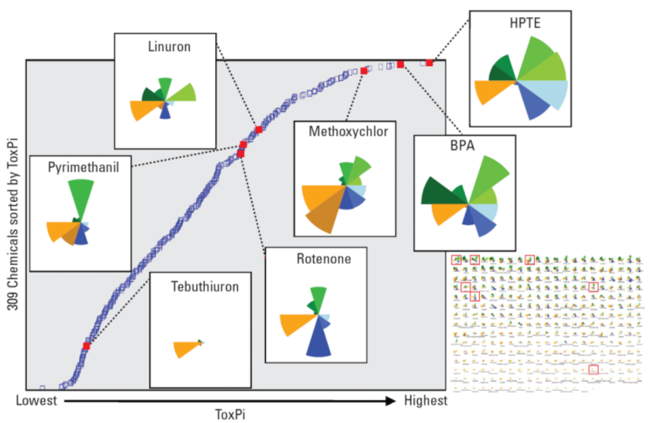
Protein Binding



Bioavailability

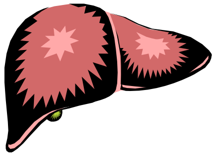


van de Waterbeemd and Gifford, *Nat Rev Drug Disc* 2:192, 2003

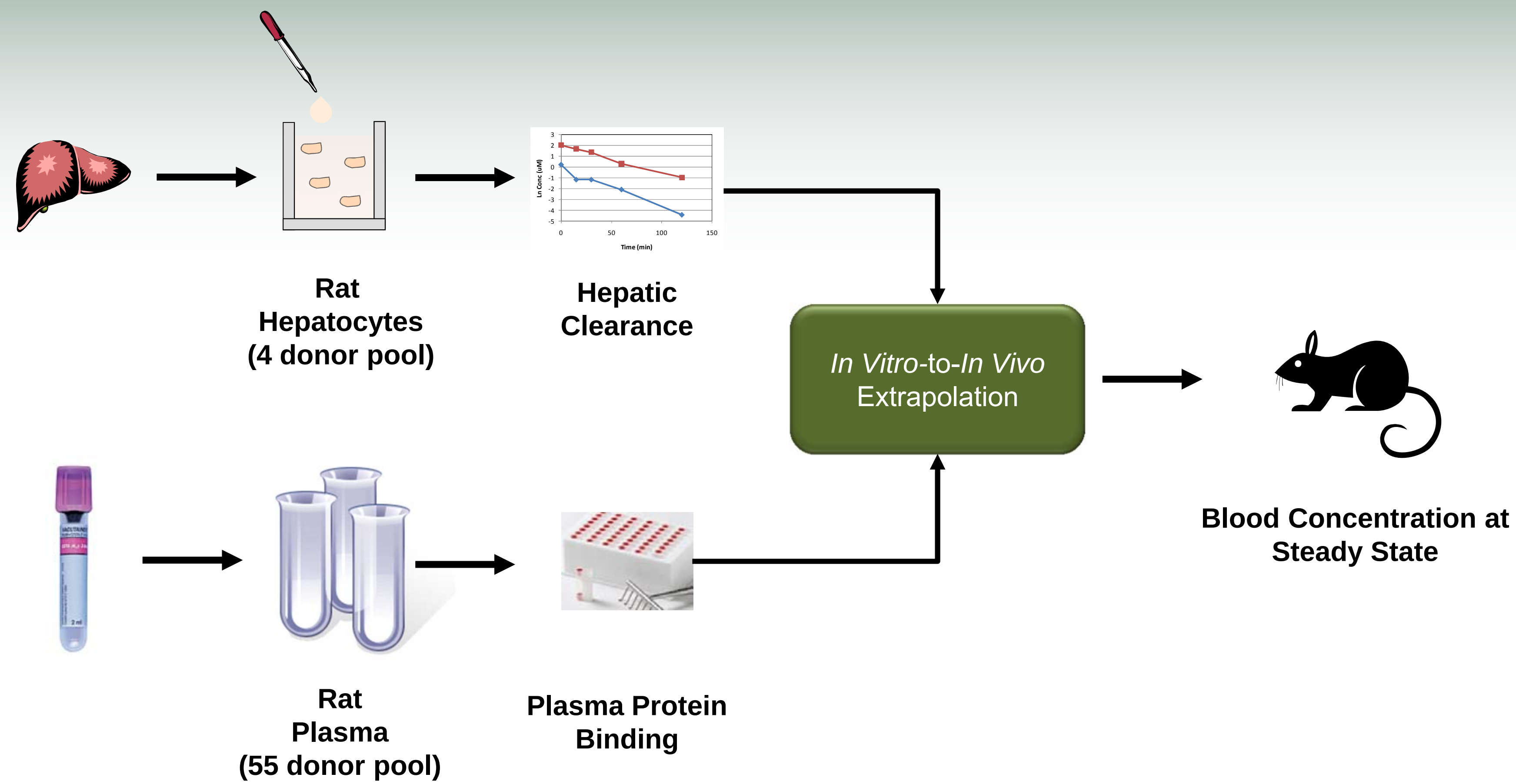


Reif *et al.* Environ Hlth Perspect 118:1714, 2010

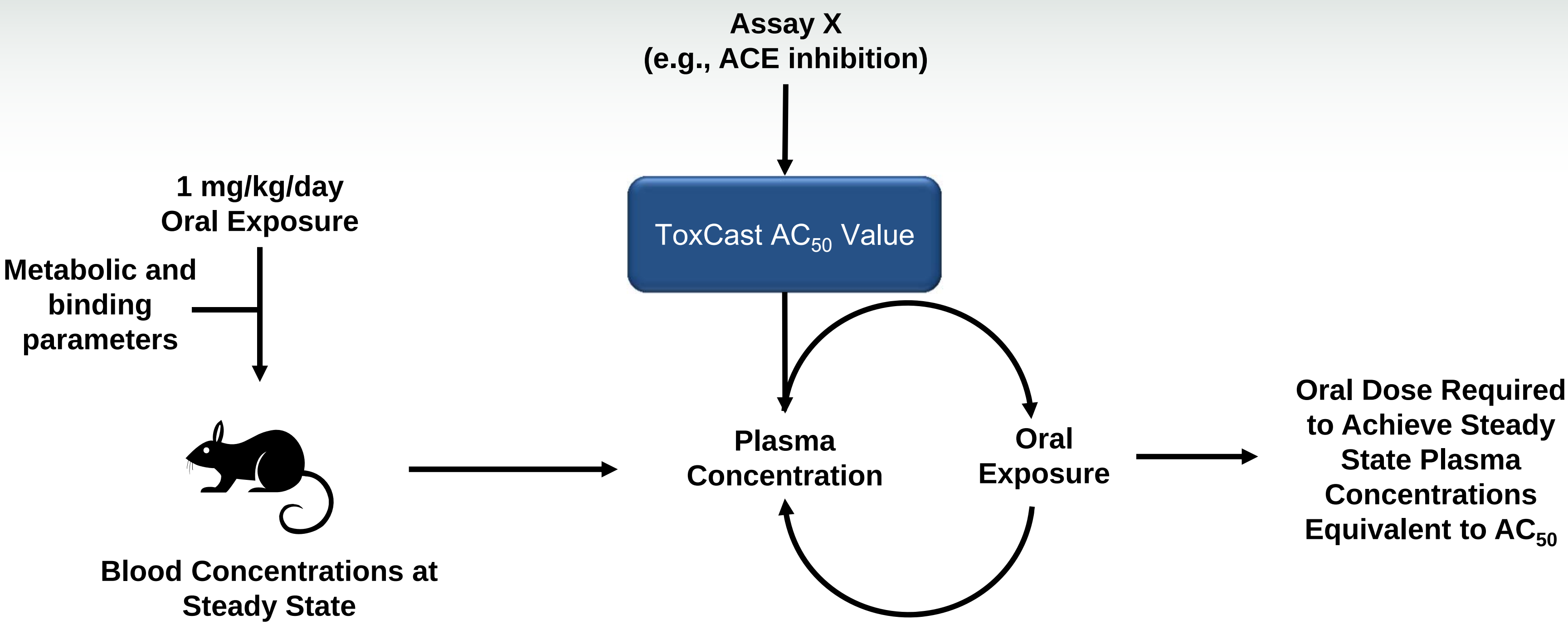
Metabolic Clearance



High-Throughput Pharmacokinetics

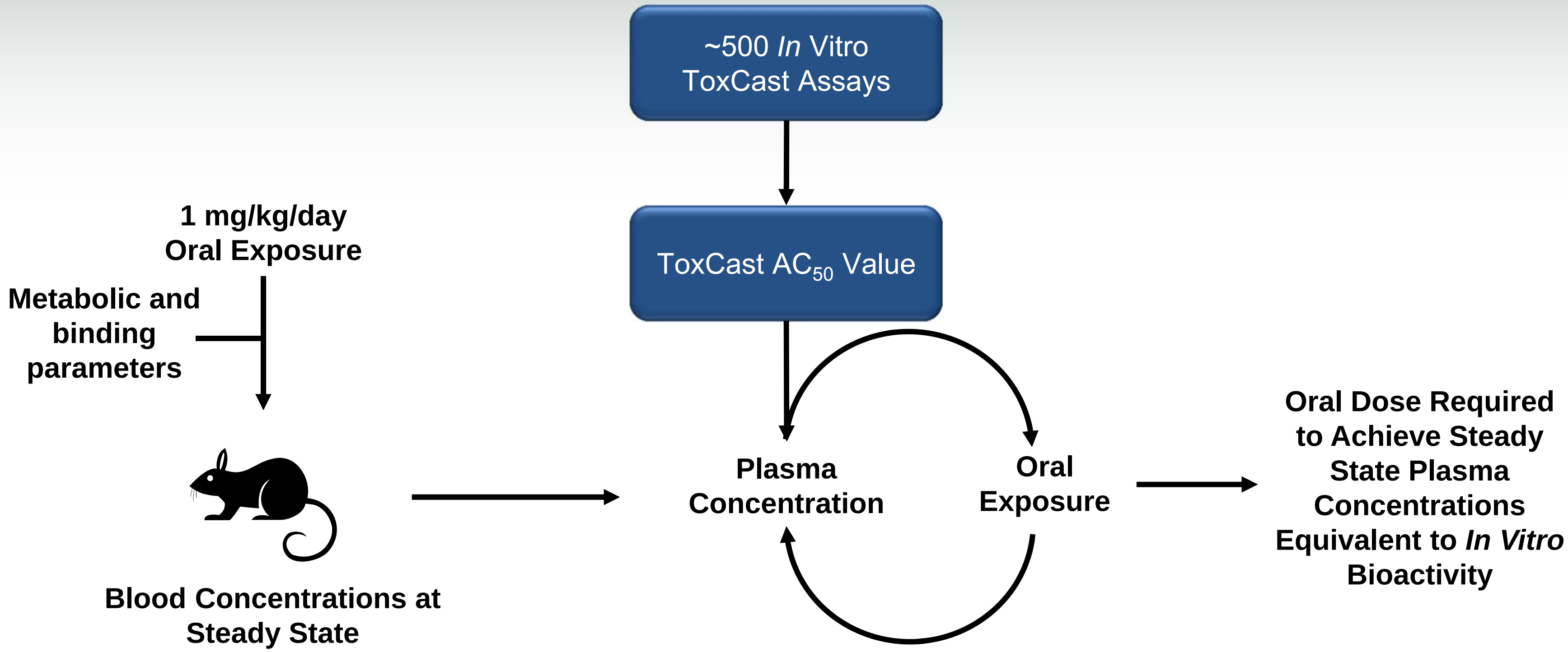


Using Reverse Dosimetry to Estimate Oral Equivalent Doses



$$\frac{\text{Oral Equivalent (mg/kg/day)}}{\text{ToxCast } AC_{50} \text{ (uM)}} = \frac{\text{1 mg/kg/day}}{\text{Upper } 95^{th} \text{ Percentile Css (uM)}}$$

Integrating Rat Dosimetry into ToxCast *In Vitro* Assays



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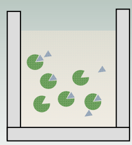
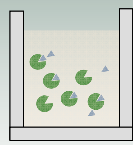
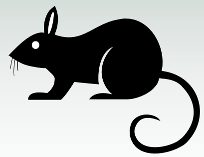
Evaluating the Effects of Dosimetry on Predictive Performance



In Vitro Assay AC_{50} Values



In Vitro Assay AC_{50} Values



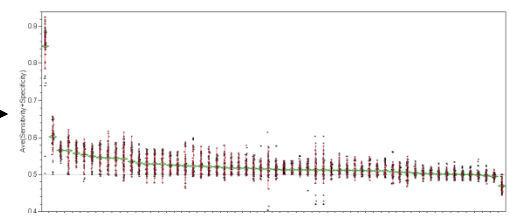
Rat *In Vivo* Endpoints

Rat Dosimetry-Adjusted Assays

Model #1

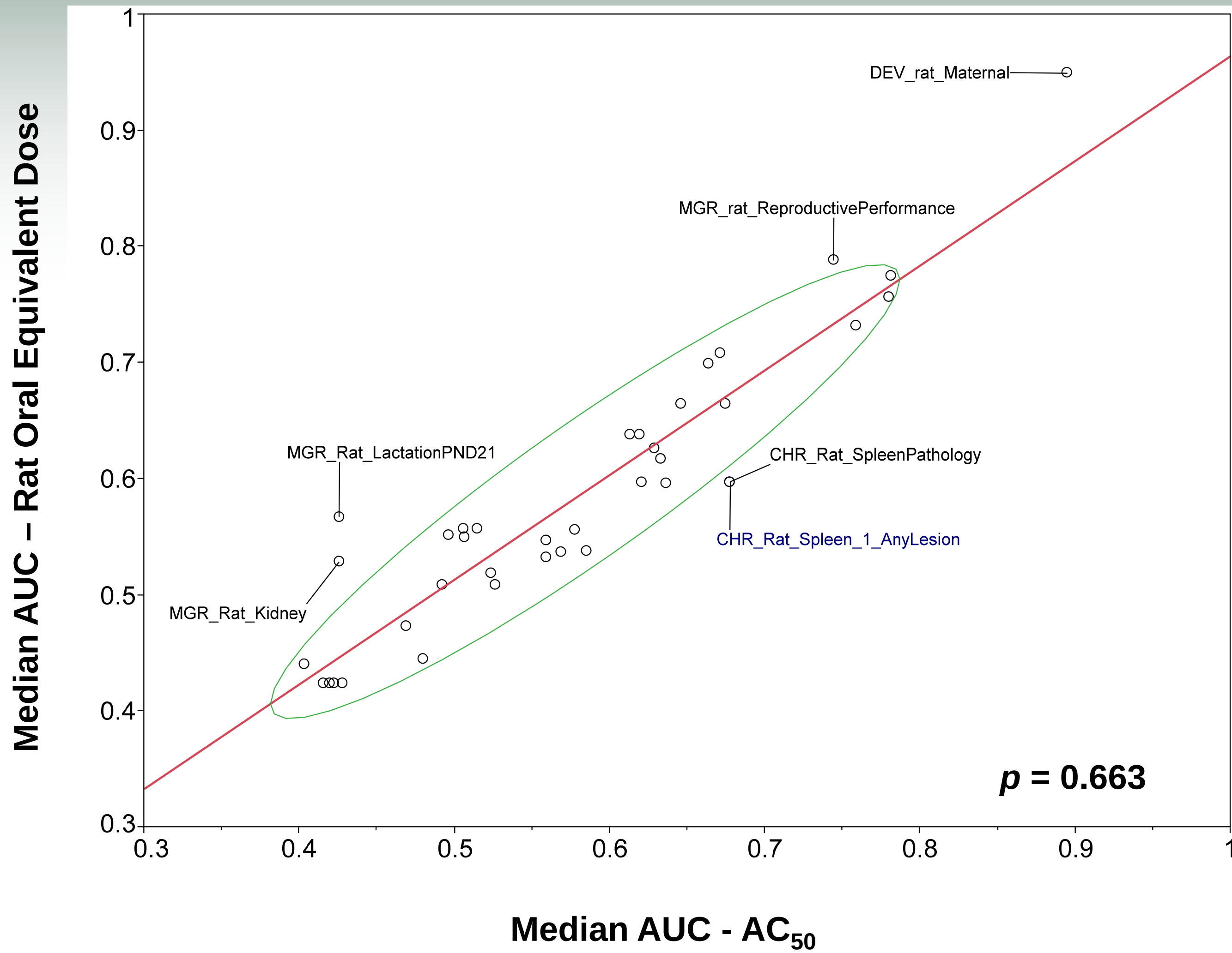
...

Model #84



Broad-based Evaluation of Whether Dosimetry Affects Predictive Performance

Adjusting *In Vitro* Assays for Dosimetry Does Not Improve Predictive Performance



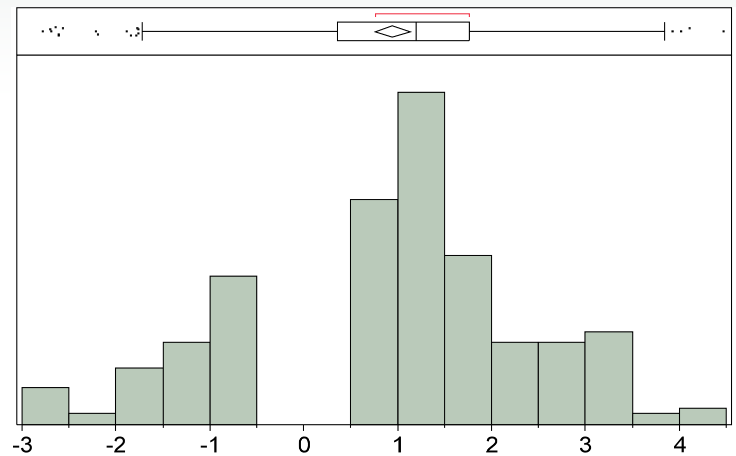
An Alternative View of the Utility of the ToxCast *In Vitro* Assays

In Vivo Endpoint	*In Vitro* Assay	Odds Ratio	p-value
Chronic Study, Rat Acetylcholineaserase Inhibition	Biochemical, Rat Acetylcholinesterase Binding	87.0	< 0.0001
	Biochemical, Human Acetylcholinesterase Binding	60.6	< 0.0001
	Biochemical, Human Butyrylcholinesterase Binding	12.8	0.0003
	Biochemical, Bovine Progesterone Receptor Binding	9.6	0.0007
Chronic Study, Mouse Liver Tumors	Cellular, Human Peroxisome Proliferator Activated Receptor Alpha Reporter	27.8	0.0021
	Biochemical, Guinea Pig Opioid Receptor, Kappa 1 Binding	22.4	0.0074
	Biochemical, Human Serotonin Transporter Binding	22.4	0.0074

[a]The *in vitro* assays for each *in vivo* endpoint were filtered to remove those with odds ratios < 5 and p-values > 0.01.

		In Vivo Animal Response: Positive	*In Vivo* Animal Response: Negative
In Vitro Assay Response	Positive	A	B
In Vitro Assay Response	Negative	C	D

Odds Ratio = (A/B)/(C/D)



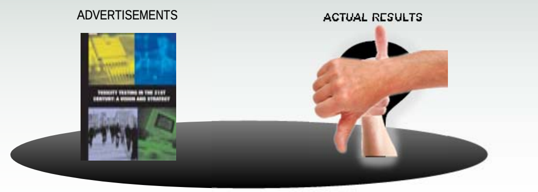
Log_2 Odds Ratios for All Significant *In Vitro* Assay: *In Vivo* Endpoint Combinations

Thomas *et al., Tox Sci., In Press*

Evaluating the Role of New Technologies in a Data-Driven Tox and Risk Assessment Framework

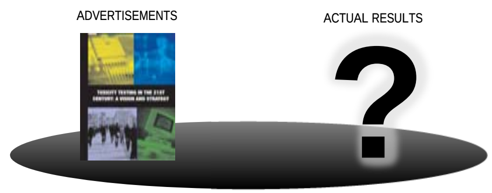
MODE OF ACTION

HAZARD



DOSE RESPONSE ASSESSMENT

EXPOSURE

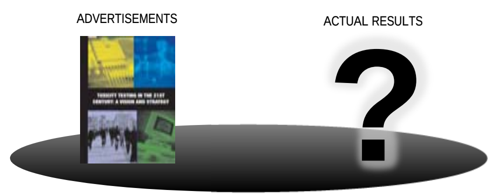


Evaluating the Role of New Technologies in a Data-Driven Tox and Risk Assessment Framework

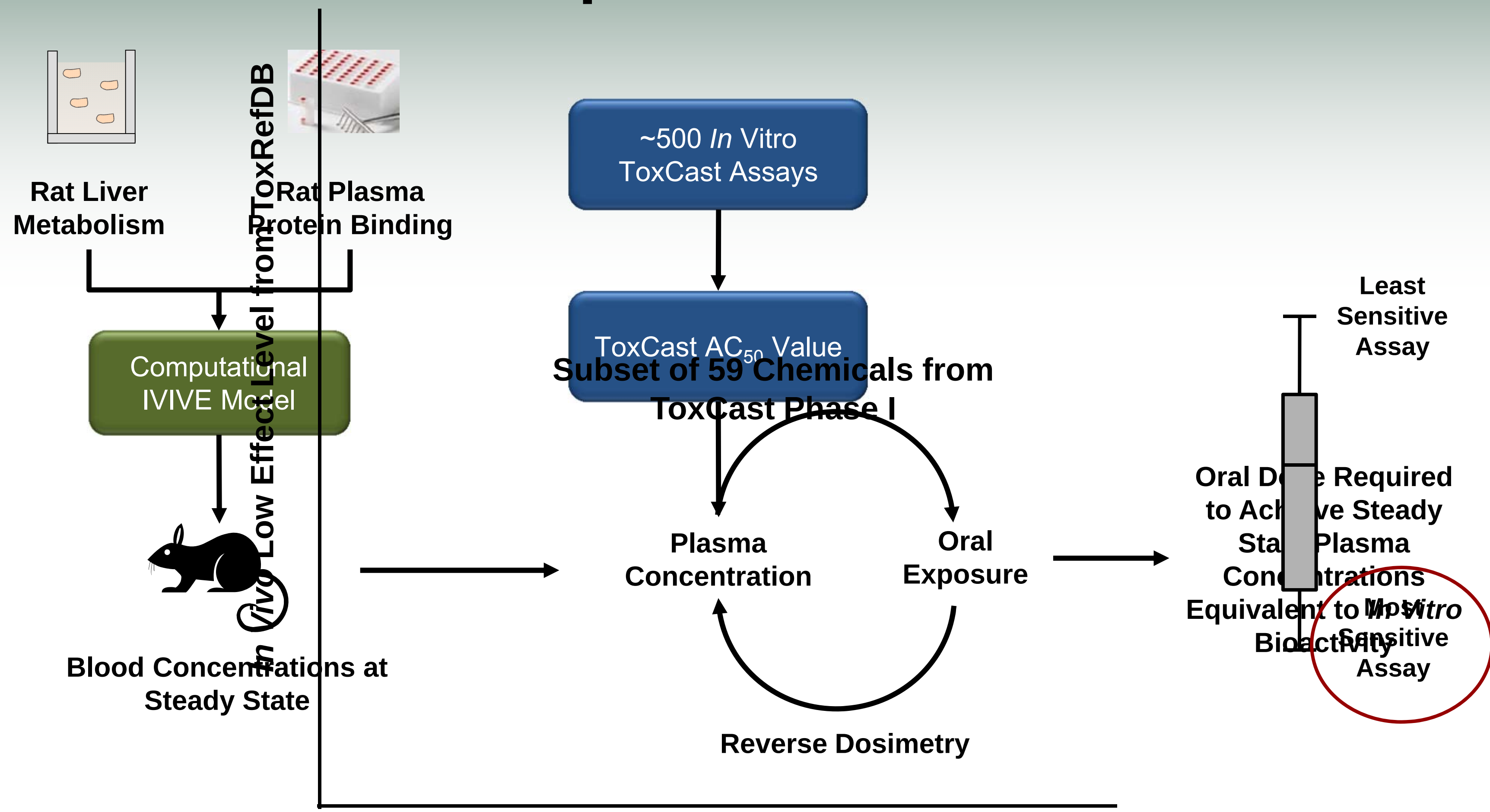
MODE-OF-ACTION

DOSE RESPONSE ASSESSMENT

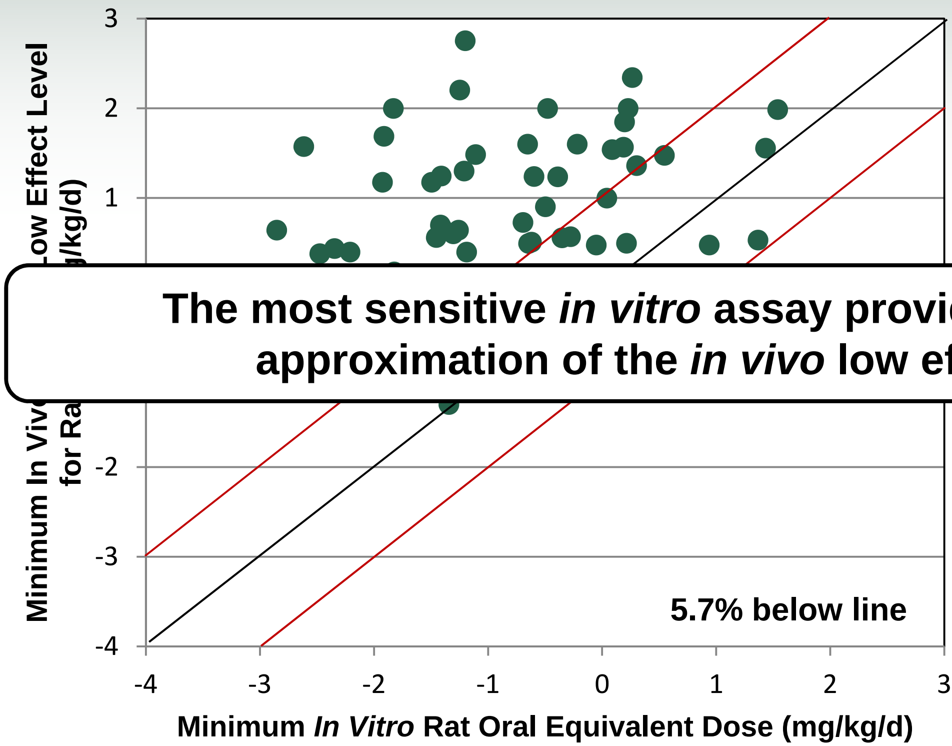
EXPOSURE



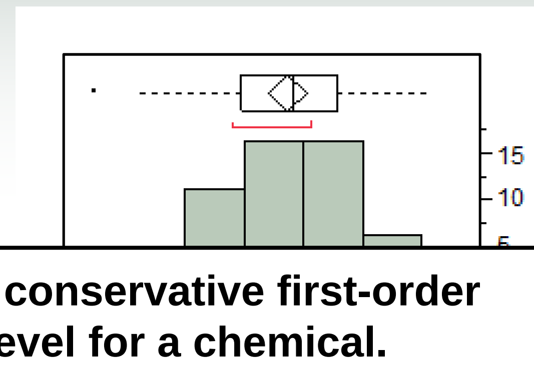
Evaluating the *In Vitro* ToxCast Assays for *In Vivo* Dose-Response Assessment



Comparison of *In Vivo* Low Effect Levels with Dosimetry Adjusted *In Vitro* Assays



The most sensitive *in vitro* assay provides a conservative first-order approximation of the *in vivo* low effect level for a chemical.

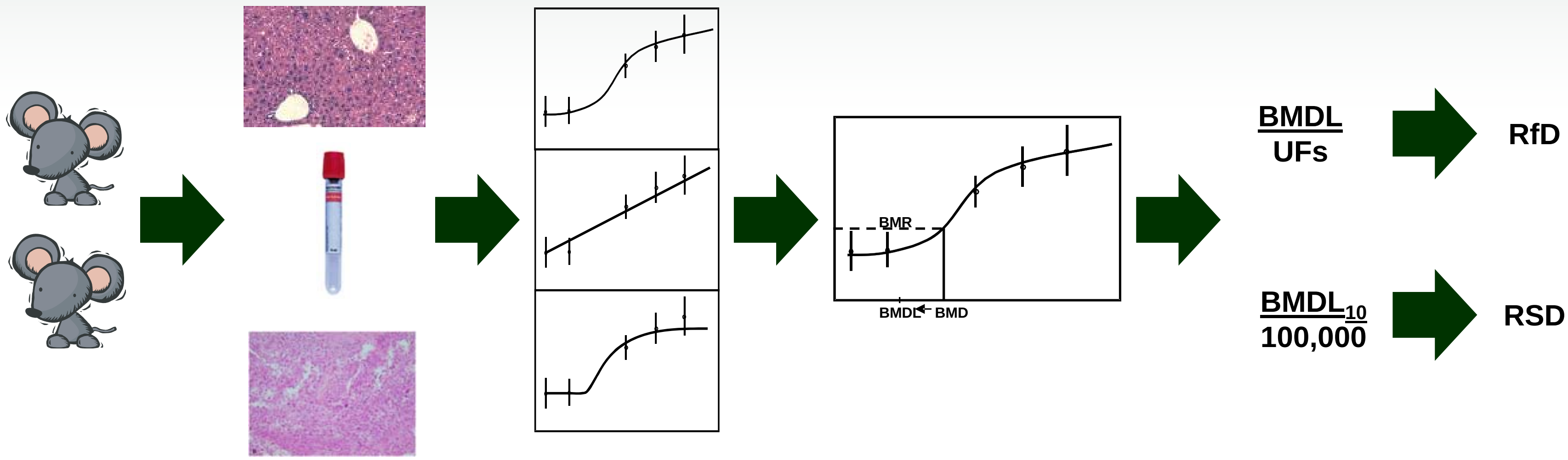


Min Oral Equivalent Dose

Distribution Summary Statistics

Median	1.82	(66.07)
Upper Quartile	2.55	(354.81)
Lower Quartile	0.95	(8.91)

Traditional Risk Assessment Paradigm Based on *In Vivo* Pathological and Physiological Responses



Subchronic and Chronic Animal Studies

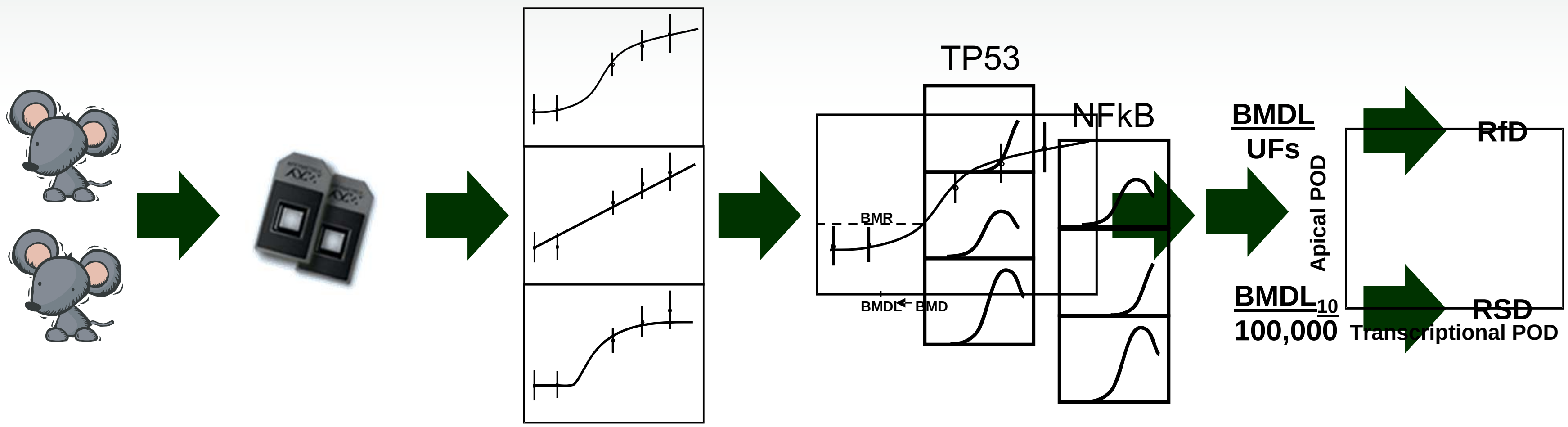
Pathological Responses

Fit Data with Statistical Models

Identify Point of Departure (i.e., BMD)

Derive Safe Exposure Level

Integrating *In Vivo* Transcriptomics Into the Traditional Risk Assessment Paradigm

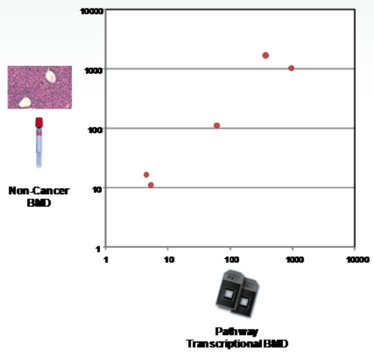


Subchronic Animal Studies | **Transcriptional Responses** | **Fit Each Gene with Statistical Models** | **Identify Point of Departure (i.e., BMD)** | **Group Genes By Signaling Pathway** | **Derive Safe Exposure Level** | **Compare *In Vivo* Apical and Transcriptional PODs**

Thomas *et al., Tox Sci.*, 2011
Thomas *et al., Mut Res.*, 2012

Evaluating *In Vivo* Transcriptomics for Dose Response Assessment

Part I



Relationship Between Apical and Transcriptional Points-of-Departure Following a Subchronic Exposure

Thomas *et al.*, *Tox Sci.*, 2011
Thomas *et al.*, *Mut Res.*, 2012

Part II

Relationship Between Apical and Transcriptional Points-of-Departure As a Function of Time

Experimental Study Design

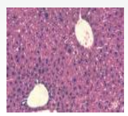
Chemical[a]	Route	Doses[b]	Rodent Model	Time Point	Target Tissue
1,4-Dichlorobenzene	Gavage	100, <u>300</u>, 400, 500, <u>600</u> mg/kg	Female B6C3F1 mice	90 d	Liver
Propylene glycol mono-t-butyl ether	Inhalation	25, <u>75</u>, <u>300</u>, 800, <u>1200</u> ppm	Female B6C3F1 mice	90 d	Liver
1,2,3-Trichloropropane	Gavage	2, <u>6</u>, <u>20</u>, 40, <u>60</u> mg/kg	Female B6C3F1 mice	90 d	Liver
Methylene Chloride	Inhalation	100, 500, <u>2000</u>, 3000, <u>4000</u> ppm	Female B6C3F1 mice	90 d	Liver, Lung
Naphthalene	Inhalation	0.5, 3, <u>10</u>, 20, <u>30</u> ppm	Female B6C3F1 mice	90 d	Lung

[a]All chemicals previously tested by the U.S. National Toxicology Program
[b]Underlined doses used in NTP two-year rodent bioassay

Measured apical (histological and organ weight; n = 10) and gene expression changes (n = 5) at each dose in the target tissue.

Thomas *et al., Tox Sci.*, 2011
Thomas *et al., Mut Res.,* 2012

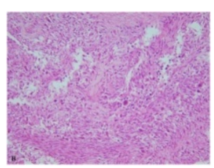
Noncancer and Cancer Points-of-Departure for Apical Endpoints



Noncancer Endpoints

Chemical	Endpoint	BMD (mg/kg-d or mg/m^3)[a]	BMDL (mg/kg-d or mg/m^3)[a]
DCBZ	Relative Liver Weight	174.6	112.0
PGBE	Relative Liver Weight	2067.0	1687.2
TCPN	Bronchiole Epithelial Degeneration	24.9	16.7
MECL	Periportal Vacuolation	2170.6	1036.3
NPTH	Bronchiole Epithelial Degeneration	16.9	11.2

[a]BMD = Dose at 10% extra risk or 1 SD; BMDL = 95% lower bound on BMD.



Cancer Endpoints

Chemical	Tissue	BMD (mg/kg-d or mg/m^3)[a]	BMDL (mg/kg-d or mg/m^3)[a]
DCBZ	Liver	218.2	158.3
PGBE	Liver	1774.0	865.7
TCPN	Liver	22.8 (2.8)[b]	13.0 (1.3)[b]
MECL	Liver	3544.6	1930.5
MECL	Lung	790.7	632.3
NPTH	Lung	119.5	91.7

[a]BMD = Dose at 10% extra risk; BMDL = 95% lower bound on BMD

[b]BMD and BMDL values calculated using a multi-stage Weibull model per the EPA IRIS summary.

Identifying Cellular Pathway BMDs that Correlate Noncancer Endpoints

Pathway ID	Pathway Name	Partial Correlation Coefficient	Partial Correlation *P*-value
	Top 10 GeneGo Pathway Maps with Highest Positive		
2325	Androstenedione and testosterone biosynthesis and metabolism p.1/ Rodent version		
2324	Pentose phosphate pathway/ Rodent version		
844	Cortisone biosynthesis and metabolism		
665	Immune response_Lectin induced complement pathway		
846	Androstenedione and testosterone biosynthesis and metabolism p.1		
138	Regulation of lipid metabolism_Regulation of acetyl-CoA carboxylase 1 activity in keratinocytes		
726	Regulation of lipid metabolism_Insulin regulation of fatty aci methabolism		
400	G-protein signaling_N-RAS regulation pathway		
399	G-protein signaling_K-RAS regulation pathway		
2998	Muscle contraction_nNOS Signaling in Skeletal Muscle		

Lung and liver injury shown to increase pentose phosphate activity. Studies suggest that organisms reorient cellular metabolism from glycolysis to the pentose phosphate pathway under stress (Grant J Biol 2008).

Lectin complement pathway plays a major role in the clearance of apoptotic cells (Stuart et al. J Immunol 2005).

Ras plays a role in regenerative cell proliferation (Nojima et al. Nat Cell Biol 2008) and re-epithelialisation following injury regulated by TGFβ through the Ras pathway (Secker et al. Exp Cell Res 2008).

Thomas *et al.*, *Mut Res*, 2012

Identifying Pathway BMDs that Correlate Cancer Endpoints

Pathway ID	Pathway Name
	Top 10 GeneGo Pathways with Highest Positiv
2749	Cell adhesion_Alpha-4 integrins in cell migration and adhesion
4583	Cell cycle_Influence of Ras and Rho proteins on G1/S Transition
3173	Immune response_IL-7 signaling in T lymphocytes
539	Development_VEGF signaling and activation
2748	Immune response_IL-23 signaling pathway
496	Translation _Regulation of EIF4F activity
836	Cholesterol metabolism
814	TCA
535	Development_ERBB-family signaling
631	Development_Thrombopoietin-regulated cell processes

Expression of α-4 integrins has been associated with cellular transformation and metastasis (Holzmann et al. Curr Top Microbiol Immunol 1998).

Ras and Rho proteins regulate G1 cell-cycle progression and are oncogenes (Bos Cancer Res 1989; del Peso et al. Oncogene 1997). Activation of K-Ras is an early event that often occurs in chemically-induced lung tumors (Wakamatsu et al. Toxicol Pathol 2007).

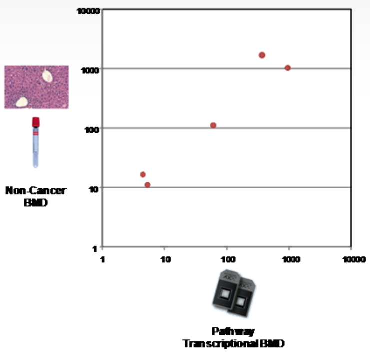
eIF4F is a complex of proteins that includes eIF4A, eIF4E, and eIF4G. eIF4E is an proto-oncogene that regulates the translation of a specific subset of tumor-promoting mRNAs (Robert and Pelletier Expert Opin Ther Targets 2009).

Role of Vegf and Erbb signaling well established in cancer.

Thomas *et al.*, *Mut Res*, 2012

Evaluating *In Vivo* Transcriptomics for Dose Response Assessment

Part I



Relationship Between Apical and Transcriptional Points-of-Departure Following a Subchronic Exposure

Part II

Relationship Between Apical and Transcriptional Points-of-Departure As a Function of Time

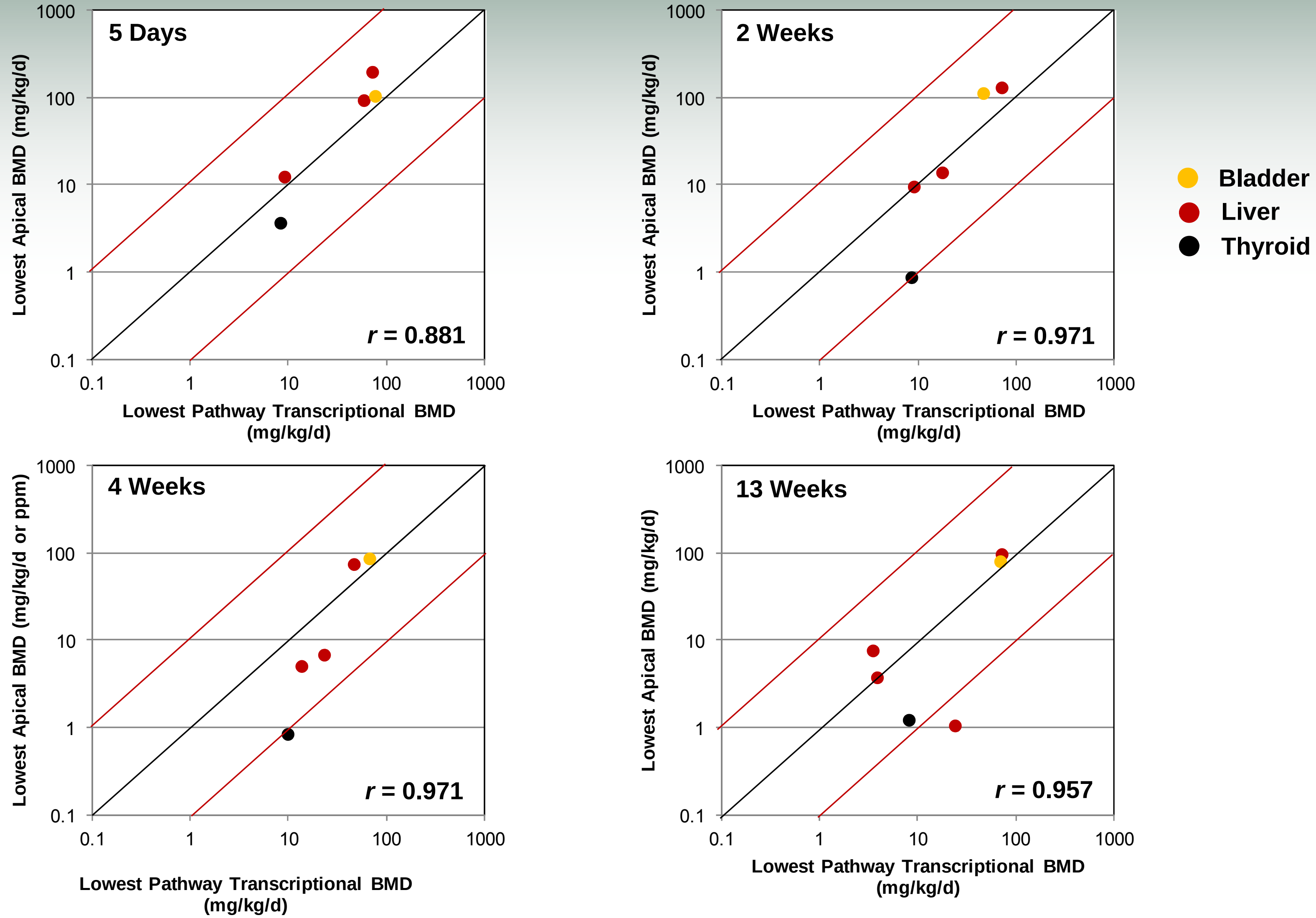
Experiment Assessing Temporal Changes in Transcriptional Dose Response

Chemical	Route	Doses[a]	Rodent Model	Time Points	Target Tissue
1,2,4-Tribromobenzene	Gavage	2.5, 5, 10, 25, 75 mg/kg	Male Sprague Dawley rats	5 d, 2, 4, 13 wks	Liver
Bromobenzene	Gavage	25, (50), 100, 200, 300, 400 mg/kg	Male F344 rats	5 d, 2, 4, 13 wks	Liver
2,3,4,6-Tetrachlorophenol	Gavage	10, 25, 50, 100, 200 mg/kg	Male Sprague Dawley rats	5 d, 2, 4, 13 wks	Liver
4,4'-Methylenebis (N,N-dimethyl) benzenamine	Feed	50, 200, 375, 500, 750 ppm	Male F344 rats	5 d, 2, 4, 13 wks	Thyroid[b]
N-Nitrosodiphenylamine	Feed	250, 1000, 2000, 3000, 4000 ppm	Female F344 rats	5 d, 2, 4, 13 wks	Bladder[b]
Hydrazobenzene	Feed	5, 20, 80, 200, 300 ppm	Male F344 rats	5 d, 2, 4, 13 wks	Liver[b]

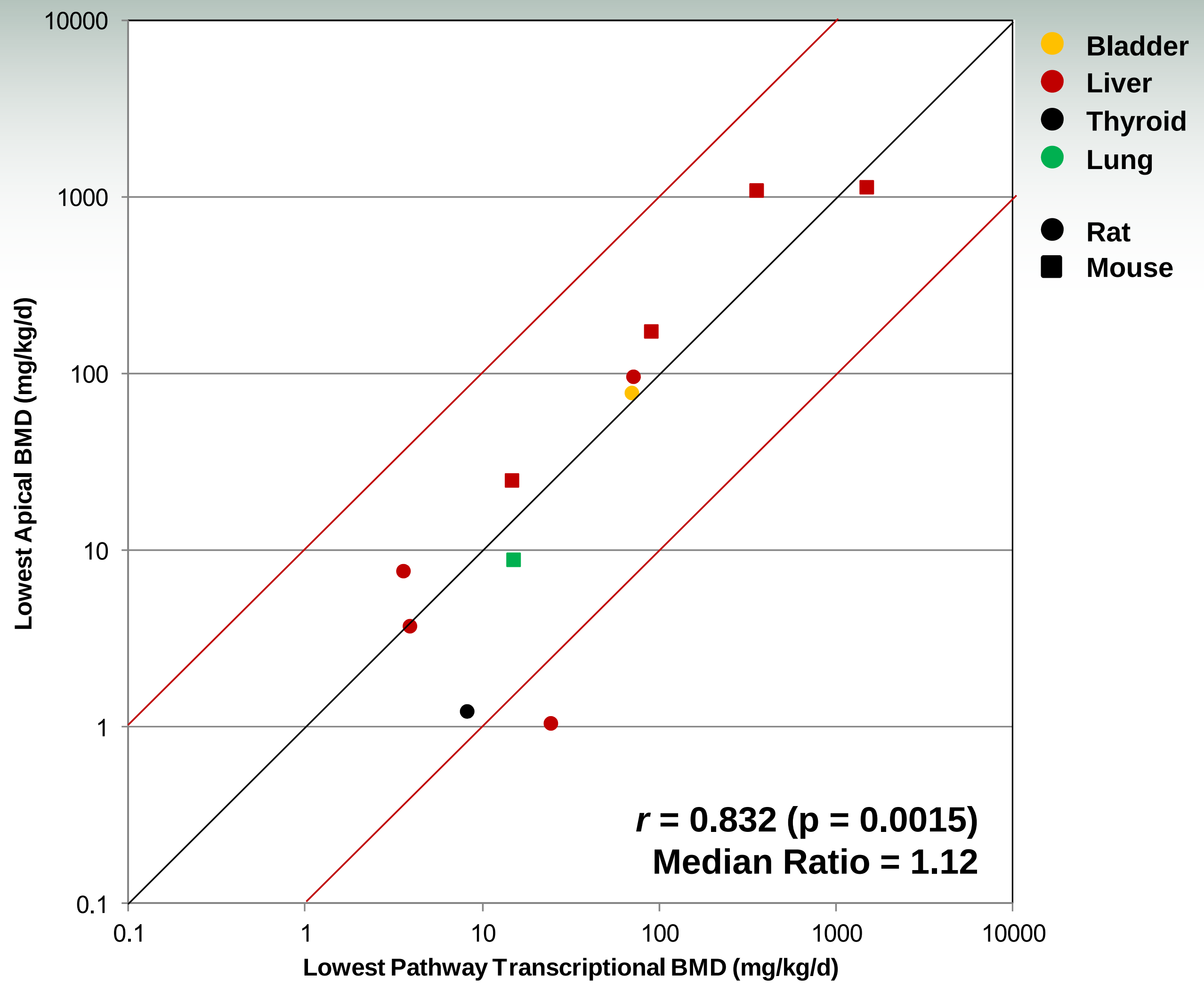
[a]Underlined doses used in previous rodent subchronic or chronic studies
[b]Have rodent cancer bioassay data

Measured apical (histological and organ weight; n = 10) and gene expression changes (n = 5) at each dose and time point in the target tissue.

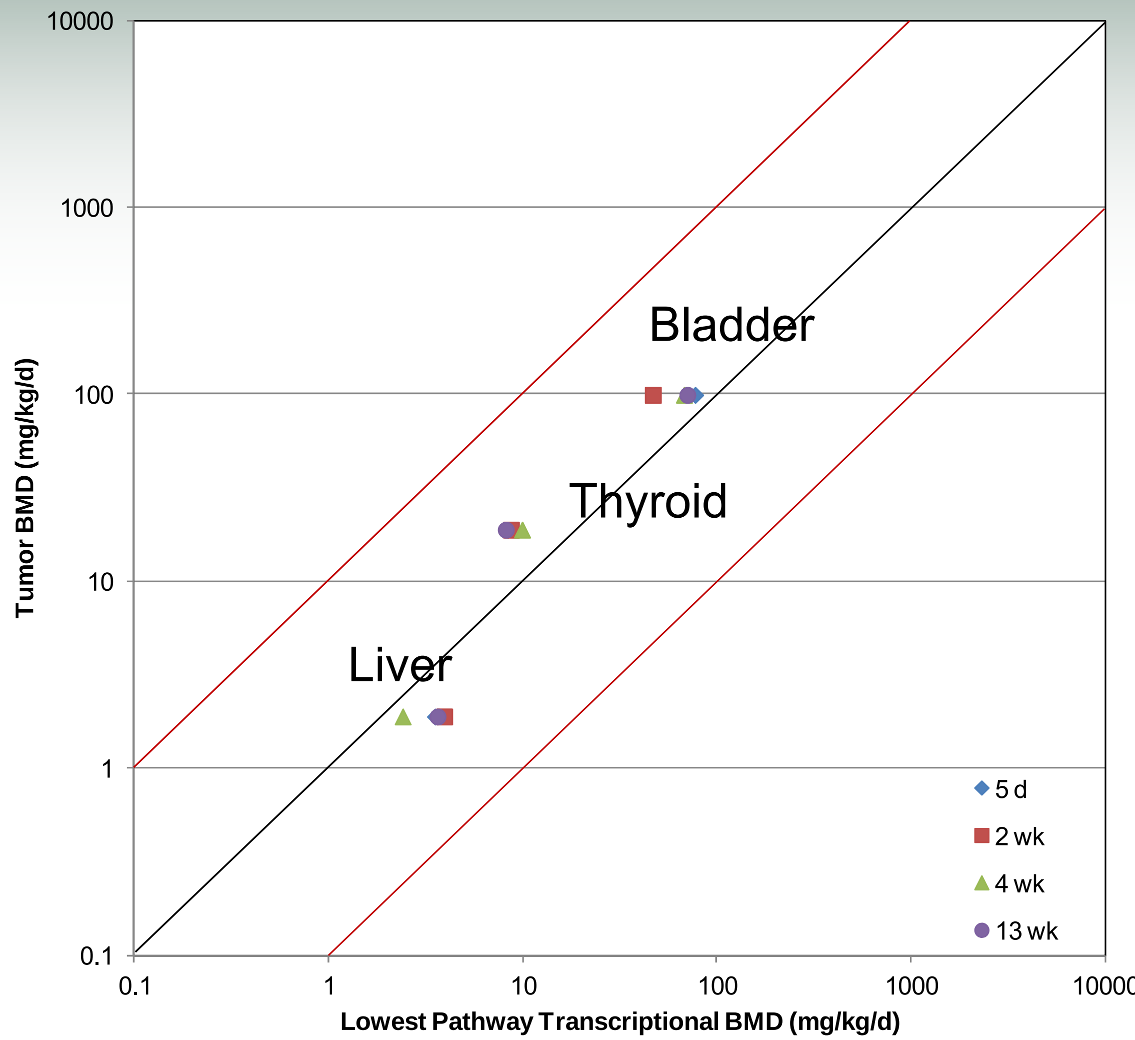
Temporal Changes in Correlation Between Non-Cancer and Transcriptional Endpoints



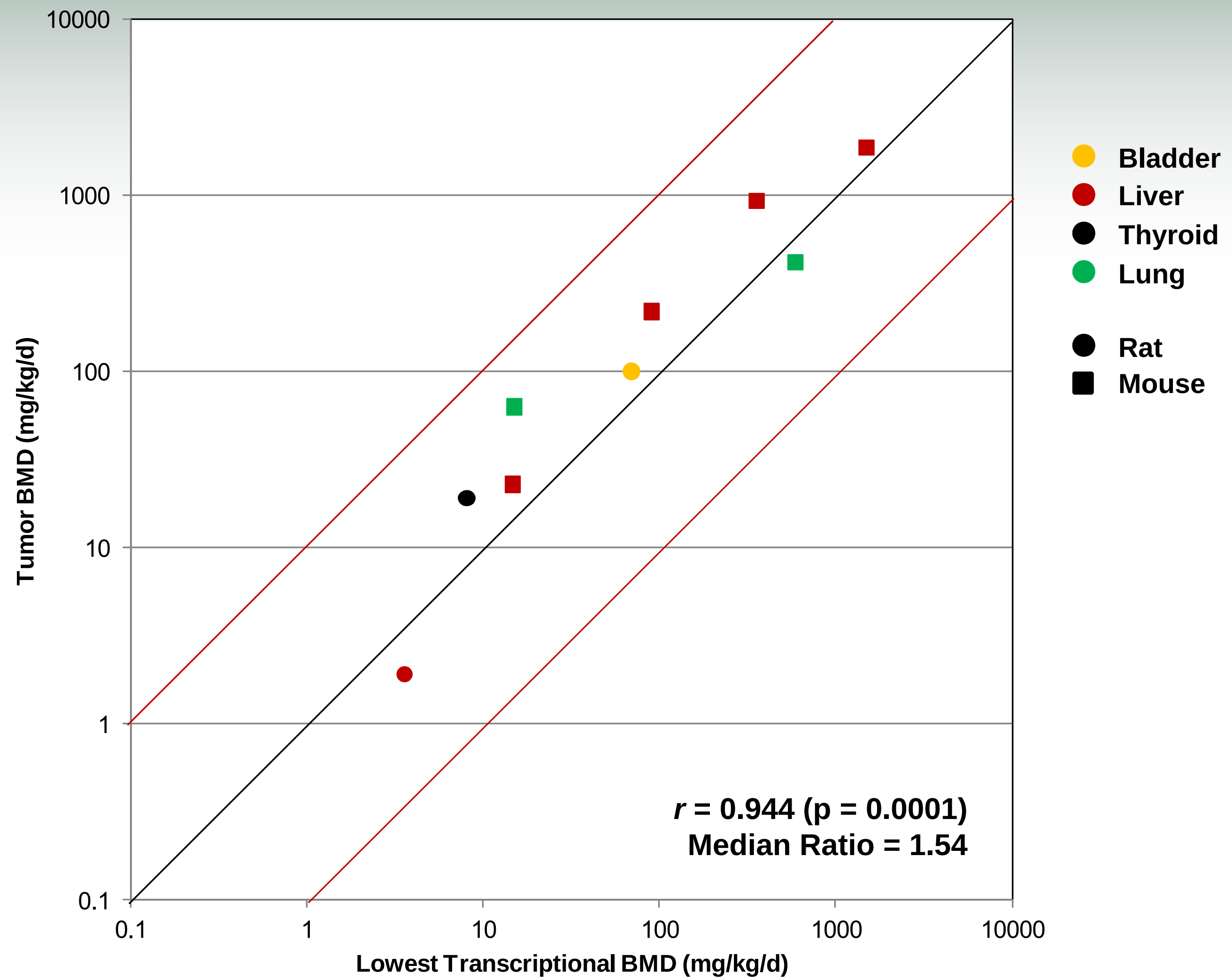
Combined Correlation Between Non-Cancer and Transcriptional Endpoints for Both Studies



Temporal Changes in Correlation Between Cancer and Transcriptional Endpoints



Combined Correlation Between Cancer and Transcriptional Endpoints for Both Studies

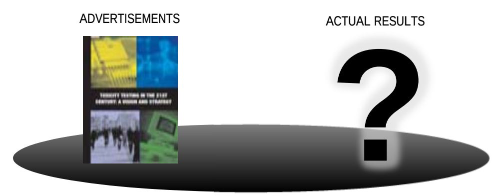


Evaluating the Role of New Technologies in a Data-Driven Tox and Risk Assessment Framework

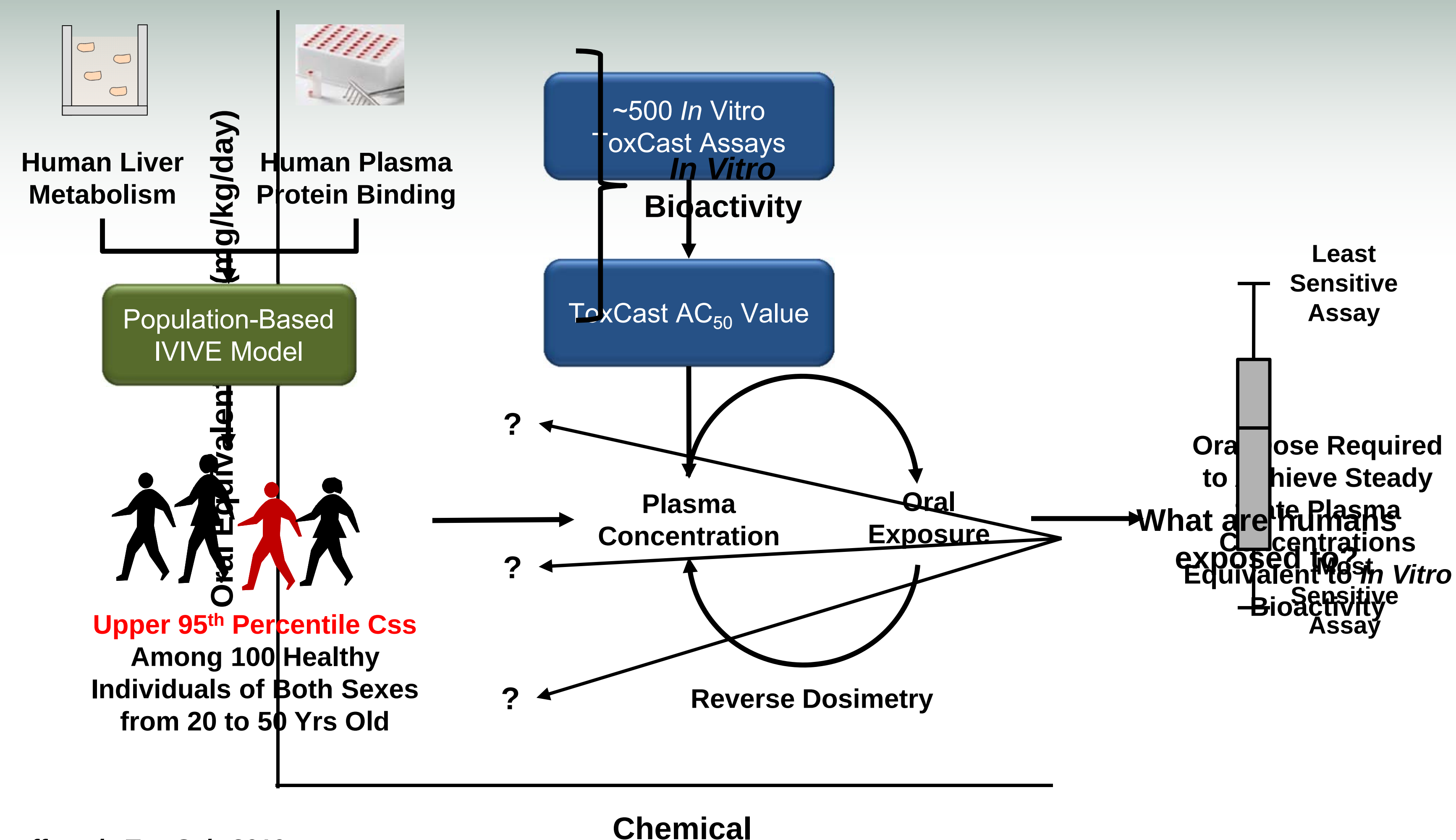
MODE-OF-ACTION

DOSE RESPONSE ASSESSMENT

EXPOSURE

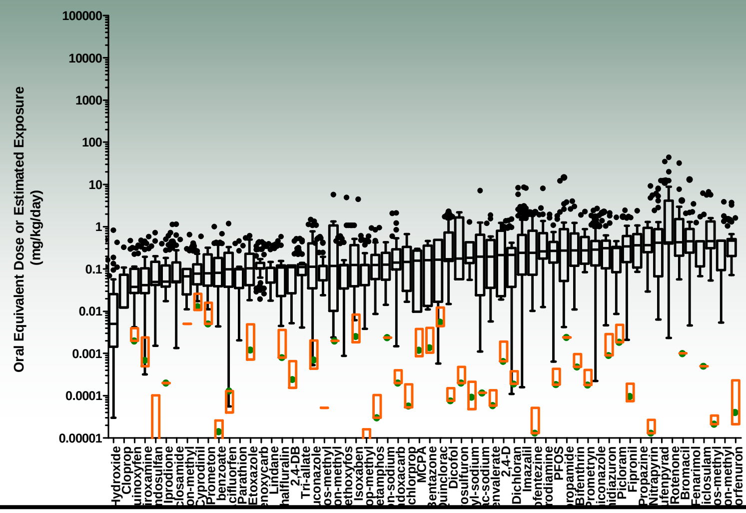


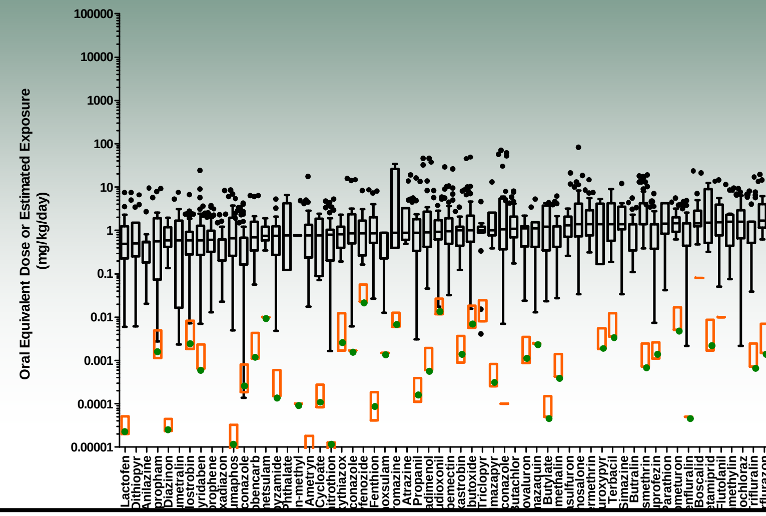
Integrating Human Dosimetry and Exposure with the ToxCast *In Vitro* Assays



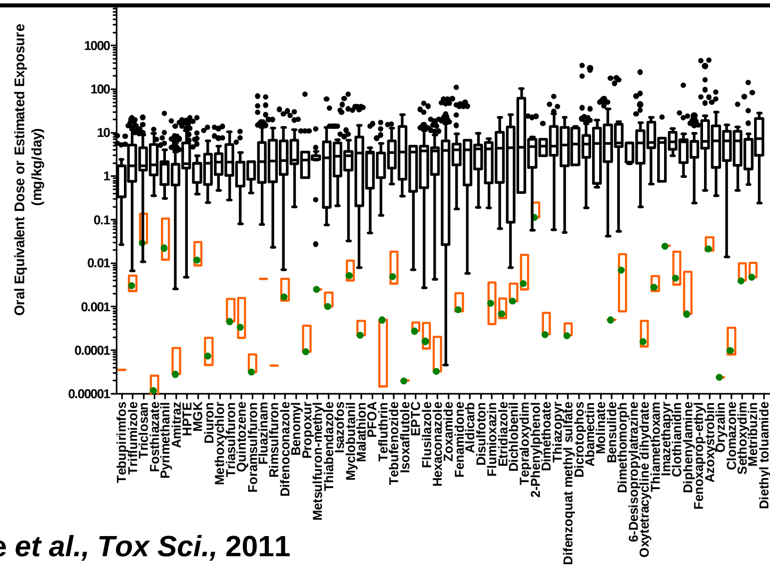
Rotroff *et al.*, *Tox Sci.*, 2010
Wetmore *et al.*, *Tox Sci.*, 2011

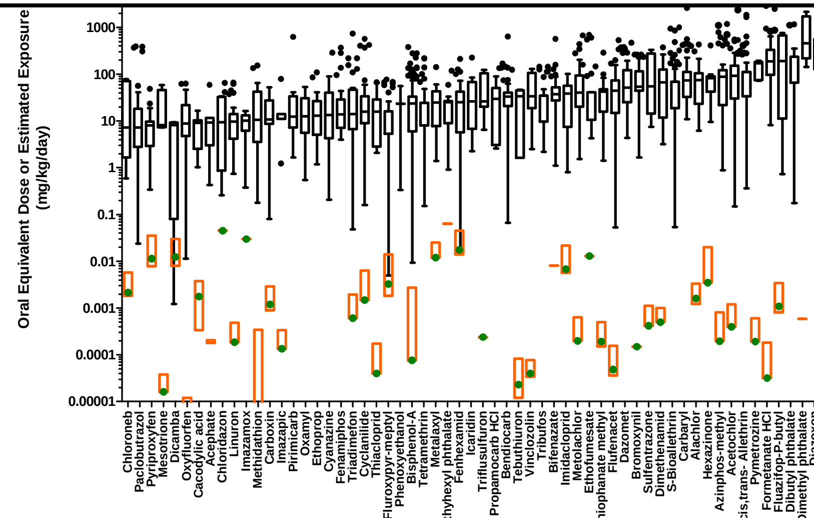
Comparing *In Vitro* Bioactive Doses with Exposure





A total of 9.9% of ToxCast Phase I chemicals have *in vitro* bioactivity at oral equivalent doses that overlap with the most highly exposed subpopulation.





Wetmore *et al., Tox Sci.*, 2011

Analysis of ToxCast Phase II Chemicals Highlight BIG Need for Exposure Information

- Approximately **80%** of the Phase I chemicals had exposure estimates derived from registration documents and biomonitoring studies
- Less than **10%** of the Phase II compounds have exposure estimates

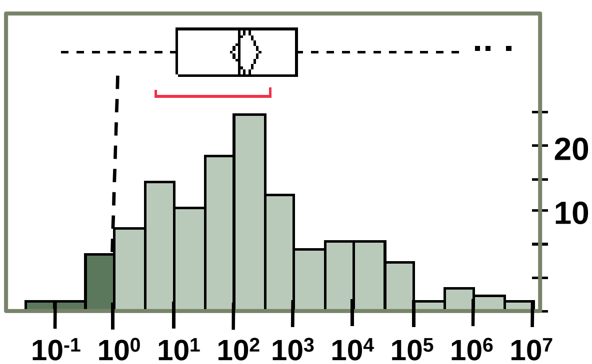
Preliminary Analysis Suggests that Better Near-Field Exposure Estimates Will Be Required

Distribution Summary Statistics

Median	123.03
Upper Quartile	1122.02
Lower Quartile	11.48

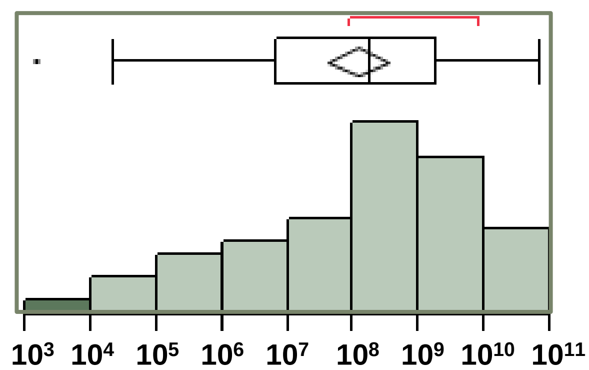
Distribution Summary Statistics

Median	175,966,502
Upper Quartile	1,784,390,901
Lower Quartile	835,968



Activity:Exposure Ratio

Registration Documents
General U.S. Population



Activity:Exposure Ratio

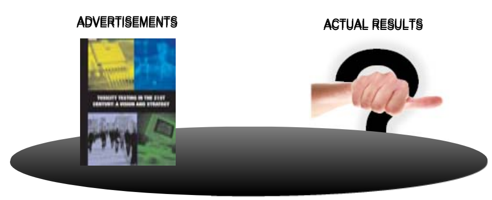
USETox
Far Field Exposure Estimates

Evaluating the Role of New Technologies in a Data-Driven Tox and Risk Assessment Framework

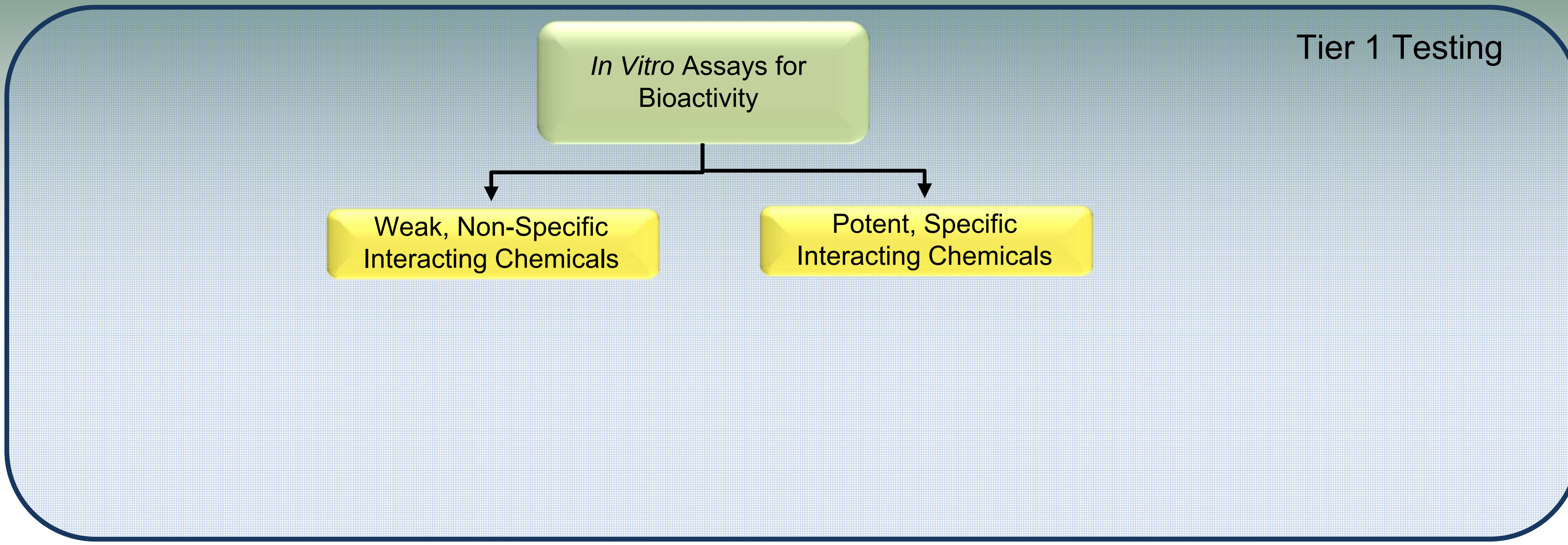
MODE-OF-ACTION

DOSE RESPONSE ASSESSMENT

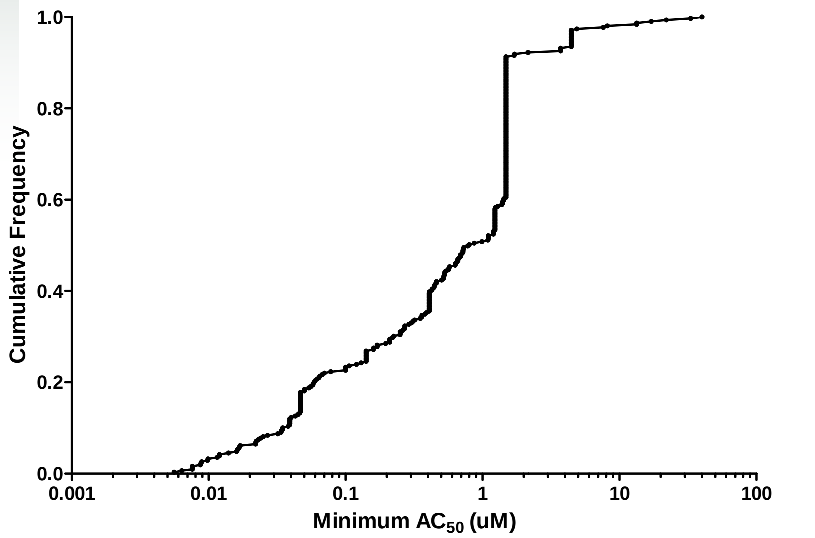
EXPOSURE

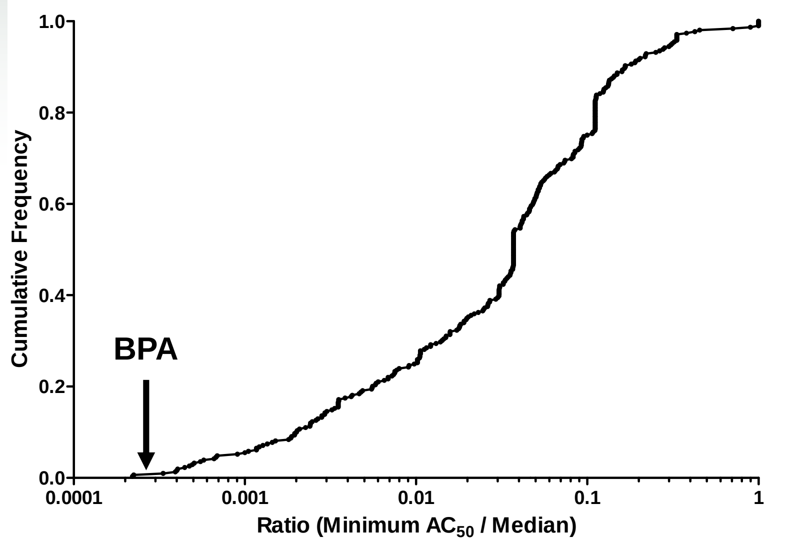


A Data-Driven 21st Century Tox and RA Framework

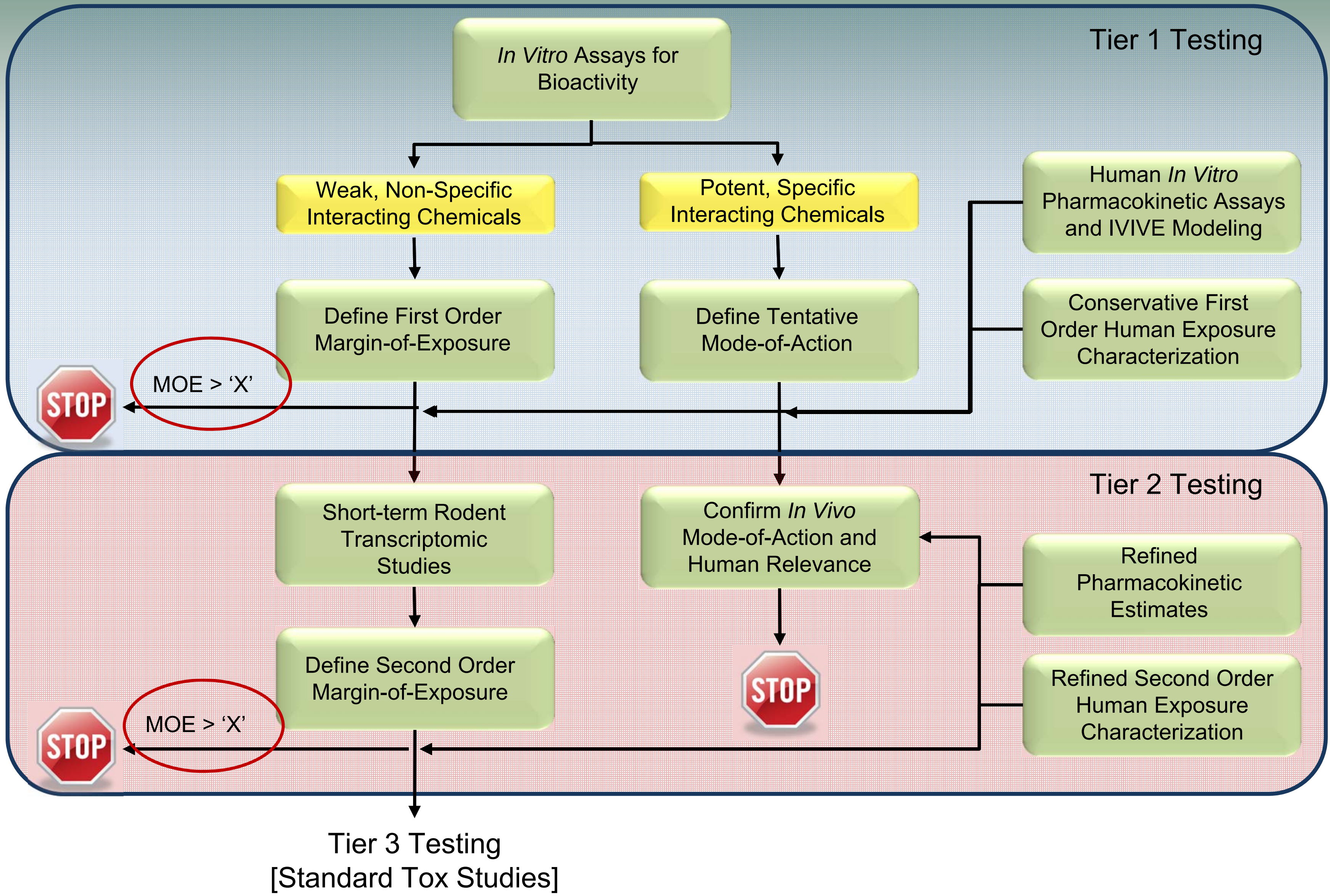


A Large Proportion of the ToxCast Phase I Chemicals Act Via Weak, Non-Specific Interactions

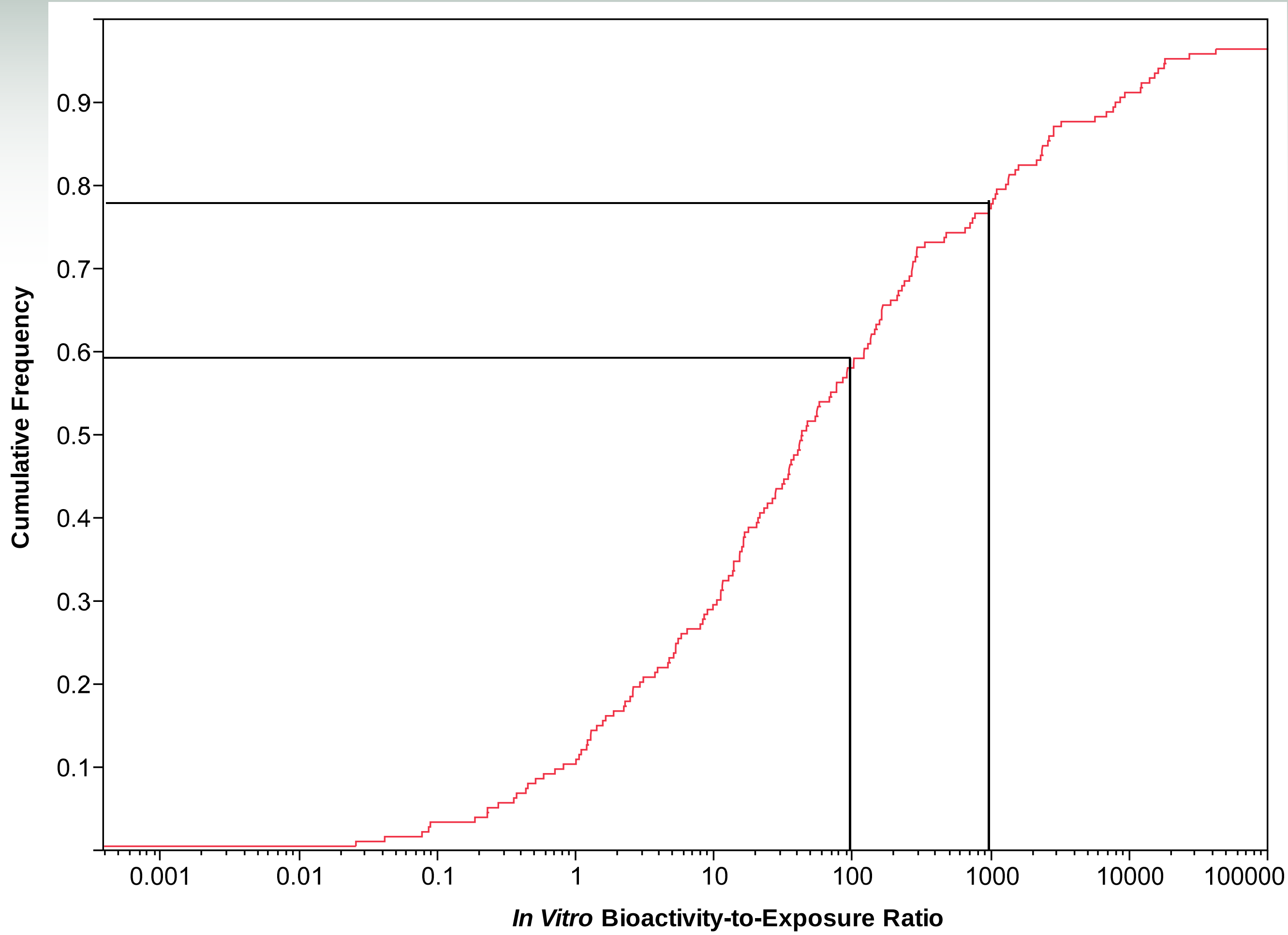




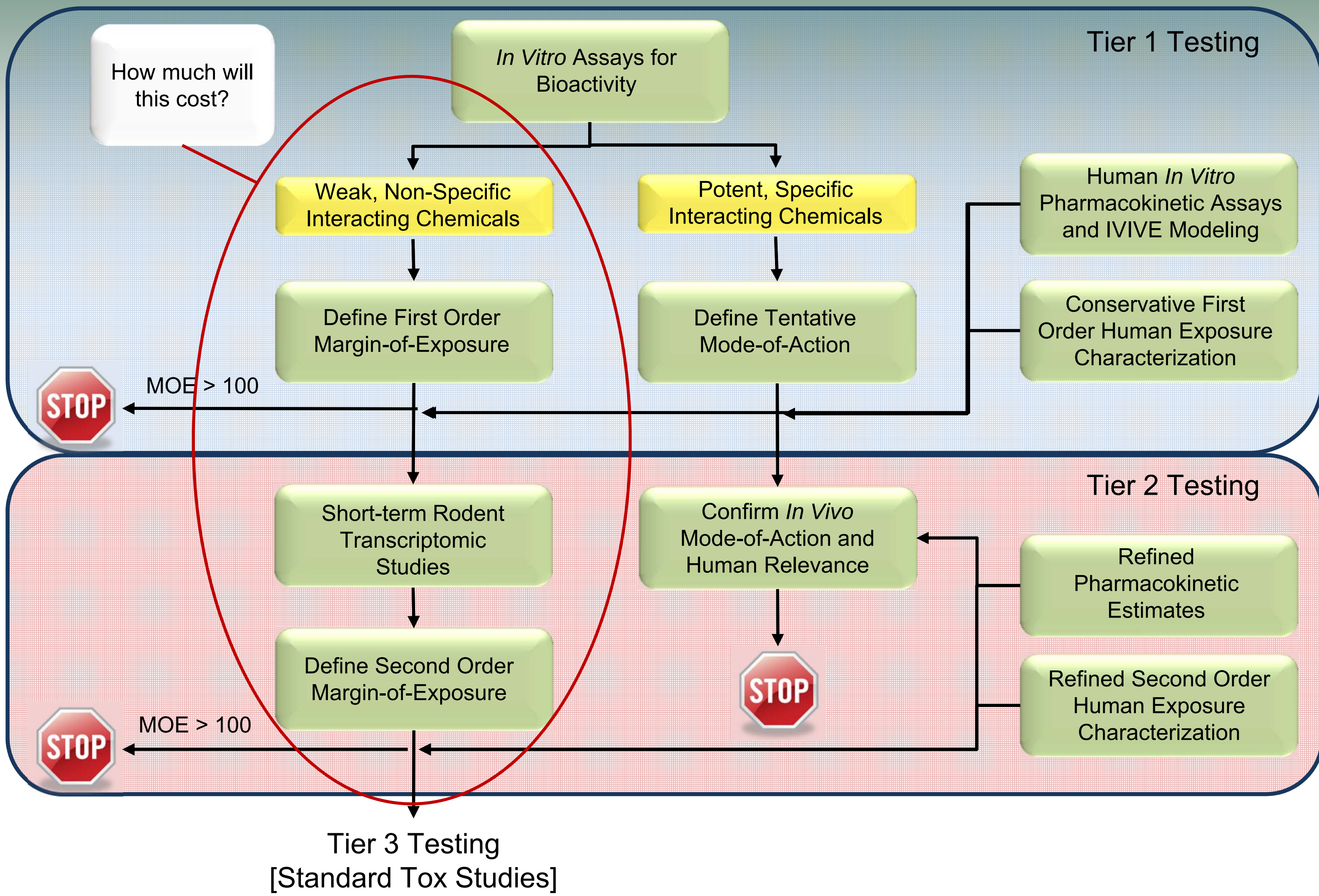
A Data-Driven 21st Century Tox and RA Framework



Comparison of *In Vivo* Low Effect Levels with Dosimetry Adjusted *In Vitro* Assays



A Data-Driven 21st Century Tox and RA Framework



Comparative Economics of the Testing of Weak, Non-Specific Interacting Chemicals

Proposed Tiered Testing Scheme

Tier	Fraction of Chemicals	Approximate Cost Per Chemical	No. Animals Per Chemical		Cost Breakdown for 10,000 Chemicals	Animal Breakdown for 10,000 Chemicals
1	0.4	$25,000[a]	0		$100,000,000.00	0
2	0.57	$150,000	100		$855,000,000.00	570,000
3	0.03	$3,200,000	1900		$960,000,000.00	570,000
				Total	$1,915,000,000.00	1,140,000

Current REACH Testing Requirements

Tonnage Band	Fraction of Chemicals[b]	Approximate Cost Per Chemical	No. Animals Per Chemical		Cost Breakdown for 10,000 Chemicals	Animal Breakdown for 10,000 Chemicals
1 - 10	0.64	$18,000.00	40		$115,755,627.01	257,235
10 - 100	0.17	$280,000.00	500		$477,170,418.01	852,090
100 - 1,000	0.08	$1,100,000.00	1100		$848,874,598.07	848,875
>1,000	0.11	$3,200,000.00	1900		$3,498,392,282.96	2,077,170
				Total	$4,940,192,926.05	4,035,370

[a]ToxCast Phase I assays cost $20,000 per chemical from Kavlock *et al.*, AATEX 14, Special Issue, 623-627
[b]From “The REACH Baseline Study”, 2009 Eurostat Report, ISSN 1977-0375

Acknowledgements

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