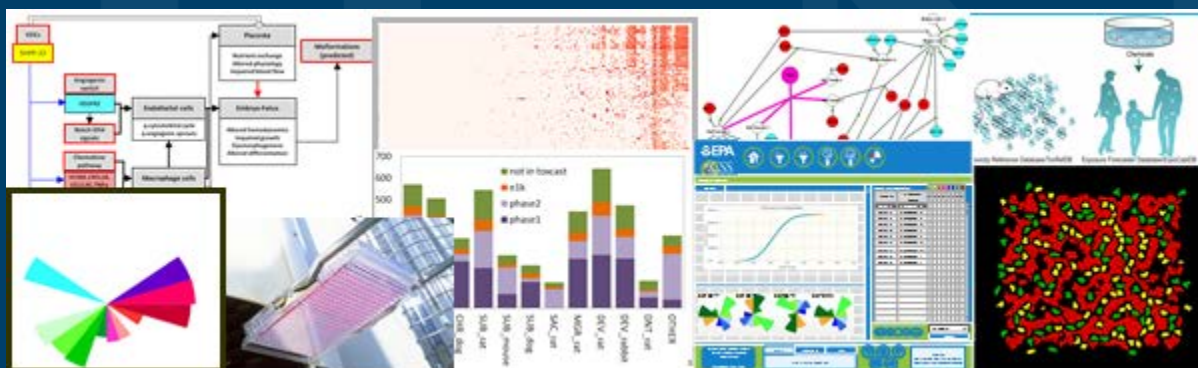


Analysis of Transcriptomic Dose Response Data in the Context of Chemical Risk Assessment

My Journey Through the Toxicogenomics Bermuda Triangle



HESI-Health Canada-McGill Workshop
May 26, 2017

Russell Thomas
Director
National Center for Computational Toxicology

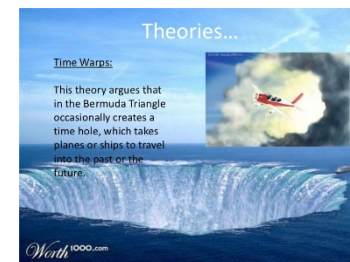
Myth of the Real Bermuda Triangle



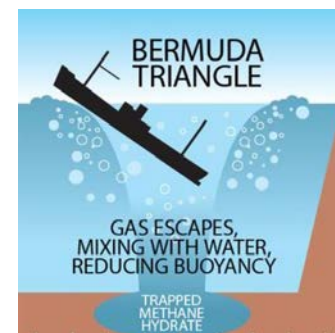
<http://onedio.co/content/new-mind-blowing-claim-about-the-bermuda-triangle-13519>



http://www.crystalinks.com/bermuda_triangle.html

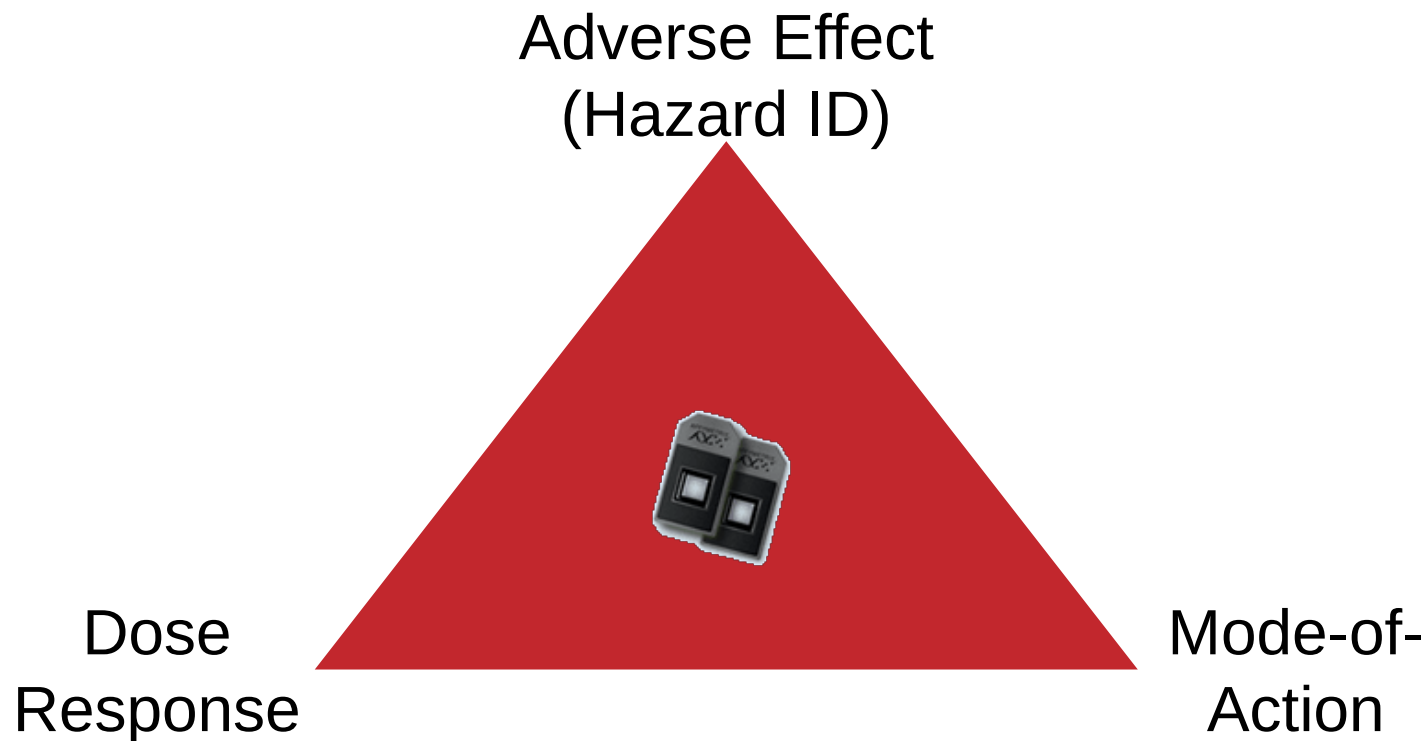


<https://www.slideshare.net/jayakanthan75/bermuda-triangle-ppt>



<http://www.mensxp.com/special-features/today/29862-the-mystery-behind-the-disappearances-in-the-bermuda-triangle-may-just-have-been-solved.html>

Bermuda Triangle of Toxicogenomics and Hazard Assessment



Initial Promise of Toxicogenomics Focused on Inferring MOA

THE NATIONAL ACADEMIES
REPORT IN BRIEF
Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment

- Applications of toxicogenomics to identify MOA have generally lacked a systematic approach
- More art than science
- Development of large reference databases difficult due to cost constraints
- Most expert committees/reports defaulted to using it as part of an overall weight-of-evidence
- Not very satisfying

users of existing data sources, and study data in new ways, perhaps on a scale approaching that of the Human Genome Project. Toxicogenomics also raises some ethical

encoded by genes. Metabolomics is the study of the products of biological processes. Such products change in response to such things as nutrition, stress, and disease states.

THE NATIONAL ACADEMIES
Advisors to the Nation on Science, Engineering, and Medicine

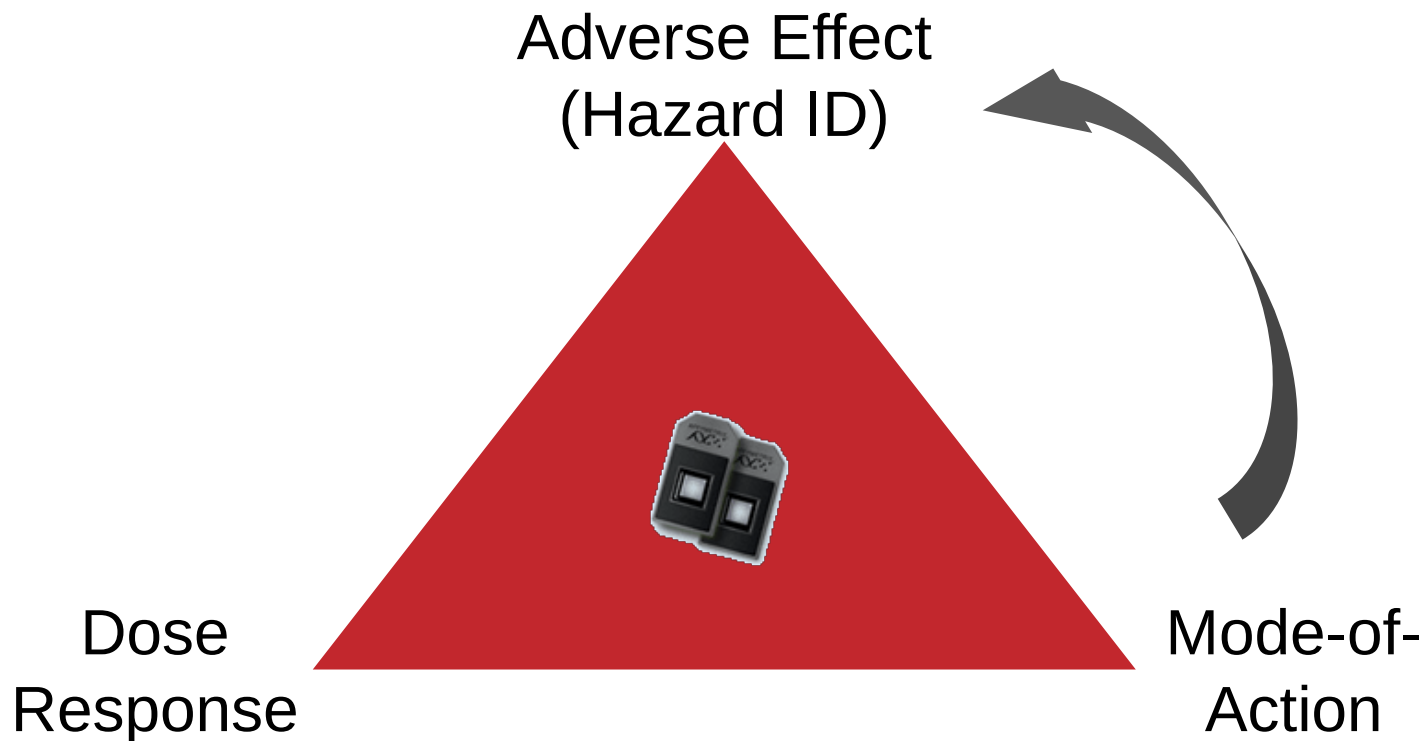
National Academy of Sciences • National Academy of Engineering • Institute of Medicine • National Research Council

MOA Generator

A Workshop Summary

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

Bermuda Triangle of Toxicogenomics and Hazard Assessment



Developing Statistical Classification Models to Predict Hazard

The MicroArray Quality Control (MAQC)-II study of common practices for the development and validation of microarray-based predictive models

MAQC Consortium*

Gene expression data from these predictions has not been used to generate predictive models for rodents, or of breast cancer combinations of analytical endpoints and, to minimize performance depended on performance. The conclusions and independent investigations

The Journal
Vol. 37, No. 1

'Drug

doi:
Ad

Discrimination for Genotoxic and Nongenotoxic Carcinogens by Gene Expression Profiling in Primary Mouse Hepatocytes Improves with Exposure Time

Karen Mathijs,*† Karen J. J. Brauers,* Danyel G. J. Jennen,*‡ Andre Boersma,*‡ Marcel H. M. van Herwaarden,*‡ Ralph W. H. Gottschalk,* Jos C. S. Kleinjans,*‡ and Joost H. M. van Delft*‡,§

*Department of Health Risk Analysis and Toxicology, Faculty of Health, Medicine and Life Sciences, Maastricht University, 6200 MD Maastricht, The Netherlands; †Netherlands Toxicogenomics Center, 6200 MD Maastricht, The Netherlands; and ‡TNO Quality of Life, 3700 AZ Zeist, The Netherlands

Received June 12, 2009; accepted September 11, 2009

TOXICOLOGICAL SCIENCES 124(1), 54–74 (2011)
doi:10.1093/toxsci/kfr202
Advance Access publication August 2, 2011

Development and Evaluation of a Genomic Signature for the Prediction of Carcinogenicity of Chemicals

- Most studies show 60-85% accuracy for predicting cancer-related endpoints
- Only a limited number of tissues have been evaluated
- Requires >20 compounds with adequate redundancy and diversity in mechanisms to have a robust training set (Thomas *et al.*, 2009)
- >30 organs show tumor responses in NTP database with ~50% having >10 chemicals in at least one species/sex
- Difficult to justify as a comprehensive screen for rodent carcinogenicity

Aubrecht,||
Kincaid,†
City Working

ology and Safety
Eli Lilly and
||Sanofi-aventis
Institute of
Research, Food and
8609; *Abbott
Bristol-Myers

San Francisco,

the Long-term
al Chemicals

skaya,†§ Yuri Nikolsky,§

*The Hamner Institutes for Health Sciences, Research Triangle Park, North Carolina 27709; †SAS Institute Inc., Cary, North Carolina 27513; §Vavilov Institute of General Genetics, Moscow B333, 117809, Russia; and §GeneGo, Inc., St Joseph, Michigan 49085

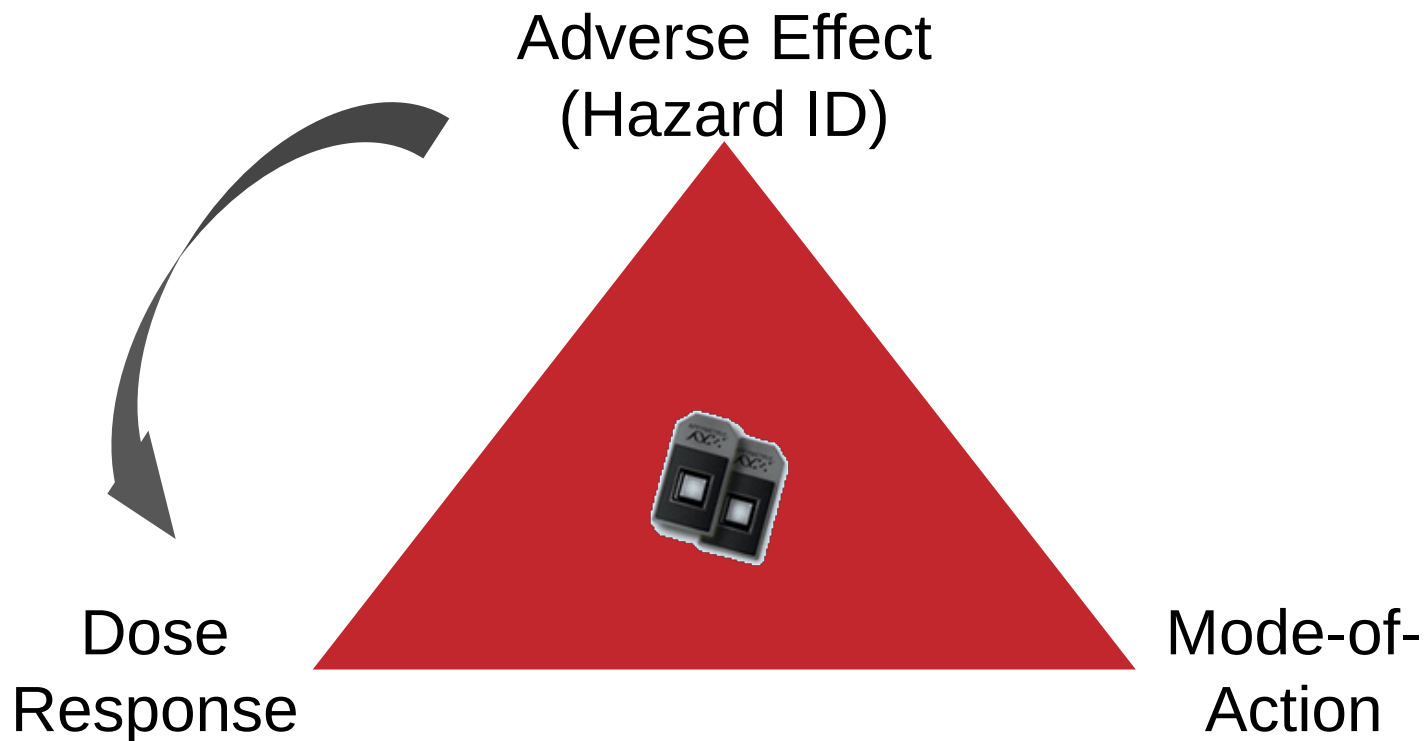
Prediction of carcinogenic potential by a toxicogenomic approach using rat hepatoma cells

Kazunari Tsujimura,^{1,2} Makoto Asamoto,^{1,2} Shugo Suzuki,¹ Naomi Hokaikado,¹ Kumiko Ogawa¹ and Tomoyuki Shirai¹

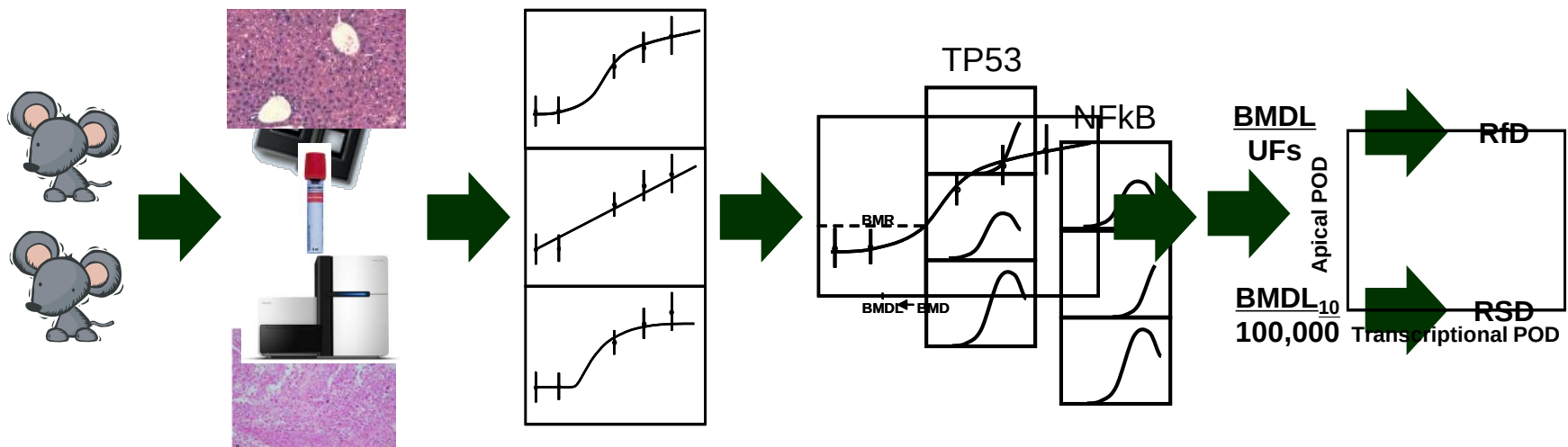
¹Department of Experimental Pathology and Tumor Biology, Nagoya City University, Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan; ²Chemicals Evaluation and Research Institute, Hita Laboratory, Tokyo 112-0004, Japan

(Received April 4, 2006/Revised June 1, 2006/Accepted June 8, 2006/Online publication August 11, 2006)

Bermuda Triangle of Toxicogenomics and Hazard Assessment



Using Transcriptomics to Define Dose Response



Subchronic Animal Studies
Chronic Animal Studies
Transcriptional Responses
Toxicological Response Considered Adverse

Fit Data with Statistical Models
Dose-Response Models

Identify Point of Departure (POD) and Calculate Summary Value (usually the median pathway BMD)
Dose-Response Models
and Calculate Summary Value (usually the median pathway BMD)

Derive Safe Exposure Levels
Dose-Response Models
and Transcriptional PODs

Thomas *et al.*, *Tox Sci.*, 2011
Thomas *et al.*, *Mut Res.*, 2012
Thomas *et al.*, *Tox Sci.*, 2013

In Vivo Study to Assess Transcriptional and Apical Correlation

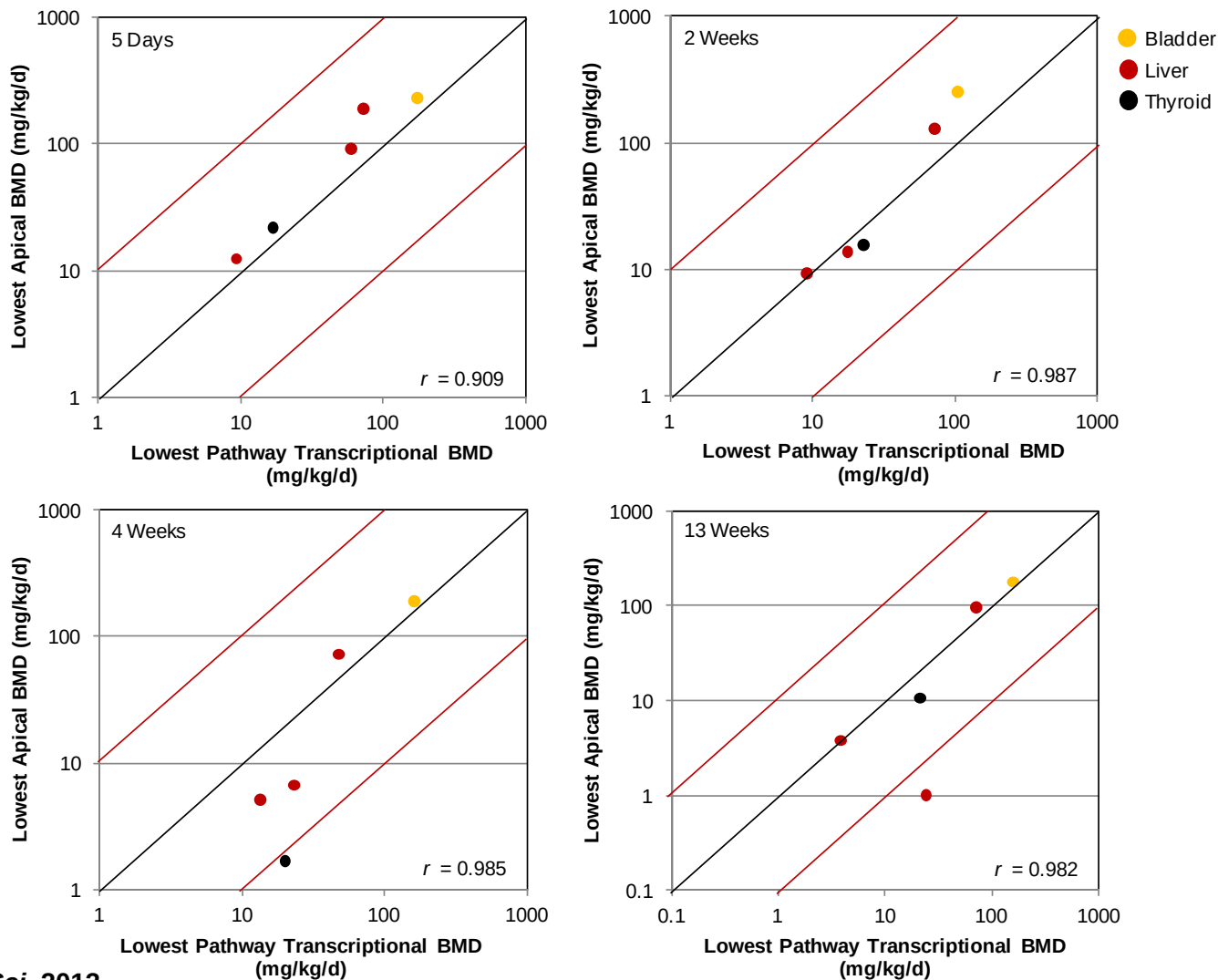
Chemical	Route	Doses ^c	Rodent Model	Time Point	Target Tissue
1,2,4-Tribromobenzene ^a	Gavage	<u>2.5</u> , <u>5</u> , <u>10</u> , 25, 75 mg/kg	Male Sprague Dawley rats	5 d, 2, 4, 13 wks	Liver
Bromobenzene ^a	Gavage	25, (<u>50</u>), <u>100</u> , <u>200</u> , 300, <u>400</u> mg/kg	Male F344 rats	5 d, 2, 4, 13 wks	Liver
2,3,4,6-Tetrachlorophenol ^a	Gavage	10, <u>25</u> , 50, <u>100</u> , <u>200</u> mg/kg	Male Sprague Dawley rats	5 d, 2, 4, 13 wks	Liver
4,4'-Methylenebis (N,N-dimethyl) benzenamine ^b	Feed	50, 200, <u>375</u> , 500, <u>750</u> ppm	Male F344 rats	5 d, 2, 4, 13 wks	Thyroid ^b
N-Nitrosodimethylaniline ^b	Feed	250, 1000, 2000, 3000, 4000 ppm	Female F344 rats	5 d, 2, 4, 13 wks	Bladder ^b
Measured apical (histological and organ weight; n = 10) and gene expression changes (n = 5) at each dose and time point in the target tissue.					
Propylene glycol mono-t-butyl ether ^b	Inhalation	25, <u>75</u> , <u>300</u> , 800, <u>1200</u> ppm	Female B6C3F1 mice	13 wks	Liver
1,2,3-Trichloropropane ^b	Gavage	2, <u>6</u> , <u>20</u> , 40, <u>60</u> mg/kg	Female B6C3F1 mice	13 wks	Liver
Methylene Chloride ^b	Inhalation	100, 500, <u>2000</u> , 3000, <u>4000</u> ppm	Female B6C3F1 mice	13 wks	Liver, Lung
Naphthalene ^b	Inhalation	0.5, 3, <u>10</u> , 20, <u>30</u> ppm	Female B6C3F1 mice	13 wks	Lung
1,4-Dichlorobenzene ^b	Gavage	100, <u>300</u> , 400, 500, <u>600</u> mg/kg	Female B6C3F1 mice	13 wks	Liver

^aChemicals in IRIS database for non-cancer endpoints only

^bChemicals previously tested by the U.S. National Toxicology Program

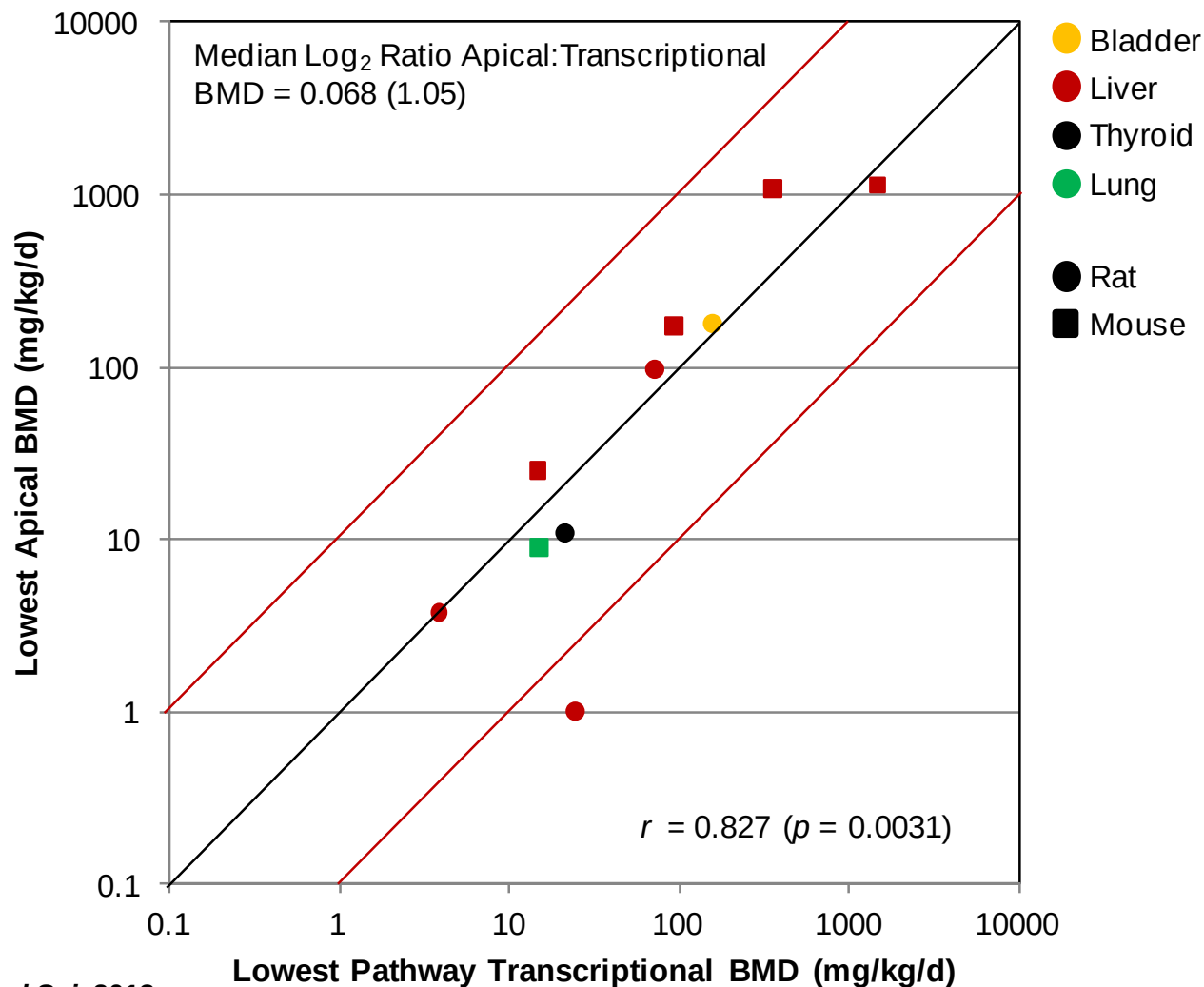
^cUnderlined doses used in NTP two-year rodent bioassay or IRIS database

Temporal Changes Between Transcriptional and Non-Cancer PODs



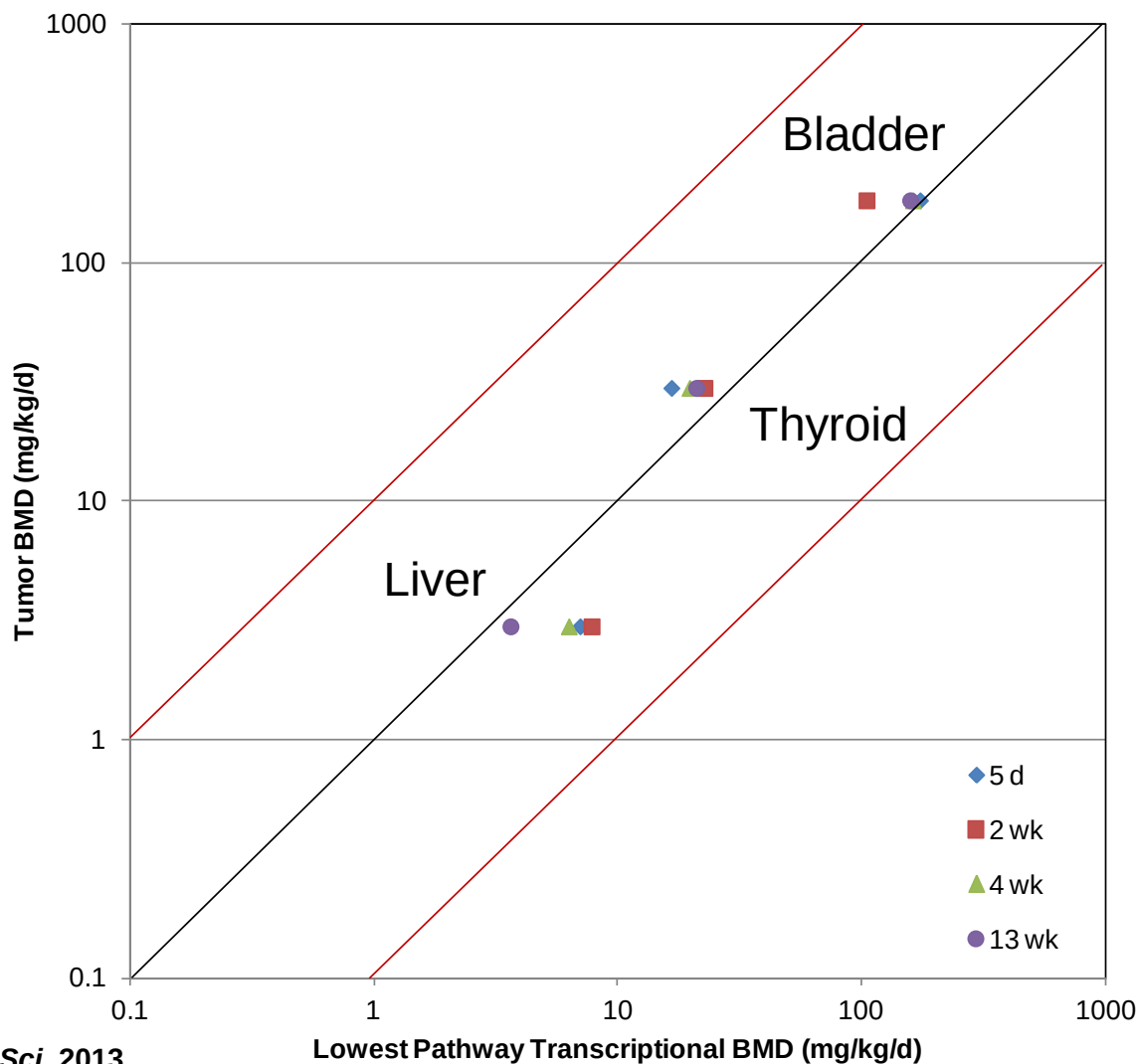
Thomas *et al.*, *Toxicol Sci*, 2013

Combined Correlation Between Non-Cancer and Transcriptional PODs



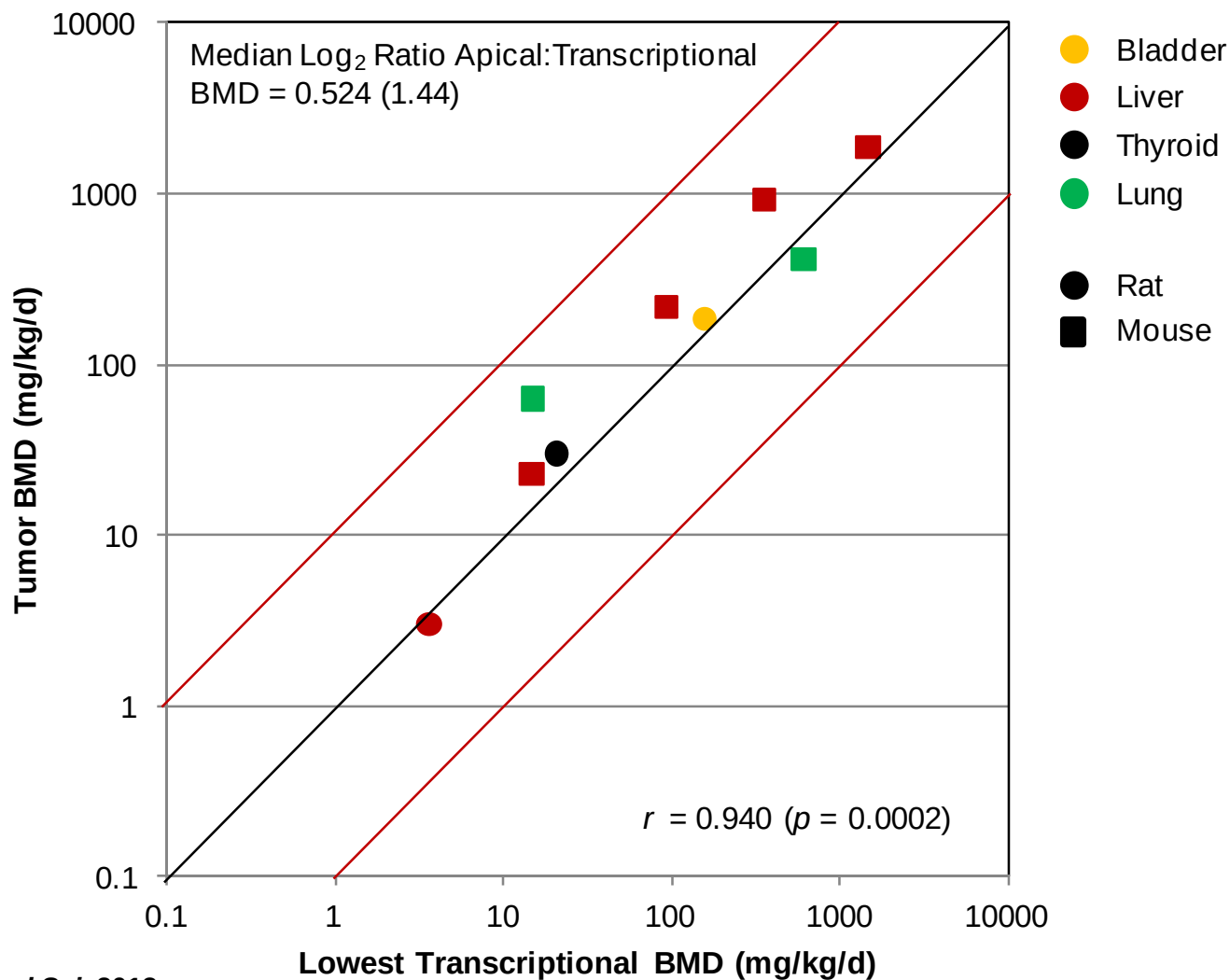
Thomas *et al.*, *Toxicol Sci*, 2013

Temporal Changes Between Transcriptional and Cancer PODs



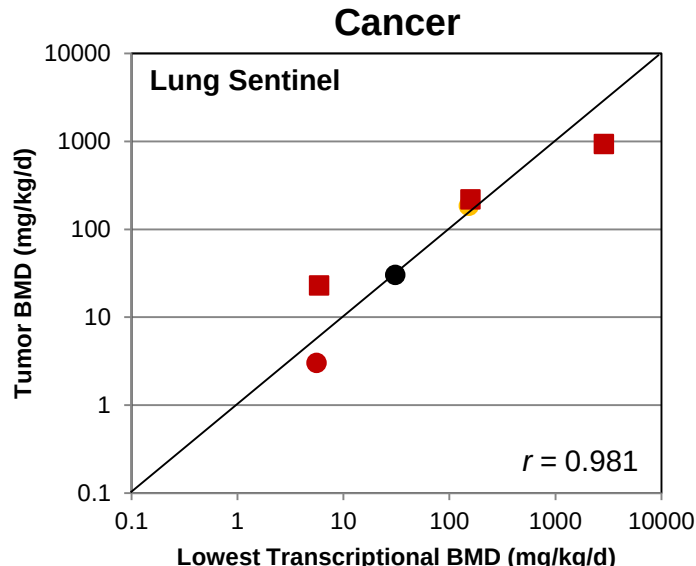
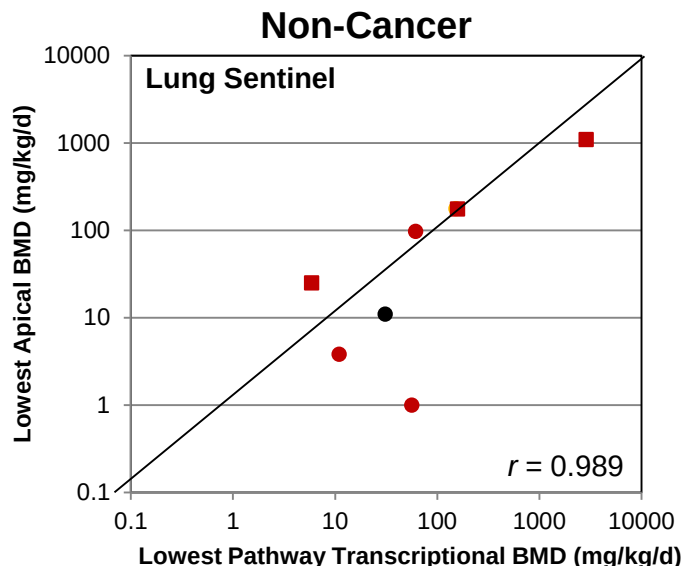
Thomas et al., *Toxicol Sci*, 2013

Combined Correlation Between Cancer and Transcriptional PODs



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

Correlation With Transcriptional PODs in Sentinel Tissue



Target Tissue

● Bladder

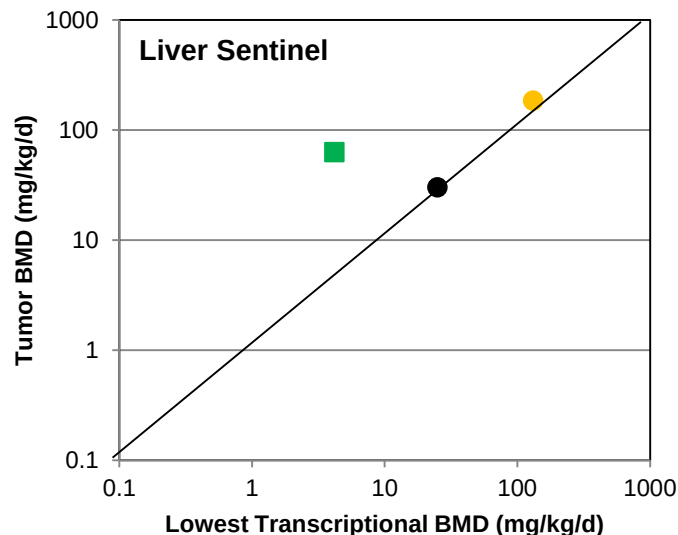
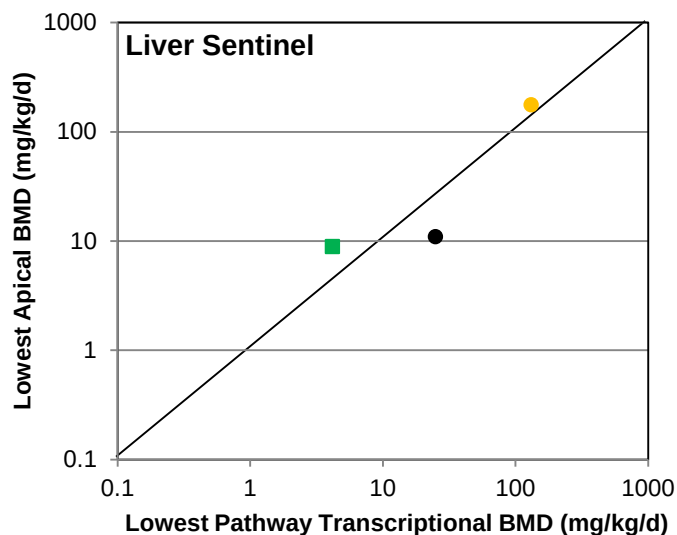
● Liver

● Thyroid

● Lung

● Rat

■ Mouse



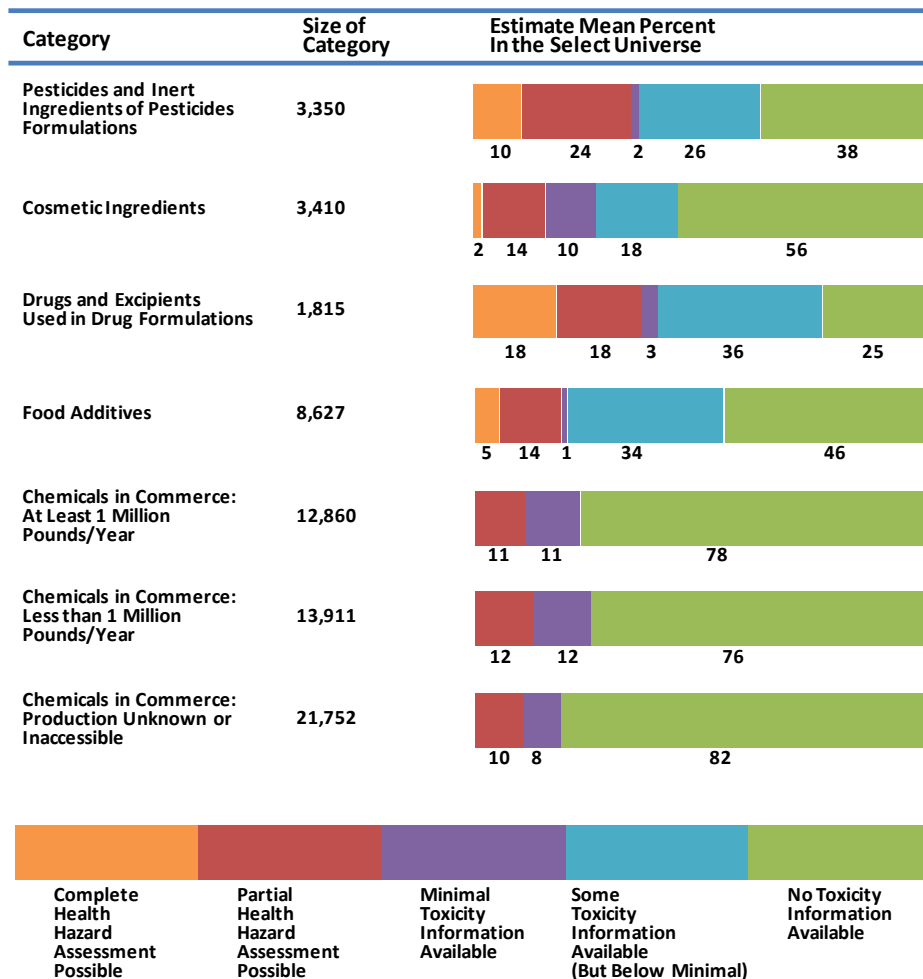
What Did These Studies Tell Us...

- Transcriptomic dose response alterations correlate with both noncancer- and cancer-related apical endpoints
- Correlation between apical responses and transcriptional no effect levels appear stable over time
- The average ratio apical and transcriptional points-of-departure for the most sensitive response was less than two-fold
- Transcriptional points-of-departure in sentinel tissues may provide reasonable surrogates for those in the target tissue

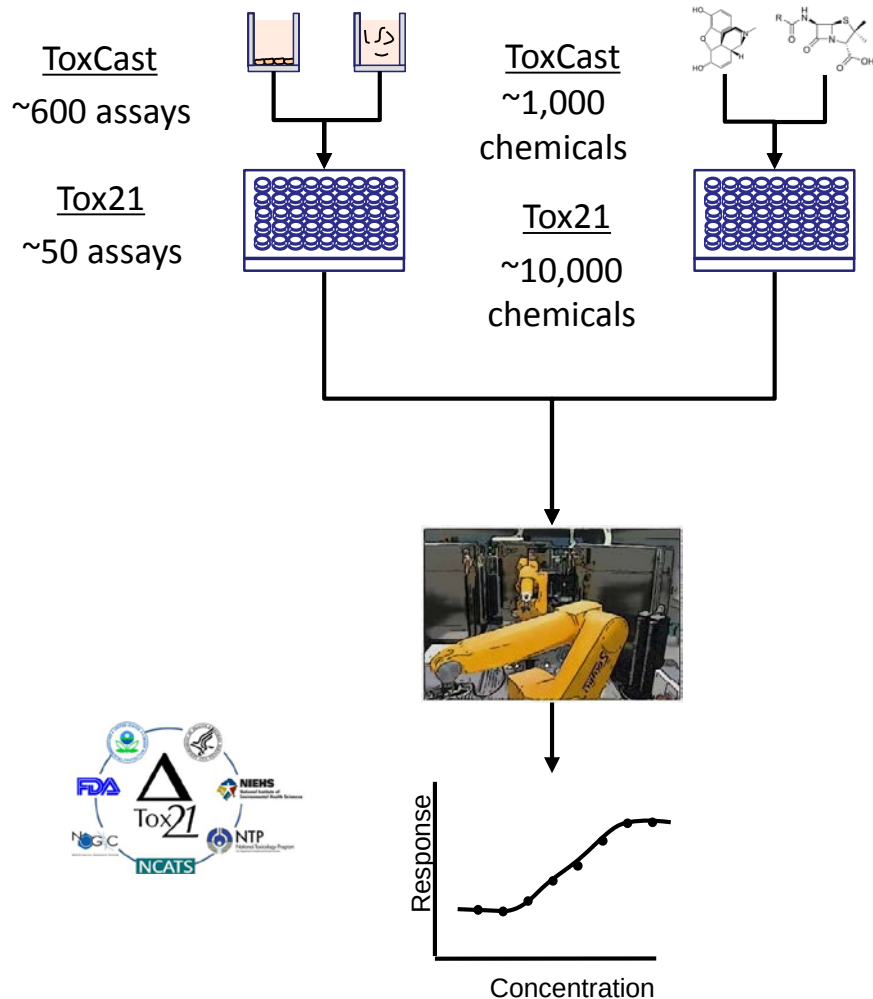
But, There are Other Challenges for EPA to Consider

- 1984 US NRC report
- Major challenge is too many chemicals and not enough data
- Total = 65,725
- No tox data = 46,000

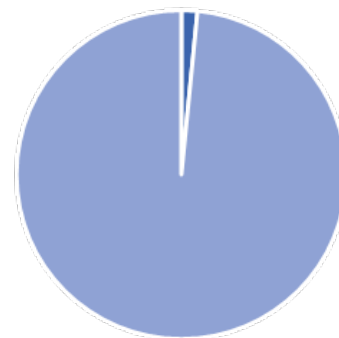
US National Research Council, 1984



Using High-Throughput Screening to Address Data Gap

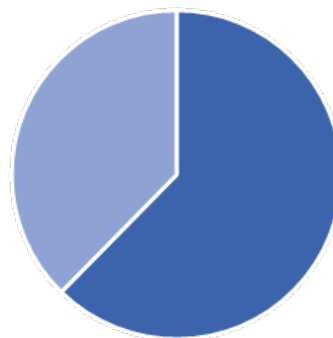


Gene Coverage



■ ToxCast
■ Not in ToxCast

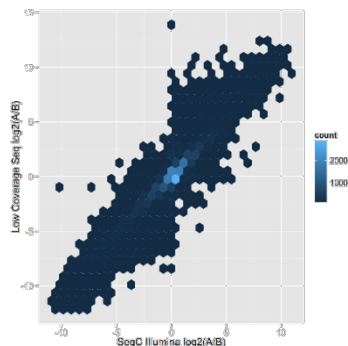
Pathway Coverage*



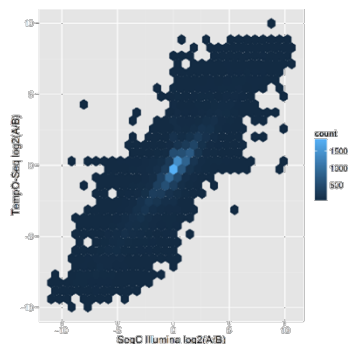
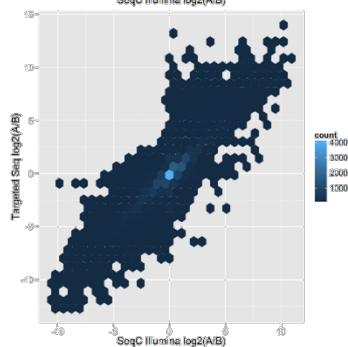
*At least one gene from pathway represented

Searching for a High-Throughput Toxicogenomics Platform

Technical Comparison



TruSeq
 r^2 0.74



Low Coverage
 r^2 0.83

Functional Comparison

TruSeq
0/5 (0%)

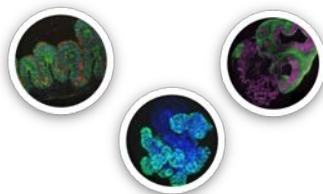
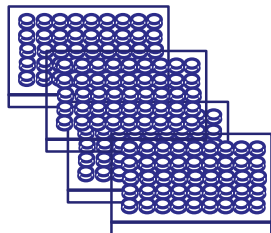
Requirements:

- Low cost
- Whole genome
- 384 well
- Automatable

TruSeq
30%

Low Coverage
0/5 (0%)

Developing a Portfolio of TGX Experimental and Analytical Tools



High-Throughput Toxicogenomics Screen

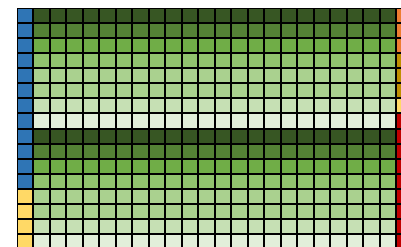
- Multiple cell types
- Thousands of chemicals
- Whole transcriptome (EPA)
- S1500+ (NTP)

Assay Design for Rigorous QC and Performance Validation

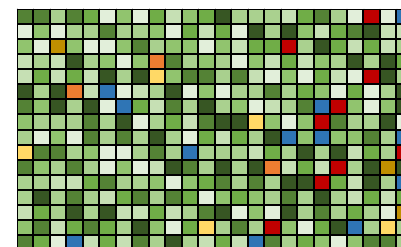
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
A	MAQC-A (Us)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	non-treated
B	MAQC-A (Us)	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	non-treated
C	MAQC-B (Us)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	non-treated
D	MAQC-B (Us)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	DMSO
E	Bulk Lysate (DMSO)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	DMSO
F	Bulk Lysate (DMSO)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	DMSO
G	Bulk Lysate (Trichostatin)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	DMSO [No Label]
H	Bulk Lysate (Trichostatin)	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	Trichostatin (1 µM)
I	Lysis Buffer (Us)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	Trichostatin (1 µM)
J	Lysis Buffer (Us)	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	Trichostatin (1 µM)
K	MAQC-A (Them)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	Genistein (10 µM)
L	MAQC-A (Them)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	Genistein (10 µM)
M	MAQC-B (Them)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Genistein (10 µM)
N	MAQC-B (Them)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	Sirolimus (0.1 µM)
O	Lysis Buffer (Them)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	Sirolimus (0.1 µM)
P	Lysis Buffer (Them)	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	Sirolimus (0.1 µM)
No Cells																								

Screen Design

- Large bank of cytogenetically and functionally characterized cells
- 8 point concentration response
- Single time point
- Parallel HCI screen

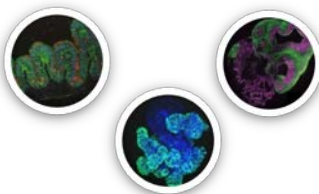
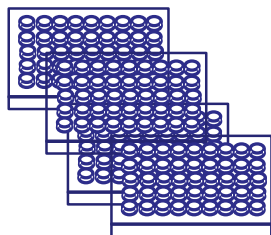


↓
Randomized treatment



Josh Harrill, Unpublished

Developing a Portfolio of TGX Experimental and Analytical Tools



High-Throughput Toxicogenomics Screen

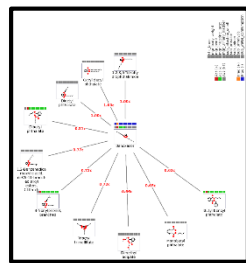
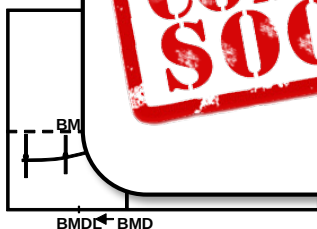
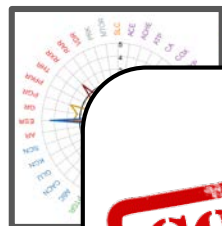
- Multiple cell types
- Thousands of chemicals
- Whole transcriptome (EPA)
- S1500+ (NTP)

Mode of Action/MIE

Reference Chemicals

**COMING
SOON!**

- Large scale screen of 1,000 chemicals (ToxCast I/II) in single cell type this summer
- Additional screens across multiple cell types/lines
- Additional reference chemicals and genetic perturbations (RNAi/CRISPR/cDNA)

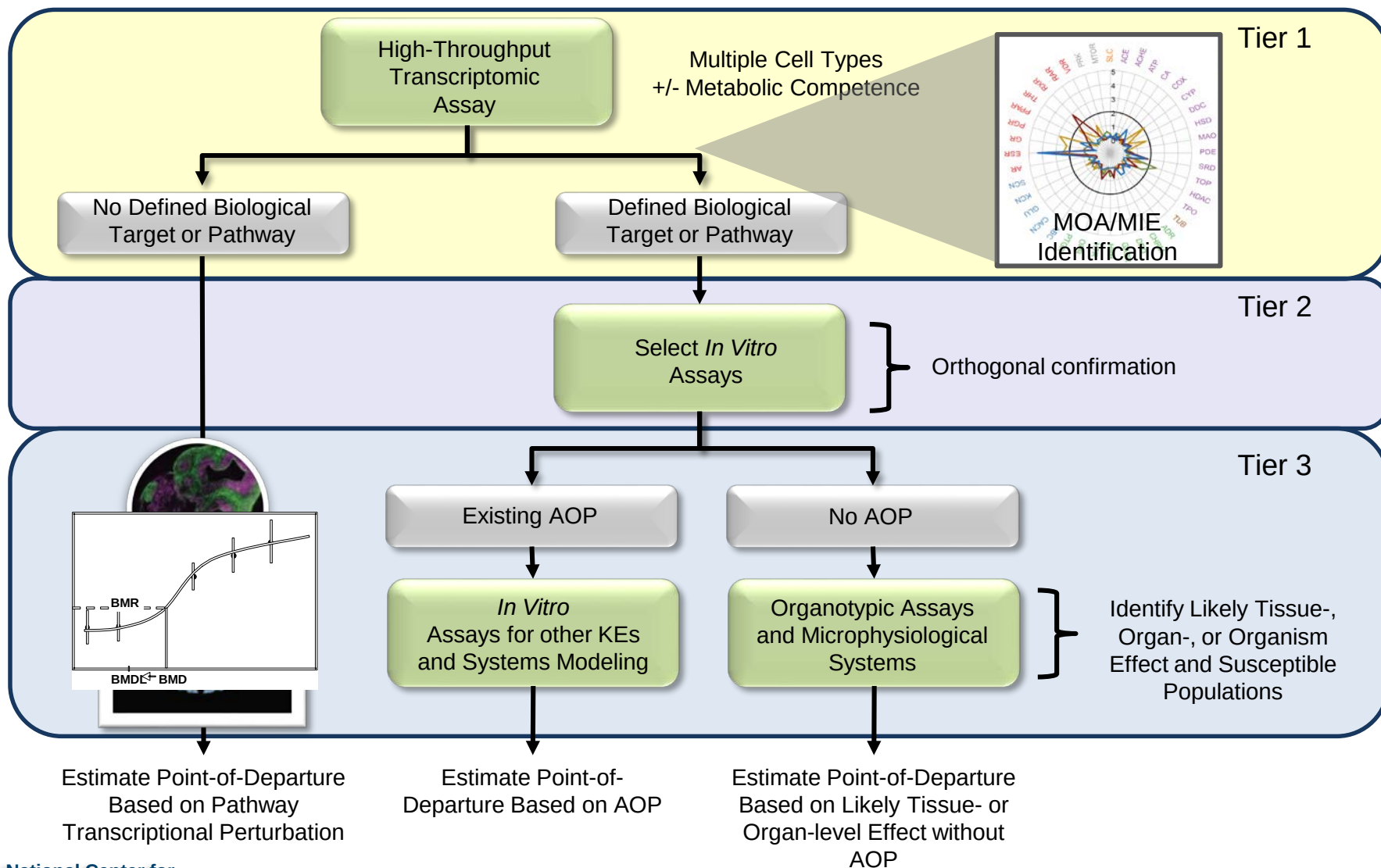


Shah et al., 2016

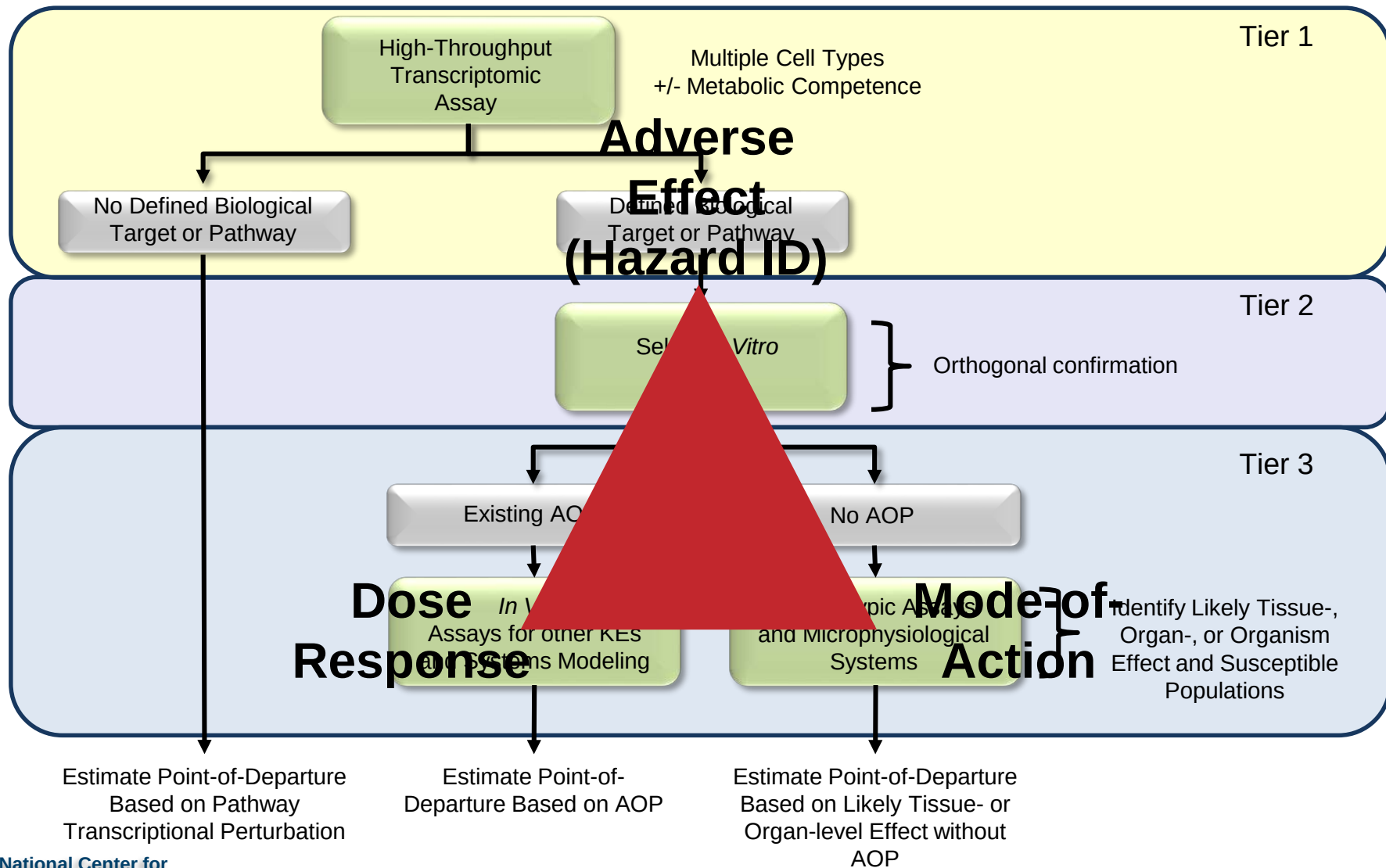
Read Across and Category Approach

- GenRA tool
- Chemical and Biological Read Across
- Quantitative estimates of uncertainty

Integrating Components Into a Tiered Testing and Assessment Strategy



Hitting All the Points of the Toxicogenomics Bermuda Triangle



Keys to Breaking Out of the Toxicogenomics Bermuda Triangle

- Develop best practices and data use recommendations that cover a range of regulatory decisions
- Systematize and convergence on analysis approaches
- Develop flexible validation approaches based on performance criteria and reference standards (e.g., MAQC) that adapt to evolution in technology
- Characterize qualitative and quantitative uncertainty in application of the technology to specific regulatory decisions while also doing this for legacy approaches
- Continue progress in the transition apical to molecular/pathway-based endpoints as a basis for safety-related decisions

Need evolutionary leap, not incremental advances

Thank You for Your Attention!

Tox21 Colleagues:

NTP Crew
FDA Collaborators
NCATS Collaborators

NCEA Colleagues:

Scott Wesselkamper
Nina Wang
Jason Lambert
Janet Hess-Wilson
Dan Petersen
Jay Zhao

Hamner Colleagues:

Barbara Wetmore
Reetu Singh
Bethany Parks
Linda Pluta
Michael Black
Eric Healy
Longlong Yang

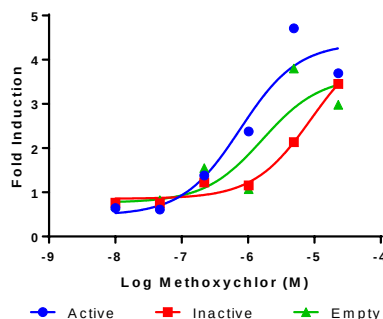


EPA's National Center for Computational Toxicology

Beginning to Address Metabolic Competence

“Extracellular” Approach

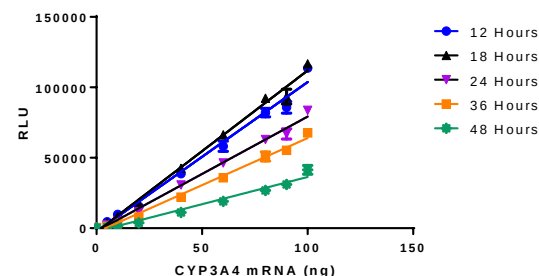
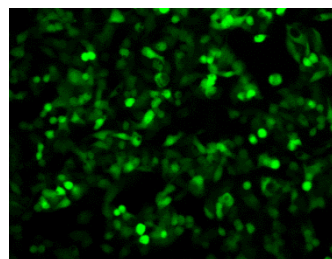
Chemicals metabolism in the media or
buffer of cell-based and cell-free assays



More closely models effects of hepatic
metabolism and generation of circulating
metabolites

“Intracellular” Approach

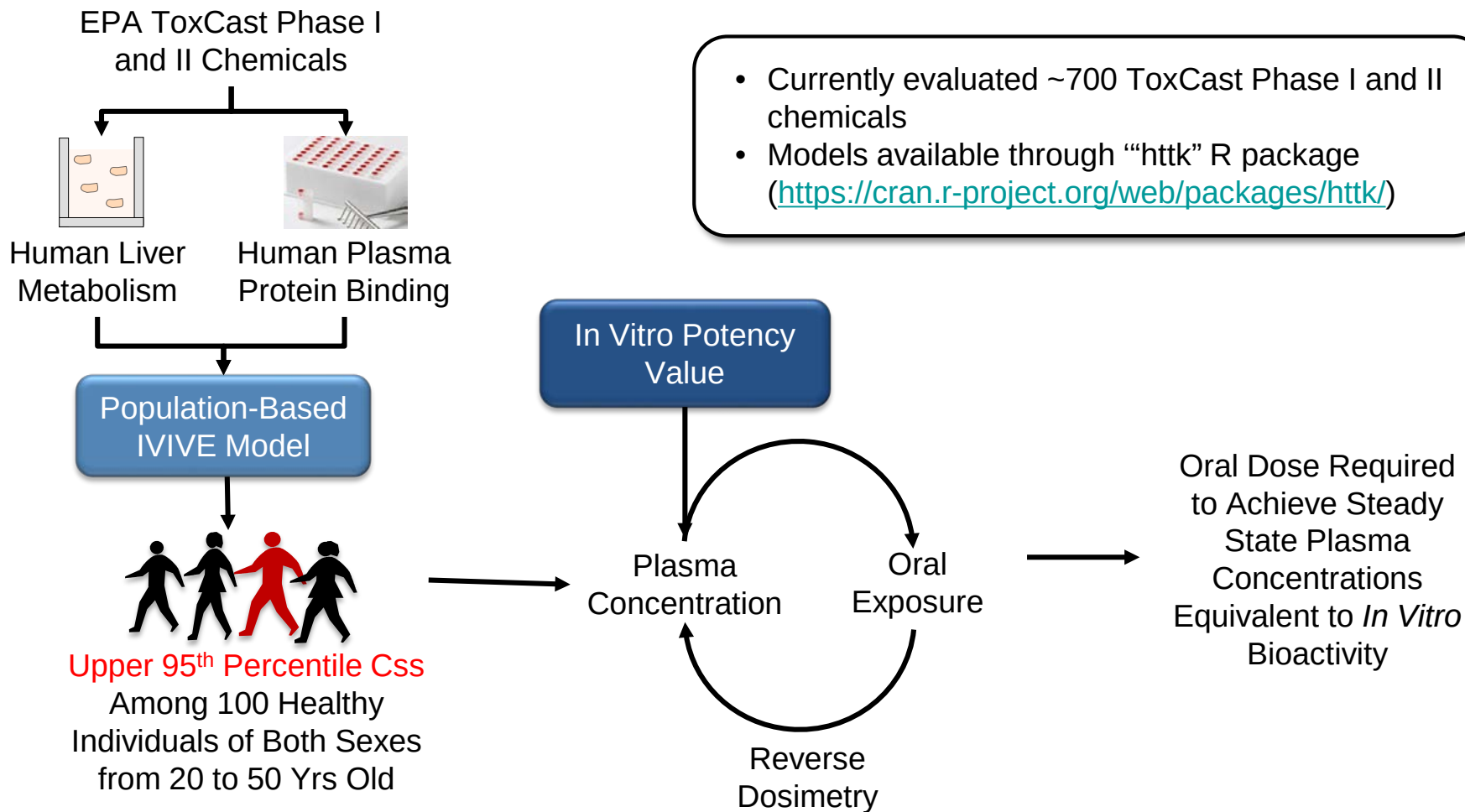
Capable of metabolizing chemicals
inside the cell in cell-based assays



More closely models effects of target
tissue metabolism

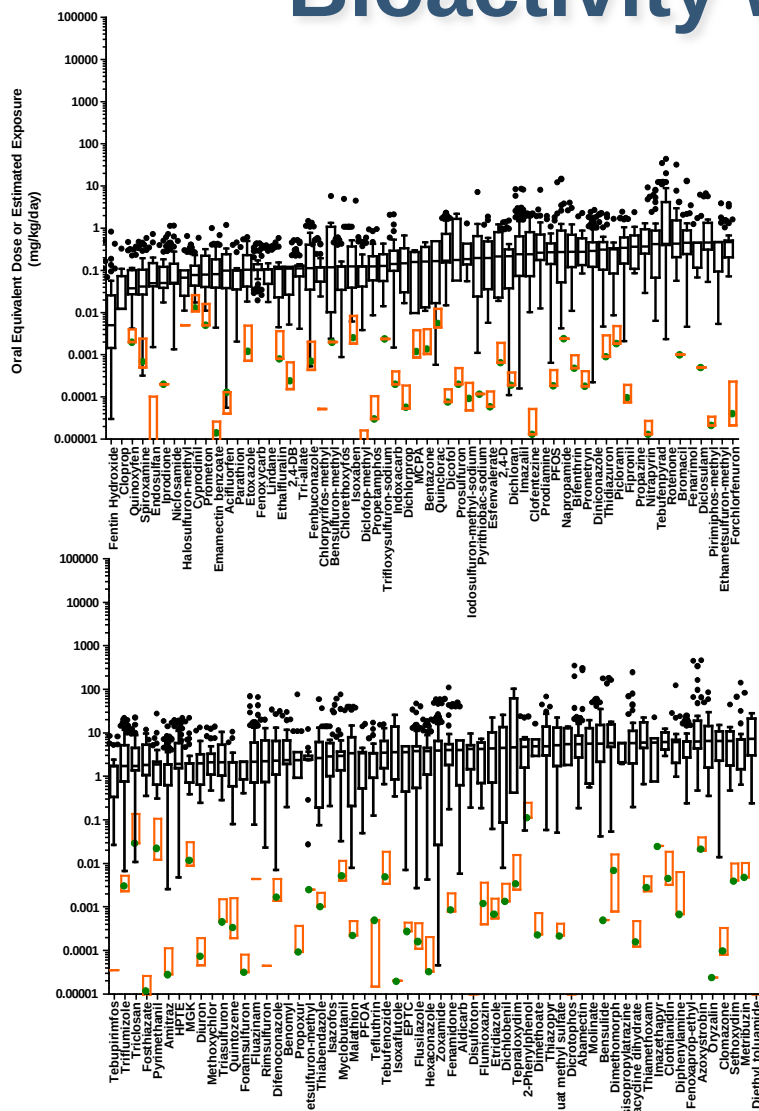
Integrated approach to model *in vivo*
metabolic bioactivation and detoxification

Adding the High-Throughput Toxicokinetic Component



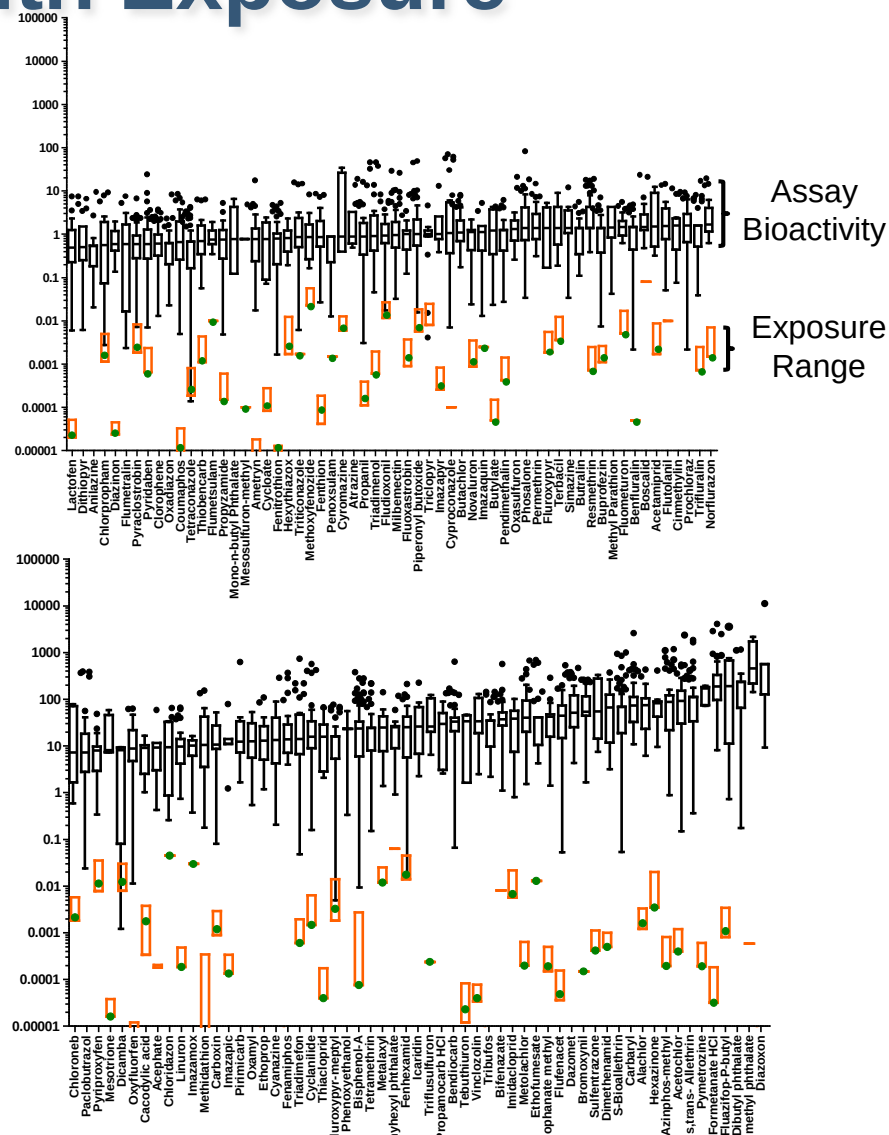
Rotroff *et al.*, *Tox Sci.*, 2010
Wetmore *et al.*, *Tox Sci.*, 2012

Comparing Dosimetry Adjusted Bioactivity with Exposure

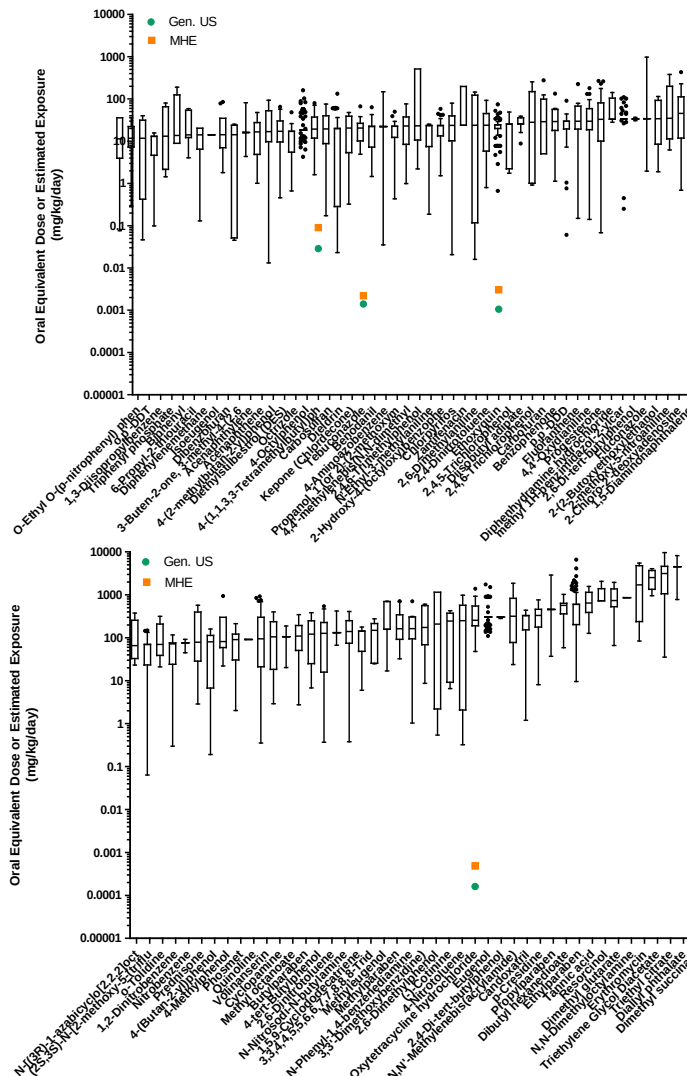
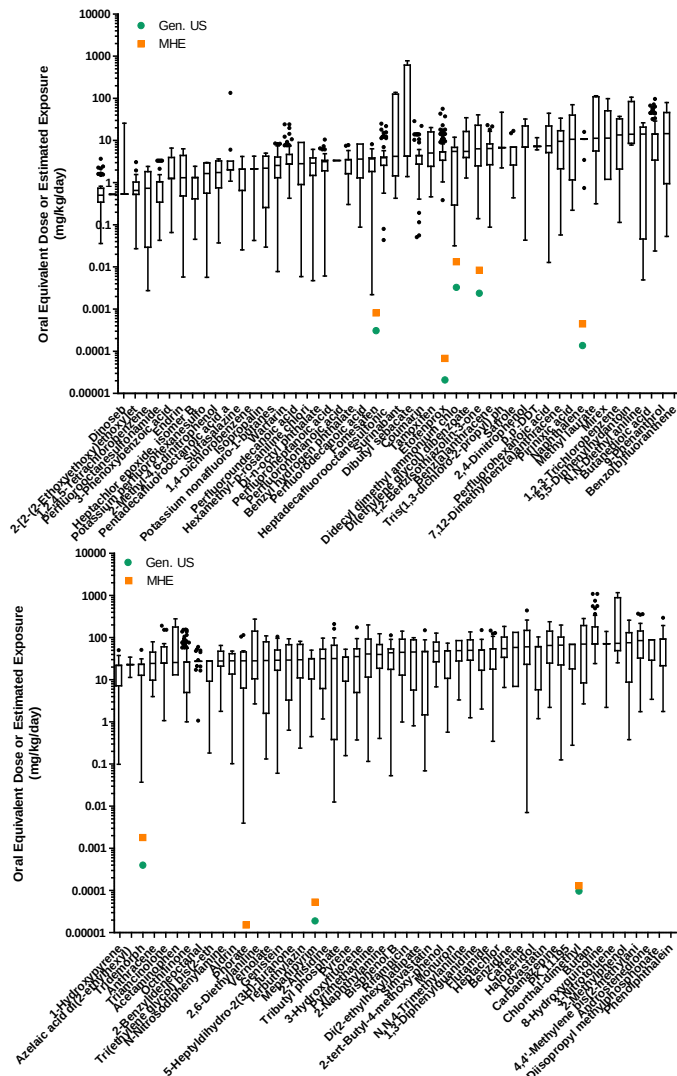


Oral Equivalent Dose or Estimated Exposure (mg/kg/day)

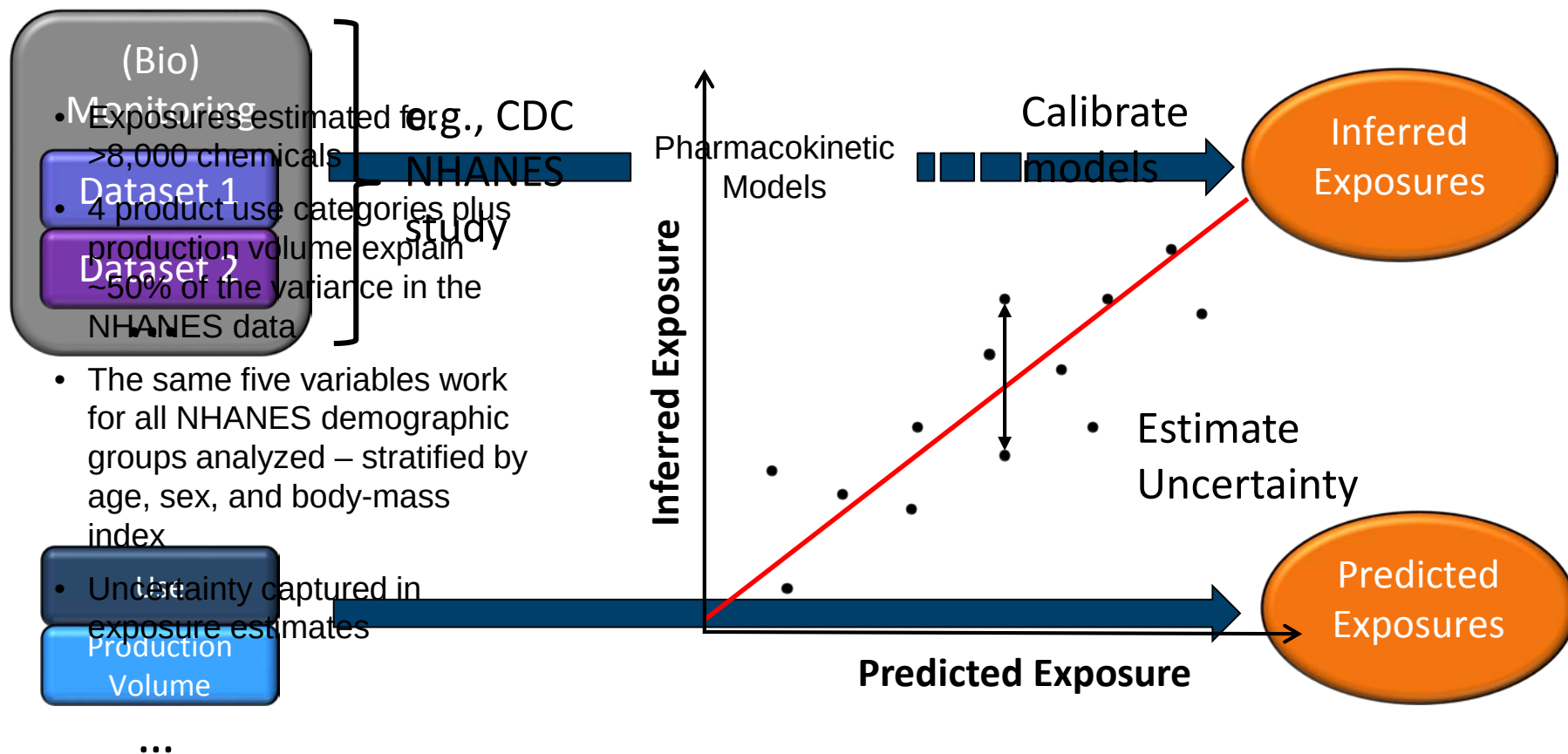
Oral Equivalent Dose or Estimated Exposure (mg/kg/day)



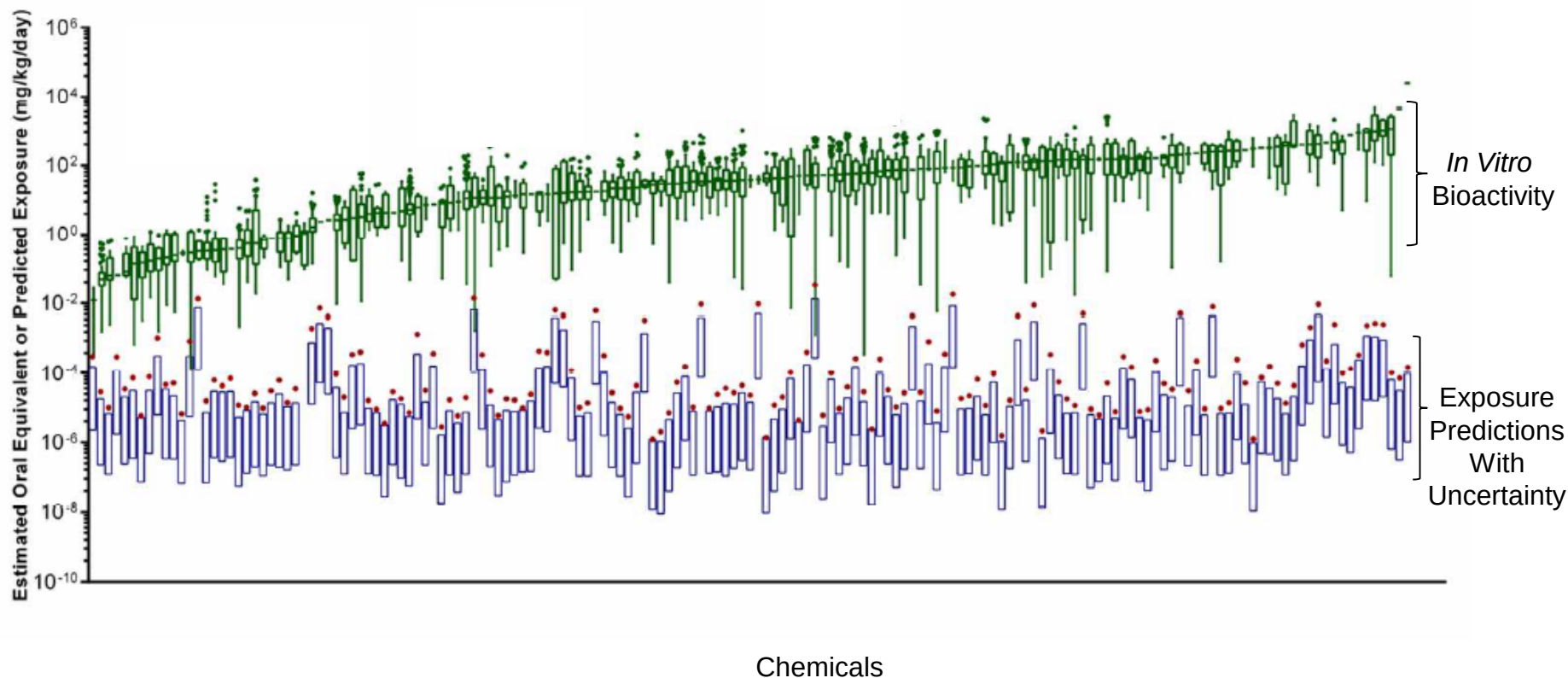
But, Exposure Information is Lacking on Most Chemicals



Adding the High-Throughput Exposure Component



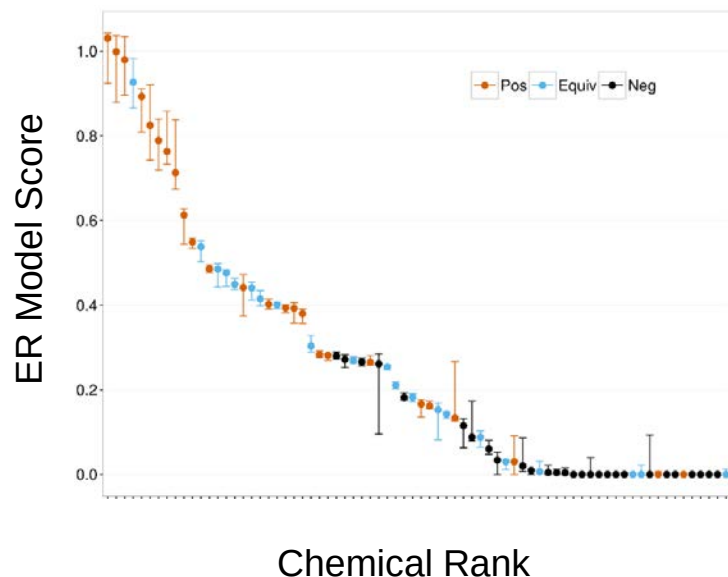
Comparing Bioactivity with Exposure Predictions for Risk Context



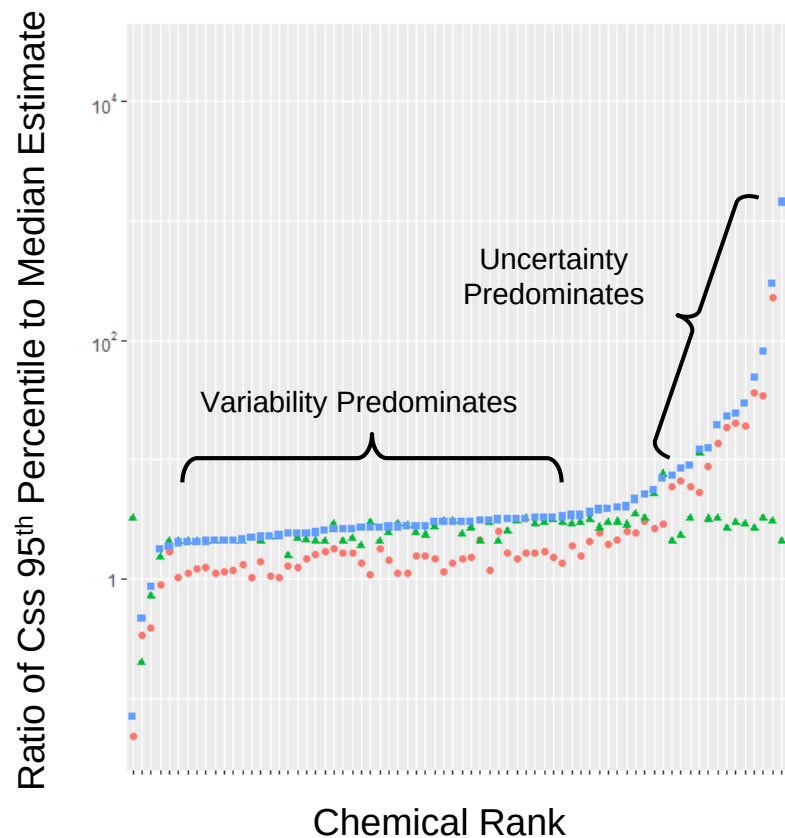
Wetmore *et al.*, *Tox Sci.*, 2015

Adding in Uncertainty and Variability for PD and PK

Propagation of Experimental Uncertainty in Models of ER Potency



Propagation of Experimental Uncertainty in High-Throughput Toxicokinetic Estimates



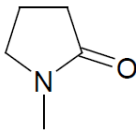
Covering All the Components of a 21st Century Risk Assessment

EPA United States Environmental Protection Agency
EPA Document# 740-R1-5002
March 2015
Office of Chemical Safety and
Pollution Prevention

TSCA Work Plan Chemical Risk Assessment

**N-Methylpyrrolidone:
Paint Stripper Use**

CASRN: 872-50-4



March 2015

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Phys Chem

Exposure

Hazard

Dose Response,

PK, and PODs

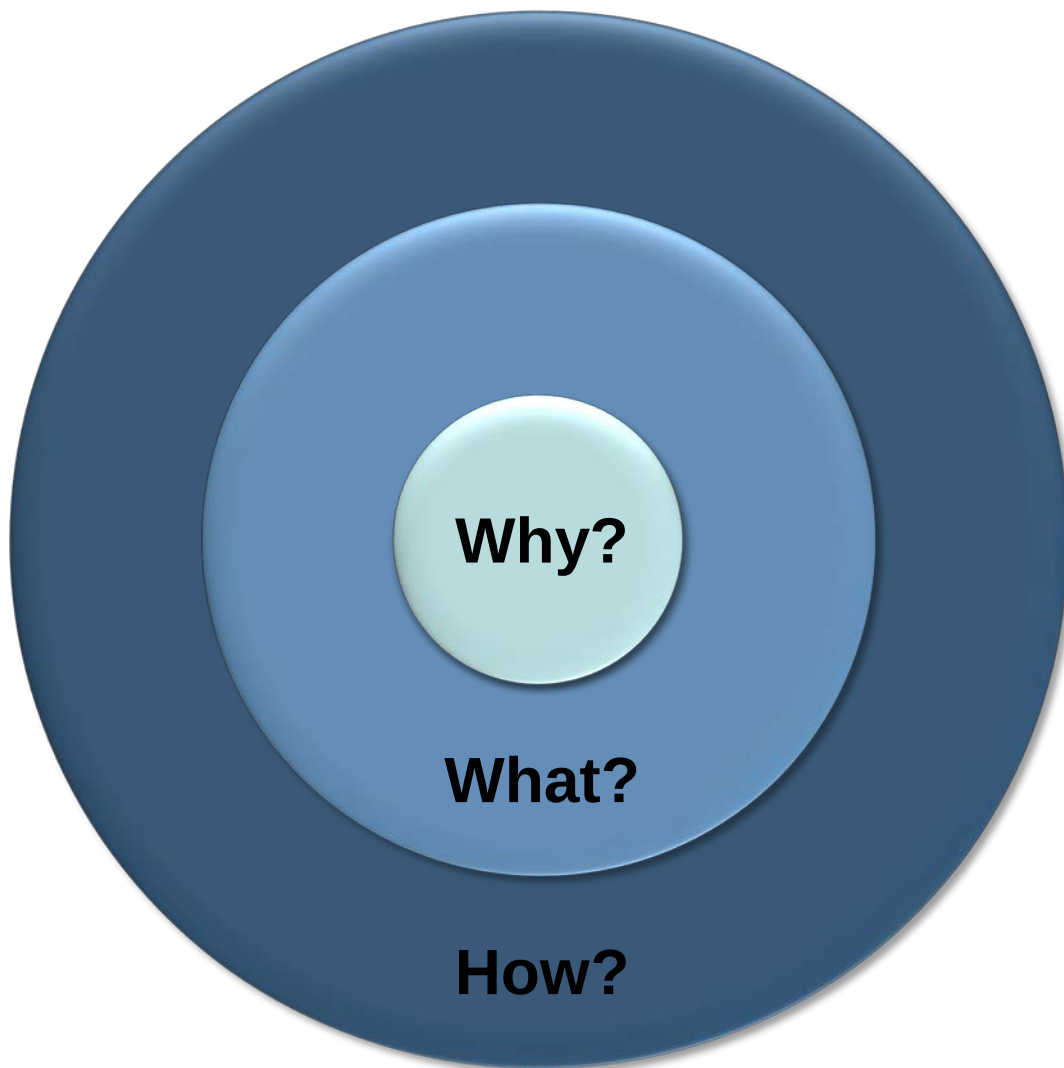
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Variability

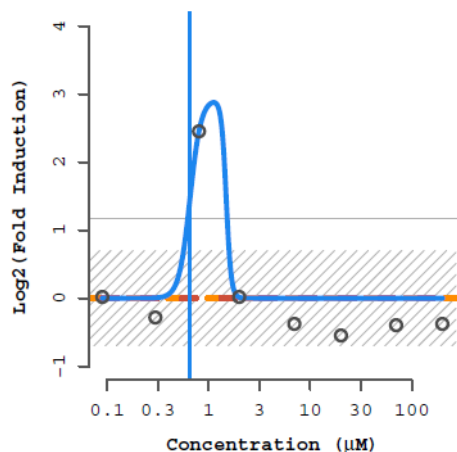
Risk Summary

Uncertainty

'Golden Circle' of 21st Century Risk Assessment



Regulatory Applications Require More Focus on Quality and Transparency



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)
- Publicly available ToxCast data analysis pipeline
 - Data quality flags to indicate concerns with chemical purity and identity, noisy data, and systematic assay errors
- Tox21 and ToxCast chemical libraries have undergone analytical QC and results publicly available
- Public posting of ToxCast procedures
 - Chemical Procurement and QC
 - Data Analysis
 - Assay Characteristics and Performance
- External audit on ToxCast data and data analysis pipeline
- Migrating ToxCast assay annotations to OECD 211 compliant format

Application to Regulatory Decisions for Endocrine Screening

Prioritization of the EDSP Universe of Chemicals

Integrated Bioactivity and Exposure Ranking

Prioritization of the Endocrine Program Universe of Chemicals: A Computational Approach for the Identification and Screening of Chemicals in the Endocrine Disruptor Screening Program

U.S. Environmental Protection Agency
Endocrine Disruptor Screening Program

Jointly developed by:

Office of Chemical Safety and Pollution Prevention
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
Mid-Continent Ecology Division (MED), Duluth, MN
Toxicity Assessment Division (TAD), RTP, NC 27111

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

December 2012

Exposure SAP White Paper

New High-throughput Methods to Estimate Chemical Exposure

Scientific Advisory Panel Meeting, July 2014

New High-throughput Methods to Estimate Chemical Exposure

1

Integrated Bioactivity and Exposure Ranking: A Computational Approach for the Identification and Screening of Chemicals in the Endocrine Disruptor Screening Program

Environmental Protection Agency
Endocrine Disruptor Screening Program

by:

Office of Chemical Safety and Pollution Prevention
Office of Research and Development (ORD)
Office of Water (OW)

Endocrine Disruptor Screening Program Interagency Center for the Development of Computational Methods (NICEATM)

Exposure SAP December 2-5

7/8/2014

35350

Federal Register / Vol. 80, No. 118 / Friday, June 19, 2015 / Notices

may claim all or part of a response confidential. EPA will issue another Federal Register document pursuant to 5 CFR 1320.5(a)(1)(iv) to announce the submission of the ICR to OMB and the opportunity to submit additional comments to OMB. If you have any questions about this ICR or the approval process, please contact the technical person listed under FOR FURTHER INFORMATION CONTACT.

Authority: 44 U.S.C. 3501 et seq.
Dated: June 10, 2015.
James Jones,
Assistant Administrator, Office of Chemical Safety and Pollution Prevention.
[FR Doc. 2015-1488 Filed 06-10-15; 8:45 am]
BILLING CODE: 6950-00-P

ENVIRONMENTAL PROTECTION AGENCY
[EPA-HQ-OPPT-2015-0305; FRL-9028-08]

Use of High Throughput Assays and Computational Tools: Endocrine Disruptor Screening Program; Notice of Availability and Opportunity for Comment

AGENCY: Environmental Protection Agency (EPA)
ACTION: Notice.

SUMMARY: This document describes how EPA is planning to incorporate an alternative scientific approach to screen chemicals for their ability to interact with the endocrine system. This will improve the Agency's ability to fulfill its statutory mandate to screen pesticide chemicals and other substances for their ability to cause adverse effects by their interaction with the endocrine system. The approach incorporates validated high throughput assays and a computational model and, based on current research, can serve as an alternative for some of the current assays in the Endocrine Disruptor Screening Program (EDSP) Tier 1 battery. EPA has partial screening results for over 1800 chemicals that have been evaluated using high throughput assays and a computational model for the estrogen receptor pathway. In the future, EPA anticipates that additional alternative methods will be available for EDSP chemical screening based on further advancements of high throughput assays and computational models for other endocrine pathways. Use of these alternative methods will accelerate the pace of screening, decrease costs, and reduce animal testing. In addition, this approach advances the goal of providing sensitive, specific, quantitative, and

and approval pursuant to 5 CFR 1320.12. EPA will issue another Federal Register document pursuant to 5 CFR 1320.5(a)(1)(iv) to announce the submission of the ICR to OMB and the opportunity to submit additional comments to OMB. If you have any questions about this ICR or the approval process, please contact the technical person listed under FOR FURTHER INFORMATION CONTACT.

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efficient screening using alternative test methods to some assays in the Tier 1 battery to protect human health and the environment.

DATES: Comments must be received on or before August 18, 2015.
ADDRESSES: Submit your comments, identified by docket (identification ID) number EPA-HQ-OPPT-2015-0305, by one of the following methods:
• **Federal eRulemaking Portal:** <http://www.regulations.gov>. Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute.
• **Mail:** Document Control Office (7407M), Office of Pollution Prevention and Toxics (OPPT), Environmental Protection Agency, 1200 Pennsylvania Ave. NW, Washington, DC 20460-0001.
• **Hand Delivery:** To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at <http://www.epa.gov/dockets/contacts.html>. Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at <http://www.epa.gov/dockets>.

FOR FURTHER INFORMATION CONTACT: For technical information contact: Jane Robbins, Office of Science Coordination and Policy (OSCP), Office of Chemical Safety and Pollution Prevention, Environmental Protection Agency, 1200 Pennsylvania Ave. NW, Washington, DC 20460-0001; telephone number: (202) 564-6622; email address: robbins.jane@epa.gov.

For general information contact: The TSCA-Hotline, ABVI-Goodwill, 422 South Clinton Ave., Rochester, NY 14620; telephone number: (202) 554-1404; email address: TSCA-Hotline@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

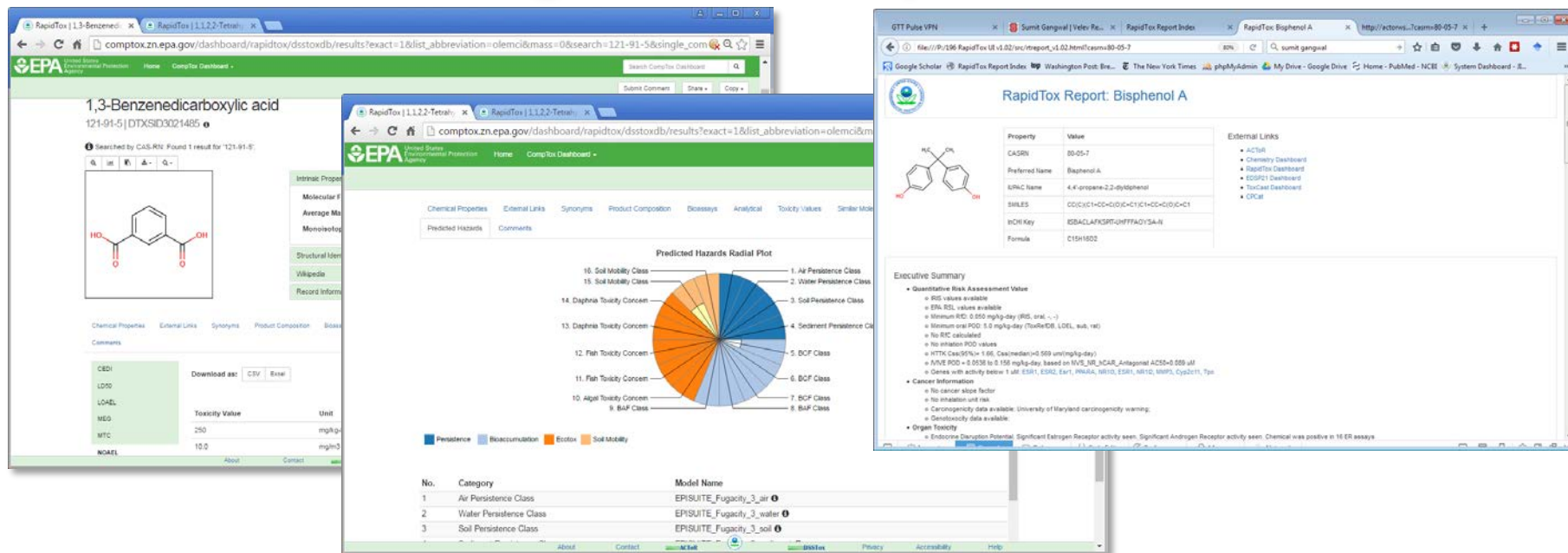
A. Does this action apply to me?

This action is directed to the public in general, and may be of interest to a wide range of stakeholders including those interested in endocrine testing of chemicals (including pesticides), and the EDSP in general. Since others also may be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action.

B. What is the agency authority for taking this action?

The EDSP is established under section 400(p) of the Federal Food, Drug and

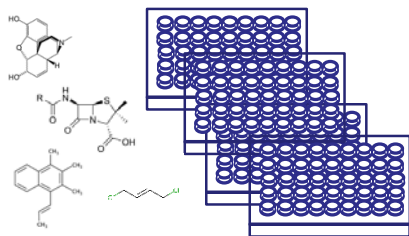
Beginning Application to Quantitative Risk Assessment Through New 'RapidTox' Dashboard



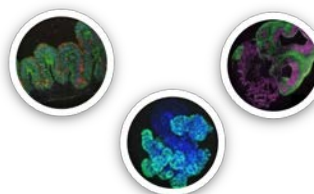
- Semi-automated decision support tool with dashboard interface for high-throughput risk assessments
- Integrate a range of information related to chemical properties, fate and transport, hazard, and exposure
- Transparent and interactive enough to enable expert users to review the assumptions made and refine the predictions
- Deliver quantitative toxicity values with associated estimates of uncertainty

Incorporating HT Toxicogenomics to Address This Challenge

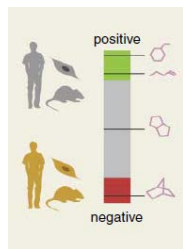
Thousands of
Chemicals



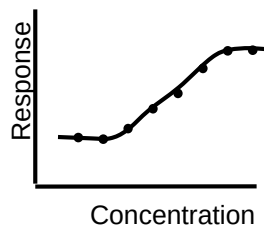
Multiple Cell Types



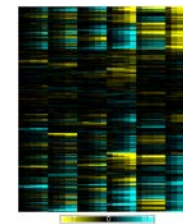
High-Throughput
Toxicogenomics



Mode-of-Action



Dose Response



Grouping and
Read Across