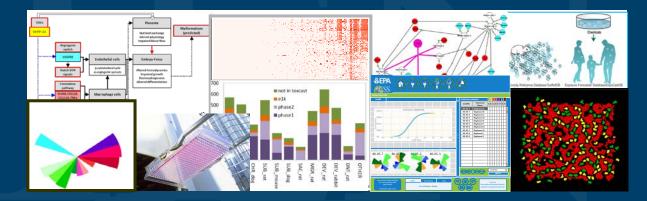


Translating Innovations in Toxicology into Chemical Safety Decision Making



Total Exposure Health Conference

September 6, 2018

Rusty Thomas Director National Center for Computational Toxicology

The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the U.S. EPA



Version 1.0 is Never Perfect...





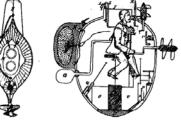


Microsoft Windows Version 1.01

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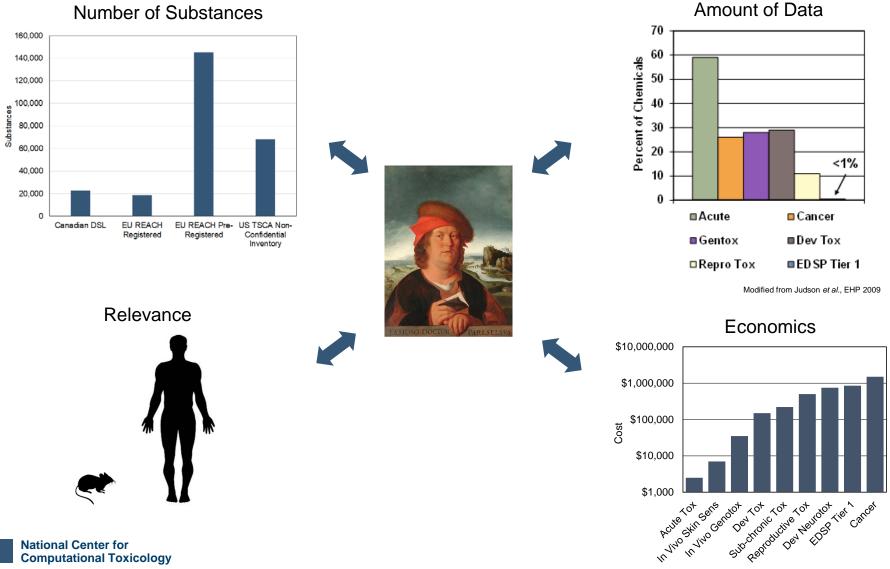








Early Versions of Toxicology Left Challenges for Fully Evaluating Safety



Computational Toxicology



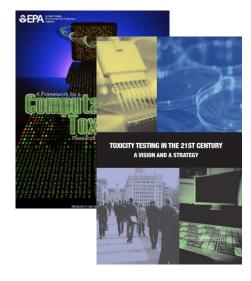
Solving the Challenges Will Require Both Innovation and Translational Tools









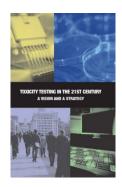


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Highlights of Technical Innovations and Translational Tools at EPA



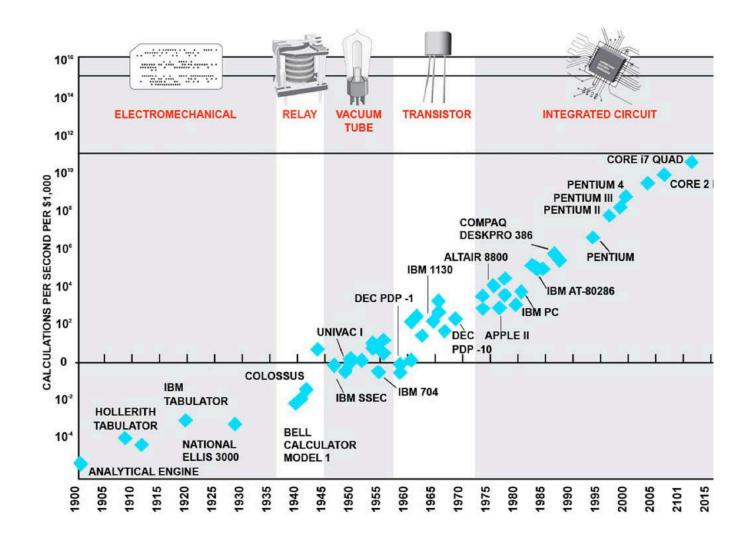


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- Move towards increased throughput
- Understanding promiscuity is the norm for environmental/commercial chemicals
- Focus on comprehensive biological coverage
- Increasingly relevant test systems
- Delivery of data and models through decision support tools
- Building confidence through regulatory focused case studies

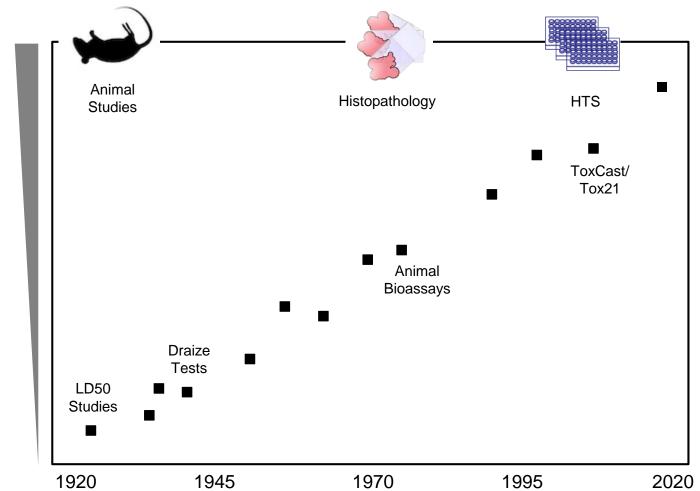


Moore's Law for Computational "Throughput" and Coverage





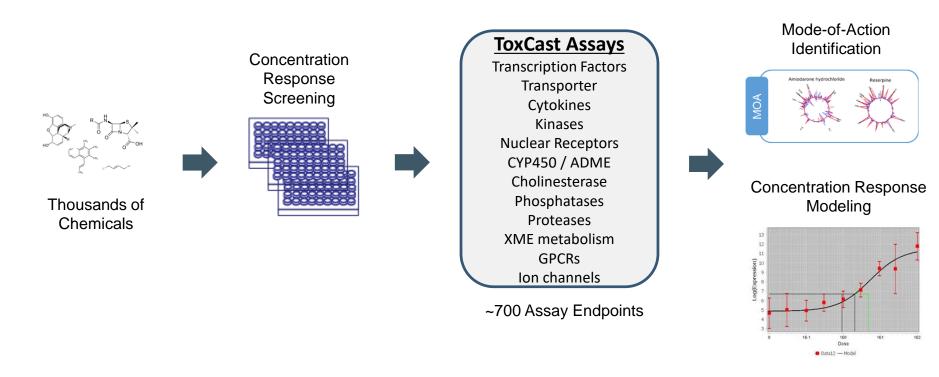
Rusty's Law for Toxicological "Throughput" and Coverage



Toxicological Coverage per \$



Innovations in High-Throughput Screening

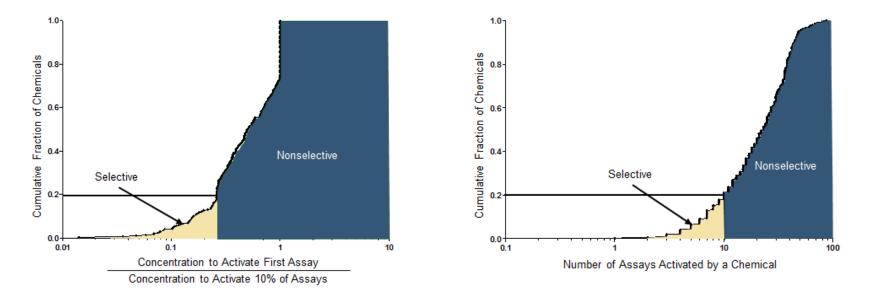


- 96, 384, and 1536-well, laboratory automation compatible
- Relatively expensive (~\$20,000 \$30,000 / chemical)
- Coverage of molecular and phenotypic responses
- Multiple assay vendors/labs



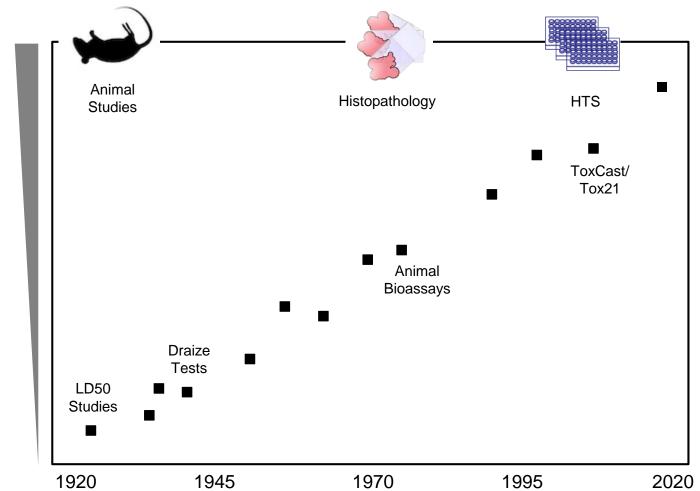
Biological Promiscuity is the Norm for Most Chemicals

- Most histological changes do not occur without upstream or downsream changes at the molecular level
- Most environmental/commercial chemicals are highly non-selective in their interactions with biological systems





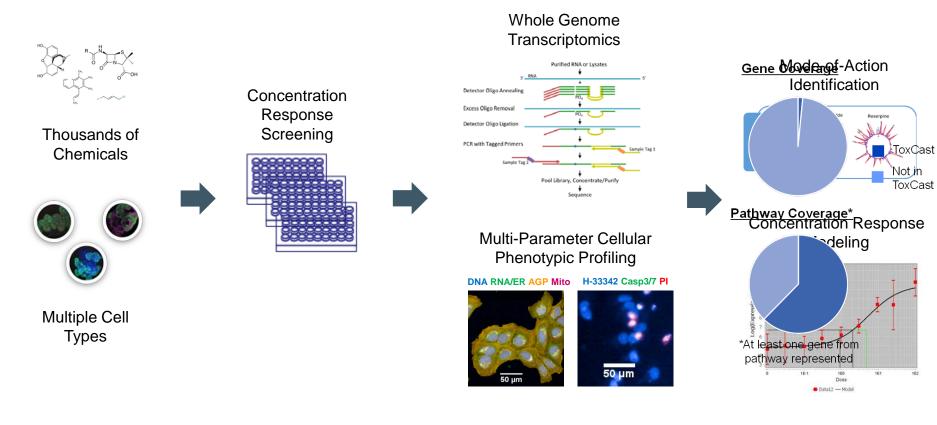
Rusty's Law for Toxicological "Throughput" and Coverage



Toxicological Coverage per \$



Innovations in High-Throughput and High-Content Screening



- 384-well, laboratory automation compatible
- Relatively inexpensive (\$2.50 \$1,500 per chemical)
- Broad complementary coverage of molecular and phenotypic responses
- Integration of reference materials and controls for performance standards
- Increased portability

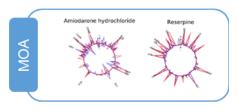


Initial Application of High-Throughput Transcriptomic Screening

Parameter	Description
Cell Type(s)	MCF7
Chemicals	2,112
Time Points:	6 hours
Concentrations:	8
Biological Replicates:	3

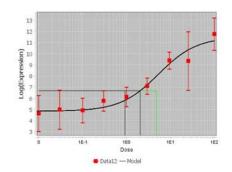
- Number of samples: 54,432
- Number of endpoints: 1.15x10⁹
- Total amount of data: ~50 TB

Mode-of-Action Identification



Currently comparing a range of approaches... Cmap, ML, Pathway

> Concentration Response Modeling



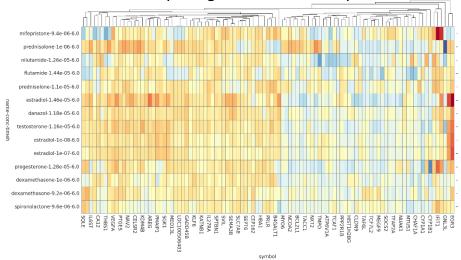
Currently comparing a range of approaches... BMDExpress, Proast, tcpl, and new NB model



Identifying Potential Biological Targets

Annotated Targets in CMap v2 and RefChem

Example Signature from CMap v2

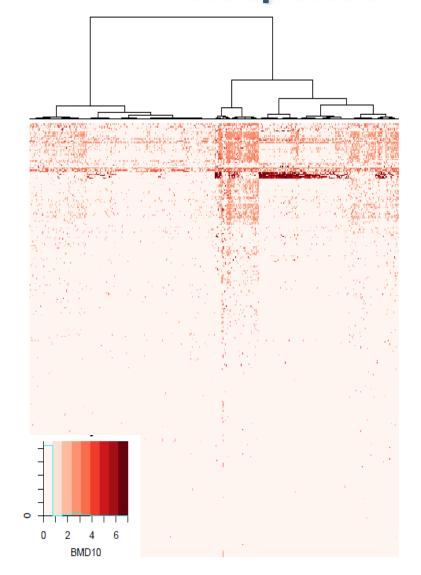


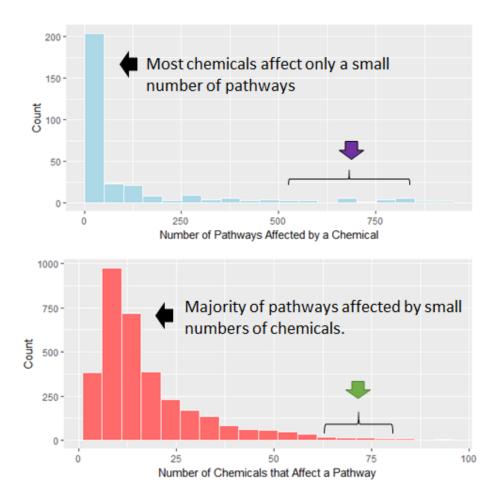
	CMap v2 / Affymetrix	HTTr-Phase	l RefChem Hits
Target	Signature size	Sensitivity	Positives
CYP2C9	131	1	1
ESR1	257	1	11
HDAC1	124	1	2
DHFR	215	1	2
NR1I2	139	1	2
PGR	115	1	1
HMGCR	236	1	1
ABCC2	357	1	1
TYMS	329	1	1
ESR2	281	0.86	7
AR	261	0.78	9
NR3C2	352	0.5	2
ABCB1	117	0.5	2
NR3C1	148	0.5	4
CA1	176	0.5	4
CA2	341	0.5	4
PTGS1	307	0.25	4

*In process of curating/testing hits to determine specificity



Characterizing Concentration Response

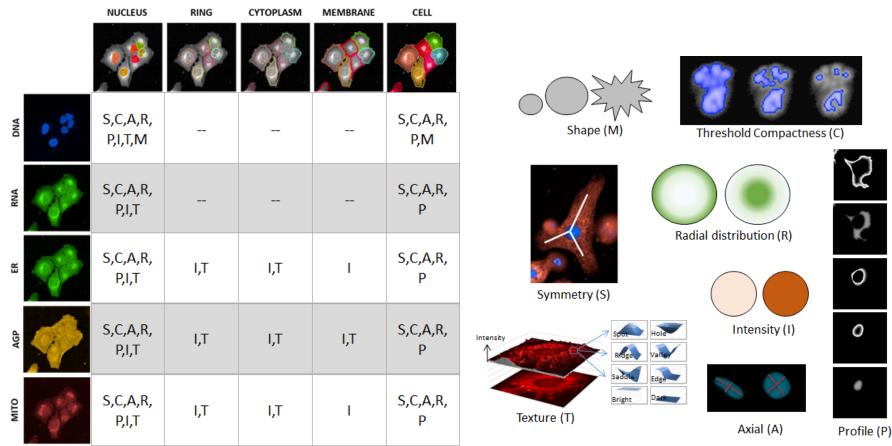




J. Harrill, I. Shah, W. Setzer, Judson Unpublished



Development of High-Throughput Phenotypic Profiling



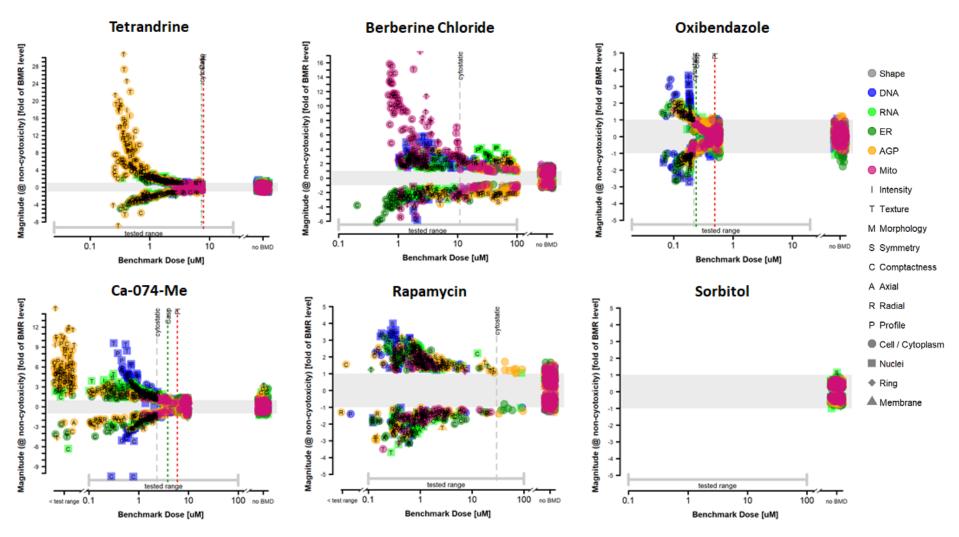
Cell Compartments

~1,300 total phenotypic endpoints

Non-Ab Dyes



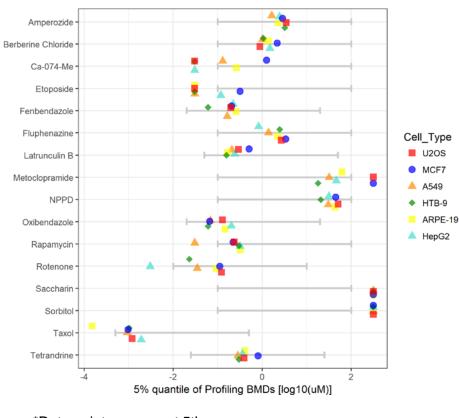
Unique Phenotypic Responses Associated with Different MOAs



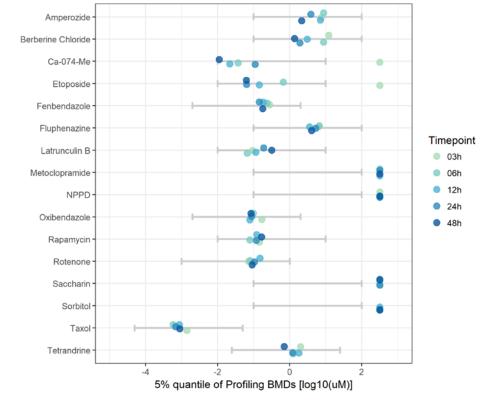


Variation in Phenotypic Potencies Across Cell Type and Time

Cell Type Differences (48 hr)



*Data points represent 5th



Time Point Differences (U2OS cells)

percentile of phenotypic BMDs

Tested range

National Center for **Computational Toxicology** J. Nyffeler, J. Harrill, Unpublished



Innovations in Incorporating Xenobiotic Metabolism

"Extracellular" Approach

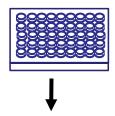
Chemical metabolism in the media or buffer of cell-based and cell-free assays

More closely models effects of hepatic

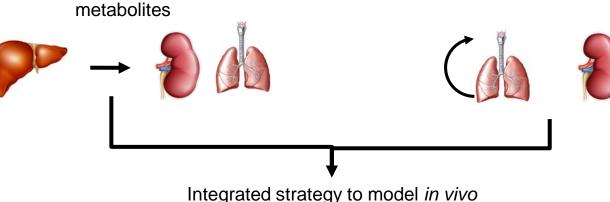
metabolism and generation of circulating

"Intracellular" Approach

Chemical metabolism inside the cell in cell-based assays



More closely models effects of target tissue metabolism

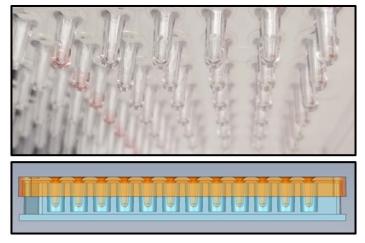


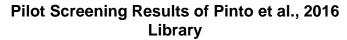
metabolic bioactivation and detoxification

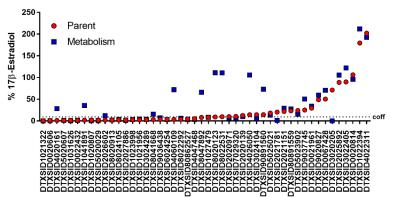


Application of Extracellular Strategy to Identify Estrogenic Metabolites

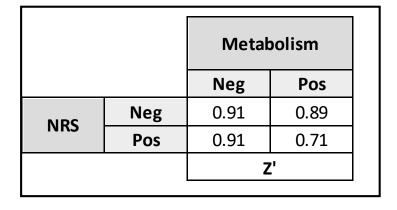
AIME Method: S9 Fraction Immobilization in Alginate Microspheres on 96- or 384-well peg

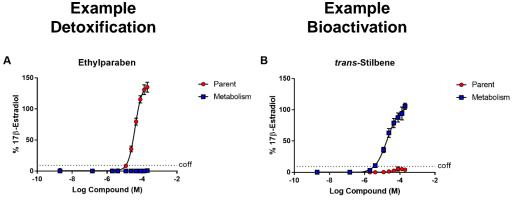






National Center for Computational Toxicology Screening Window of VM7 (formerly BG1) ER Transactivation Assay

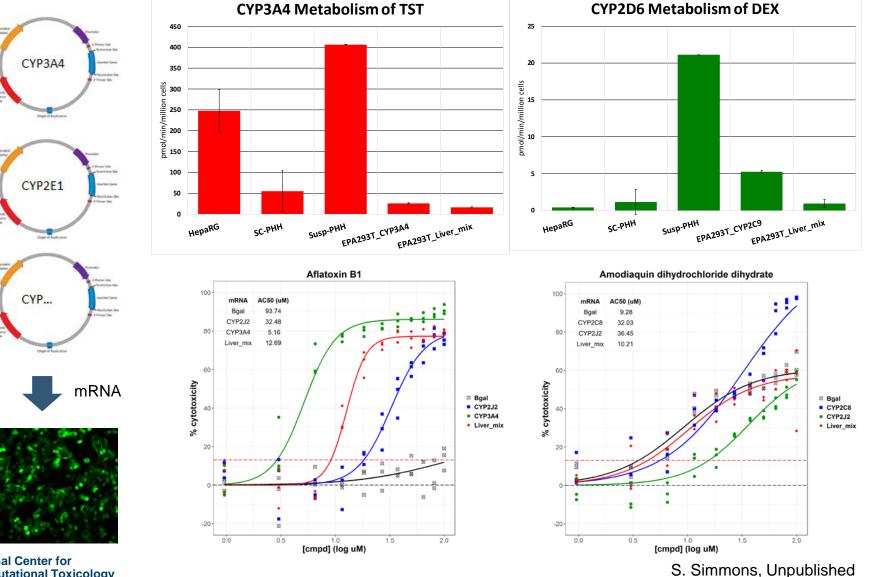




D. DeGroot, C. Deisenroth, Unpublished



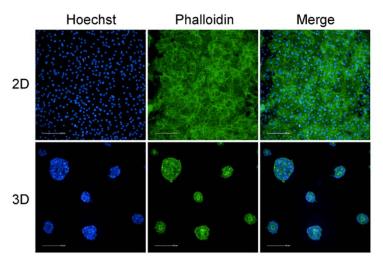
Application of Intracellular Strategy to Identify Cytotoxic Metabolites



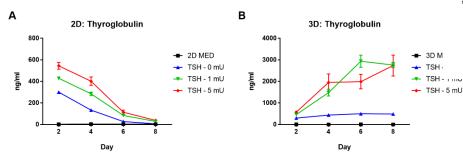


Innovating in Organotypic Culture Models to Predict Tissue Effects

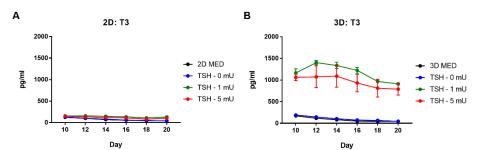
3D Microtissue Model of Primary Human Thyrocytes

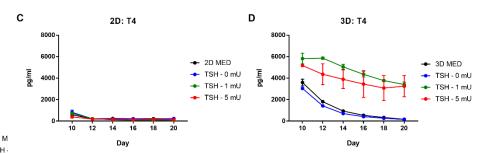


Thyroglobulin secretion is enhanced over time in a 3D culture model



Thyroid hormone is synthesized and secreted over time in a 3D culture model

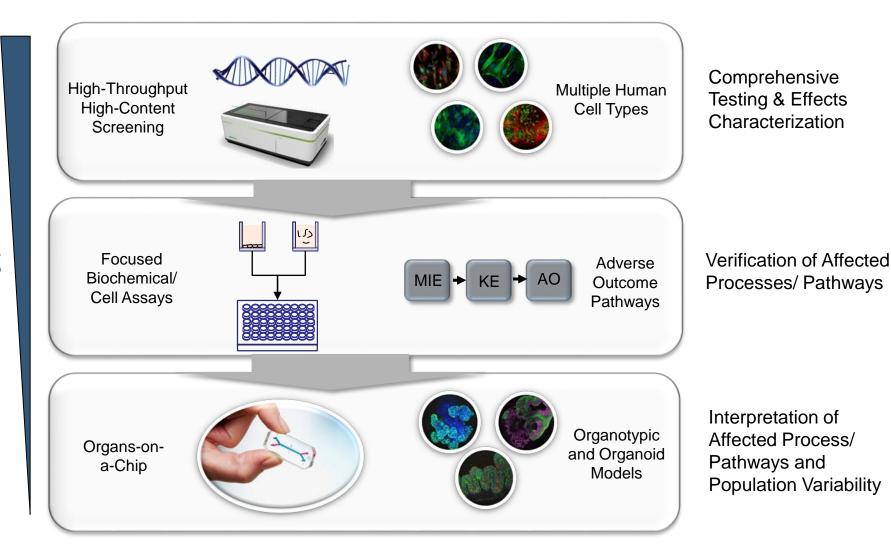




National Center for Computational Toxicology C. Deisenroth, Unpublished



Integrating New Technologies for Efficient Chemical Testing





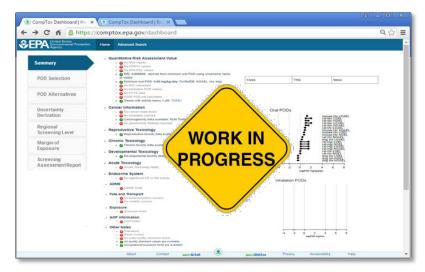
Enable Translation Through Data Visualization and Decision Support Tools

Comptox Chemicals Dashboard

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https://comptox.epa.gov/dashboard/

RapidTox Dashboard





Similar to Financial Tools, RapidTox will Have Multiple Workflows to Address Different Decision Contexts

Workflow to Calculate Your Taxes

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Close My Return	Here's an Update on Where Thi	ngs Stand So Far		
\$7,097 \$871 You Owe You Owe	Your Federal Tax Due (In Progress)	\$7,097		
Personal Info	Why did my refund change?	Is this number final?		
Wages & Income	We calculated this based on:	No! This amount is a work in progress.		
Deductions & Credits	1. What you told us about yourself	After you enter all your income, we'll check for tax breaks that can put a dent in your tax bill - and hopefully turn your tax due into a		
Other Tax Situations	(if you're married, have kids, etc.).	refund.		
Federal Review	2. The tax benefits we got you so far.			
Error Check	3. The numbers you entered from your W-2.			
State Taxes	- Learn More About How We Calculated This			
Review				
File				
	Back	Continue		

Workflows to Integrate Safety Data for Regulatory Decisions

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Summary										
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POD Alternatives	DenidTes Drieviting	tion Monle	and a second							
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Screening	chemical set, the allowable data domains, and update the weights.	Human Health								
AssessmentReport	Then select the Recelculate button	Acute	Subchronic	Chronic	DevTex	ReproTax	Cancer	Mutagenicity		Systemic Tox Mod
	and go to the prioritization tab. You can then port by the different	Si la veo	[2] In vivo	(R) In vivo	😿 In vivo	S parts	N In vivo	IN WVD	🕅 ju And	Wartin model
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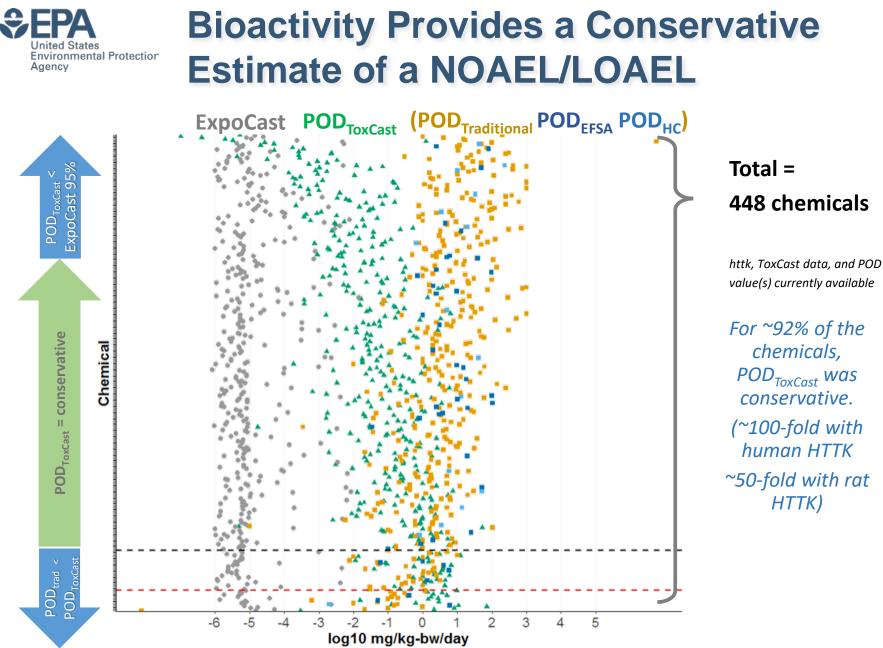
- Semi-automated decision support workflows
- Flexible integration of information related to chemical properties, fate and transport, hazard, and exposure
- Enable expert users to review the assumptions made and refine the results
- Presents alternative data together with traditional toxicology data



Translation of Results Through Regulatory Focused Case Studies

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Practitioner Insights: Regulatory Toolbox; It The recently amendes ing non-animal safety te and reports on a recent work for tests that can i	Newsteel with generation from Dalog 2016 bit , thinking, Copyright 2017 bit , thinking, Copyright 2017 manual Atlant, Inc. (100-272-1020) ma Bringing New Methods for is Time to Get Serious Concernational Series (Serious Series) (Series)	or Chemical Sa to take significa Robert Kavlock e ugency convened	nt strides towards us- xplores this challenge that lays the ground-	
Robert Kaslock is th Administrator for Se of Research Develop 2 ORD is the scientific whose leading-edge the underpitning of for the agency. The underpitning of	Chechnical Barbon December 1 , March A., "This A Barbon and Carlos and S. Thomas" and S. Thomas a	of Chemical t ¹ , ¹ Tars S. Barton- the and the second second second the second second second second second terms and second second second second terms and secon	Madaren ¹ Mauren R. Gwi tran Jerry, Wahapan D.C. 20 Mark J. Chao, OX 20 Mark S. Can and J. Chao, OX 20 Mark S. Can and J. Chao, OX 20 Mark S. Can and J. Chao, Chao M. San J. Can and J. Chao, Chao M. San J. Can and J. Chao, Chao M. San J. Can and J. Can and J. Can and J. Can and J. Can and J. Can and J. Can and J. Can and J. Can and J. Can and J. Can and J. Can and J. Can and J. Can and J. Can and J. Can	AND Under States And And A context 2771 L thand States mical Rick Accessment A context 2771 L thand States mical Rick Accessment A context 2771 L than the states mical and any states and the states
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- Multiple international case studies stemming from 2016 inter-governmental workshop
- Example: *In Vitro* Bioactivity as a Conservative Point of Departure
- Participants include EPA, Health Canada, ECHA, EFSA, JRC, and A*STAR
- Goal: Determine whether *in vitro* bioactivity from broad high-throughput screening studies (e.g., ToxCast) can be used as a conservative point-of-departure and when compared with exposure estimates serve to prioritize chemicals for future study or as lower tier risk assessment.



National Center for Computational Toxicology International case study with EPA, ASTAR, ECHA, Health Canada, and EFSA





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Take Home Messages...

- Advancing toxicology to the new and improved version will require both continued technical innovation as well as translational efforts
- New technologies exist for rapidly and comprehensively covering toxicological space at significantly less cost
- Addressing previous technical limitations such as a lack of metabolism and organ/tissue effects are within reach
- Enabling application of new technologies to chemical safety decisions with require delivery and integration using a broad range of IT tools
- Partnering with regulators on case studies will increase confidence and acceleration application to chemical risk assessment



Acknowledgements and Questions

Tox21 Colleagues: NTP FDA NCATS

EPA Colleagues: NERL NHEERL NCEA

Collaborative Partners: Unilever A*STAR ECHA EFSA Health Canada JRC

