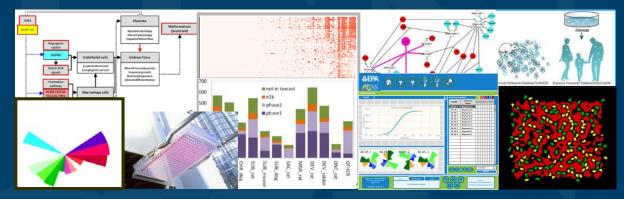


Incorporating New Technologies for 21st Century Toxicity Testing and Risk Assessment



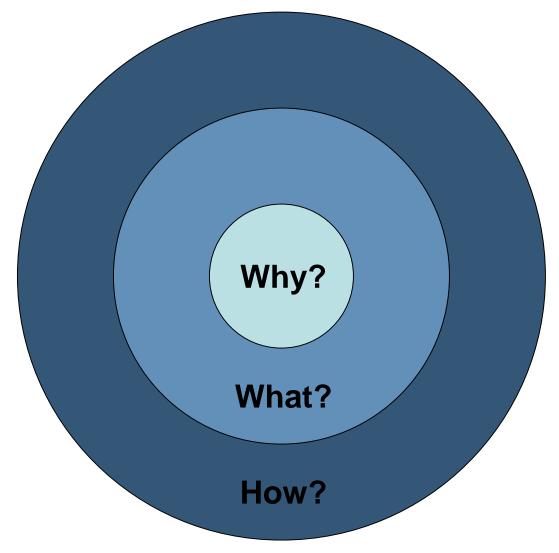
GlobalChem February 22, 2017

Russell Thomas Director National Center for Computational Toxicology

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

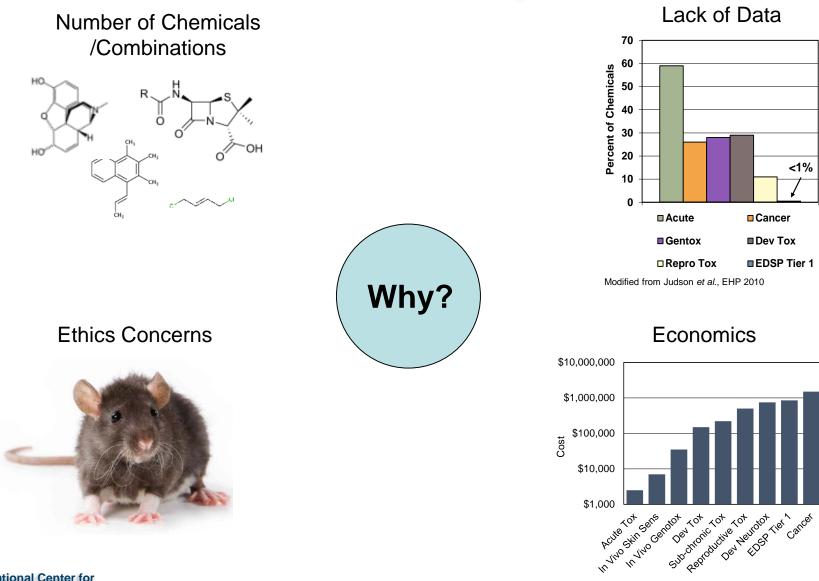


Sinek's 'Golden Circle' of 21st Century Risk Assessment



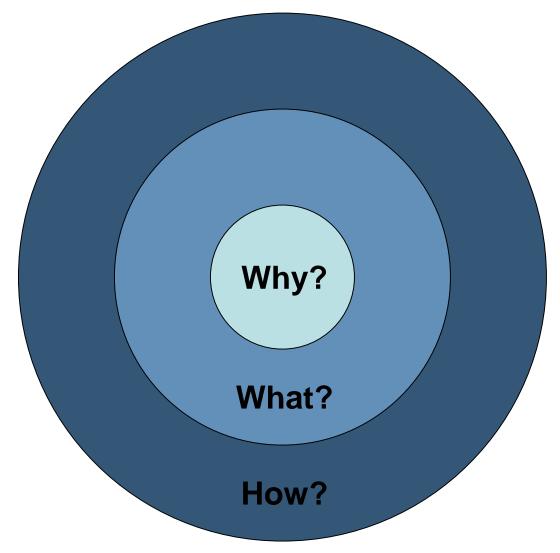


All Understand 'Why' We Need to Innovate In This Space...





'Golden Circle' of 21st Century Risk Assessment





Risk Assessments Generally Contain a Standard Set of Components

		TABLE OF CONTENTS	
United States Environmental Protection Agency	EPA Document# 740-R1-5002 March 2015	TABLE OF CONTENTS	2
	Office of Chemical Safety and Pollution Prevention	AUTHORS / CONTRIBUTORS / ACKNOWLEDGEMENTS / REVIEWERS	9
	Politition Prevention	ABBREVIATIONS	11
		EXECUTIVE SUMMARY	14
TSCA Work Plan Chemical Risk A	coccmont	1 BACKGROUND AND SCOPE	20
ISCA WORK FIGH CHEINICALKISK A	ssessment	1.1 INTRODUCTION	20
		1.2 USES AND PRODUCTION VOLUMES	21
		1.2.1 Assessment and Regulatory History	21
N-Methylpyrrolidone:		1.2.2 Scope of the Assessment	23
		1.3 PROBLEM FORMULATION	23
Paint Stripper Use		1.3.1 Physical and pice Properties	24
		1.3.2 Environmental Spectra	25
		1.3.3 Conceptual Model	26
CASRN: 872-50-4		1.3.3.1 Exposure Patiways 1.3.3.2 Health Effects and Human Receptors	26
		1.3.4 Analysis Plan	28
		2 EXPOSURE ASSESSMENT.	30
		2.1 OCCUPATIONAL EXPOSURES	20
		2.1.1 Approach and Methodology	
		2.1.1 Approach and Methodology 2.1.1 Identification of Relevant Industries	31
		2.1.1.2 Approach for Determining Occupational Exposure Data and Input Parameters for PBPK Mode	
<u></u>		2.1.1.3 Estimates of Occupational Exposure Parameters and Number of Exposed Workers	31
IN -		2.1.2 Use of Occupation Texposure Estimates in PBPK Modeling	
		2.2 CONSUMER EXPOSURES	37
		2.2.1 Approach and Methodolog	37
I		2.2.1.1 Consumer Dermal Exposure assessment	38
		2.2.1.2 Consumer Users and Residential Non-Users Inhalation Exposure Assessment	
		2.2.2 Model Outputs and Exposure Calculations	
		2.2.3 Use of Consumer Exposure Estimates in PBPK Modeling	46
March 2015		3 HAZARD IDENTIFICATION AND DOSE-RESPONSE	48
		3.1 APPROACH AND METHODOLOGY	48
		3.1.1 Selection of Peer-Reviewed Assessments for Hazard Identification and Dose-Response Analysi	is48
		3.1.2 Hazard Summary and Henard Hentification	49
		3.1.3 Selection of Developmental To cit and in the print.	60
		3.1.3.1 Decreased Fetal & PPO har on by Vight and a second	63
		3.1.3.2 Resorptions and train the track in t	65
		3.1.3.4 Conclusions and Selection of Key Endpoints	67
		3.2 DOSE-RESPONSE ASSESSMENT AND STUDY SELECTION	68
		3.2 Identification of Studies for BMD Modeling	68
		3.2 erivation of Internal Doses	69
		Dose Response	.73
			Z. 9

	Variability	
3.2.5	Considerations for ensuine ut opu the Cad in generation and a second	7
4 11114	AN HEALTH RISK CHARACTERIZATION	0
		0
4.1 RISK E		8
4.1.1	and stin its to Accurate Stranger in the Miner and Accurate and Accurate Accurate	
4.1.2	tisk istimates to the consumate Explore to TM	8
4.1.1	Risk Estimates for Chronic Occupational Exposures to NMP	9
	N HEALTH RISK CHARACTERIZATION SUMMARY.	9
	URCES OF UNCERTAINTY AND DATA LIMITATIONS	
4.3.1 4.3.2	Key Uncertainties in the Occupational Exposure Assessment	9
4.3.2	Key Uncertainty in the later of and the Ruponer Ase are standing to the second se	9
4.3.4	Key Uncer sing is in the skill as a single s	10
	SSESSMENT CONCLUSIONS	10
4.4 NOKA	SESSIVENT CONCEOSIONS	10
REFERENCES		. 10
APPENDICES		. 12
Appendix A	ENVIRONMENTAL EFFECTS SUMMARY	. 12
A-1 Acute	Foxicity to Aquatic Organisms	12
	CTOXICITY TO AQUATIC ORGANISMS.	
	Y TO SEDIMENT AND SOIL ORGANISMS	
	Y TO WILDLIFE	
	RY OF ENVIRONMENTAL HAZARD ASSESSMENT	
Appendix B	CHEMICAL REPORTING DATA	. 12
B-1 CONSUL	MER USES	12
	TRIPPING APPLICATIONS	
Appendix C	STATE NMP REGULATIONS	. 12
Appendix D	OCCUPATIONAL EXPOSURE ASSESSMENT SUPPORT INFORMATION	
D-1 SUMM	BY OF DERMAL EXPOSURE PARAMETERS. INHALATION CONCENTRATIONS AND EXPOSURE REDUCTION FACTORS	13
	EEDS AND DATA COLLECTION	
	RIES THAT EMPLOY PAINT STRIPPING ACTIVITIES	
D-4 Occup	ITIONAL PAINT STRIPPING PROCESSES AND ASSOCIATED WORKER ACTIVITIES	13
D-5 FACILIT	AND POPULATION DATA AND INFORMATION	13
D-6 DERMA	Exposure Parameters	14
D-7 Occup	ITIONAL INHALATION EXPOSURE LITERATURE DATA	14
Appendix E	CONSUMER EXPOSURE ASSESSMENT	. 15
E-1 ESTIMA	TION OF EMISSION PROFILES FOR PAINT REMOVERS/STRIPPERS	
	/ITY ANALYSIS FOR INHALATION SCENARIOS	
	tion Exposure Scenario Inputs	
E-3 INHALA	tion Model Outputs and Exposure Calculations	
	I INHALATION MODELING CASE SUMMARIES.	
E-4 INHALA		
E-4 INHALA	NMP Scenario 1. Coffee Table, Brush-On, Workshop, User in ROH during wait time, 0.45 ACH	
E-4 INHALA E-5 MCCEI E-5-1	NMP Scenario 1. Coffee Table, Brush-On, Workshop, User in ROH during wait time, 0.45 ACH Weight Fraction.	18
E-4 INHALA E-5 MCCEI	NMP Scenario 1. Coffee Table, Brush-On, Workshop, User in ROH during wait time, 0.45 ACH Weight Fraction. NMP Scenario 2. Coffee Table, Brush-On, Workshop, User in Workshop during wait time, 0.4	18 5
E-4 INHALA E-5 MCCEI E-5-1	NMP Scenario 1. Coffee Table, Brush-On, Workshop, User in ROH during wait time, 0.45 ACH Weight Fraction.	18 5 18 eight

PK, and **PODs**

New technologies and approaches will also have to cover these basic components



It All Starts With Chemistry...

CompTox Dashi	board Ho X 2 CompTox Dashboard Bin X	
- → C fi	https://comptox.epa.gov/dashboard	Q ☆ Ξ
	NAN Means Advanced Search	
	CompTox Dashboard	
	Bearch a chemical by systematic name, synonym, CAS number, or InChIKey	
	pearch a chemical by systematic name, synonym, CAS number, or InChilkey Q	
	U Single companient search (2) (priore isotopes	
	Bingle component search II Ignore instepes See shat people are saying, read the disaboard commental	
	U Single companent search () (price i lottigen See what people are saying, read the dashboard commental Need more? Use advanced search.	

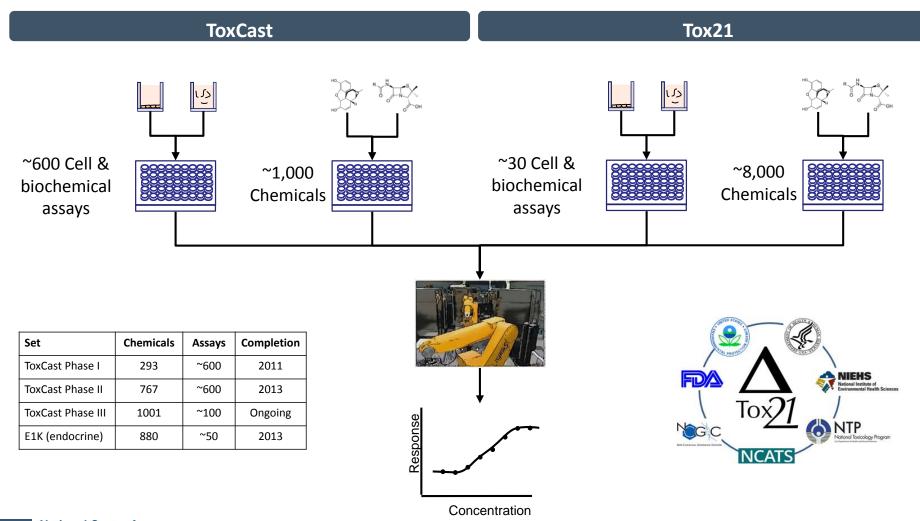
fi 🙆 https://co	omptox.epa.gov/d	ashboard/dsstoxdb/results?	utf8=∨ &search=	Bisphenol+A		C
	ever (Biteria)				dearch Compile	e Destroyers
					Dyant Danmert	Diet 1
Bisphenol A 80-05-7 DTXSID702	20182 o					
0 CANTER BY APPRIATE SAF	me Found 1 resulter Bisphanol					
a 11 6 4. c.	_	Intrac Popelae				
H _I C OH		Motecular Permula: C15+1802			Quantization (C)	
I X		Average Mass: 228 291 gmpl				
MF	>	Monoisolispie Maxa: 228.115030 g.moi			(*)	
12 C	2	Divident Medities				
HO	CH					
		Record information				
Cremita Projettes - Economic Burriery	eline Dinnine Rebuild	name Telacition Des Konne A	oction Connerts Partition Coefficient (LogP)			
Survey Octoorded Partition	elunes Epinopine Reductio	nyastar Telari Pila Das Esseur Pi Ostansi malar Jarenga	Partition Coefficient (LogP) Median	Ranga		
Durring) Celebrative Partition Confident (Lagr)	Experiment	nyumitar TarGari In tito Data Kasakur P. Ootanas wastar Adrenga at 2,53 (2)	Partition Coefficient (LogP) Median 3.43	3.43		
Dummay Outbook Wald Partition Conflicted LogP1 Inste Society	Experiment Predicted	novellar technicision per teorem P Octanoi evan Avrituja H (254 C) 242 (2)	Partition Coefficient (LogP) Median			
Durring) Celebrative Partition Confident (Lagr)	Experiment	novellar technicision per teorem P Octanoi evan Avrituja H (254 C) 242 (2)	Partition Coefficient (LogP) Median 3.43	3.43		
Surray Octowellate Partition Coditional LugP1 Institutions Listing Part	Experiment Predicted	number Tackarin Visio pra Konton P. Octoboli mater Arengo H 303 (2) 3 42 (2)	Partition Coefficient (LogP) Median 3.43	3.43		
Durmay Ostensitiytei Partition Gorticent Lup? Intern Society Interng Parts Borrig Parts	Experiment Predicted	number Tackarin Visio pra Konton P. Octoboli mater Arengo H 303 (2) 3 42 (2)	Partition Coefficient (LogP) Median 3.43 3.42	3.43		
Burriney Colonalistic Partition Calification Partie Parties Barring Part Nation Parties Dis Association Calification California Parties	Experiment Predicted Described (st. 2017) - Ex	nyashir Tablatin kita bisi Kawawa A Ootaana kaba A 333 (2) 3 42 (2) 4 107	Partition Coefficient (LogP) Median 3.43 3.42	3.43		
Burnings Ordensaturer Partition Cartinet Lupy: Harting Parts Barting Parts Vacor Partson Dat Analossien Conflictent Cartinoum	Expansion Production Dependent as: 50/ 8x Source	numenta Tandardi Hana Kanana A Ordanasa matar Arenga H 3141 3442 (2) 4 107 7 4 107	Partition Coefficient (LogP) Median 3.43 3.42	3.43		
Burriney Colonalistic Partition Calification Partie Parties Barring Part Nation Parties Dis Association Calification California Parties	Experiment Predicte Downled st: Cov Ex Source PsychologyCCT	Annual States States Annual Annua	Partition Coefficient (LogP) Median 3.43 3.42	3.43		
Surring) Colonarity Partition Colonarity Partition Colonarity Nationg Parties Surring Parties Colonarity Parties Colonarity Parties Colonarity Parties Colonarity Parties Colonarity Parties	Experiment Predicte Downled st: Cov Ex Source PsychologyCCT	Annual States States Annual Annua	Partton Coarticent (LogP) Modeo 3.43 3.42 Copertmental	2.43 3.20 0.344		

https://comptox.epa.gov/dashboard

- Chemical structure database of >700,000 unique substances with QC flags to link chemical structure with names and identifiers
- Consensus QSAR models for a range of physical chemical properties, environmental fate, and hazard characteristics
- Comprehensive physical-chemical property database (experimental and predicted)

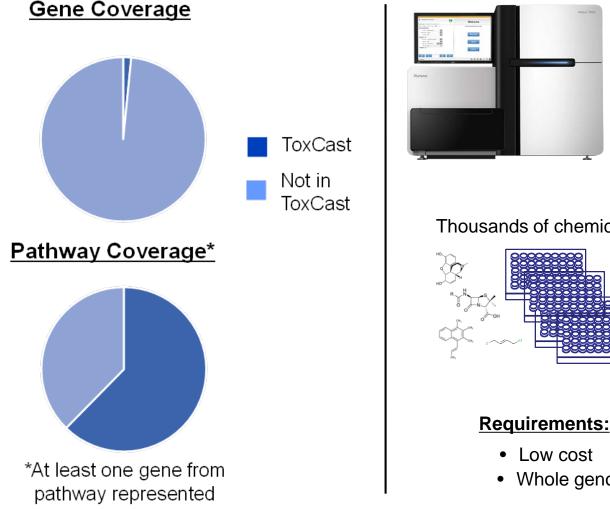


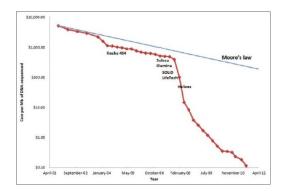
Adding the High-Throughput Hazard Screening Component



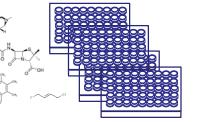


Beginning to Address Concerns for Increased Biological Coverage





Thousands of chemicals

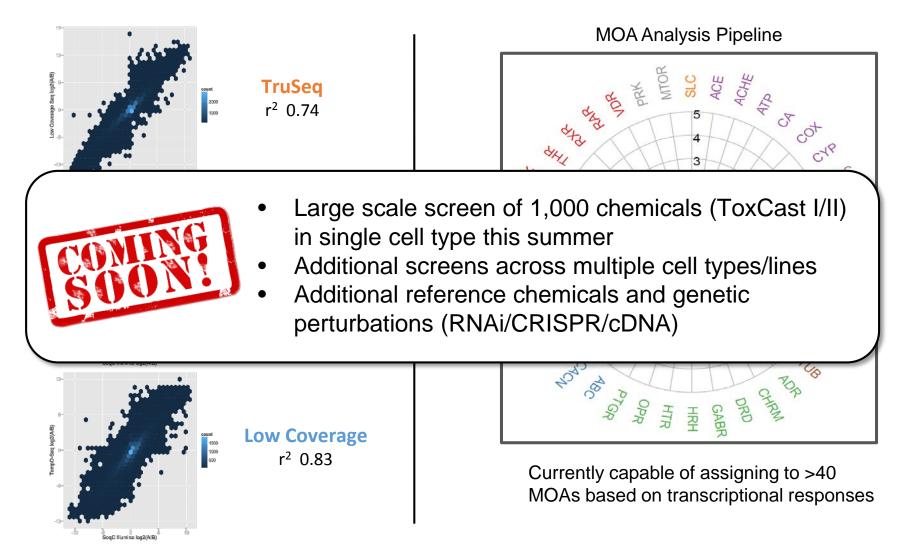


Multiple Cell Types

- Whole genome
- 384 well
- Automatable

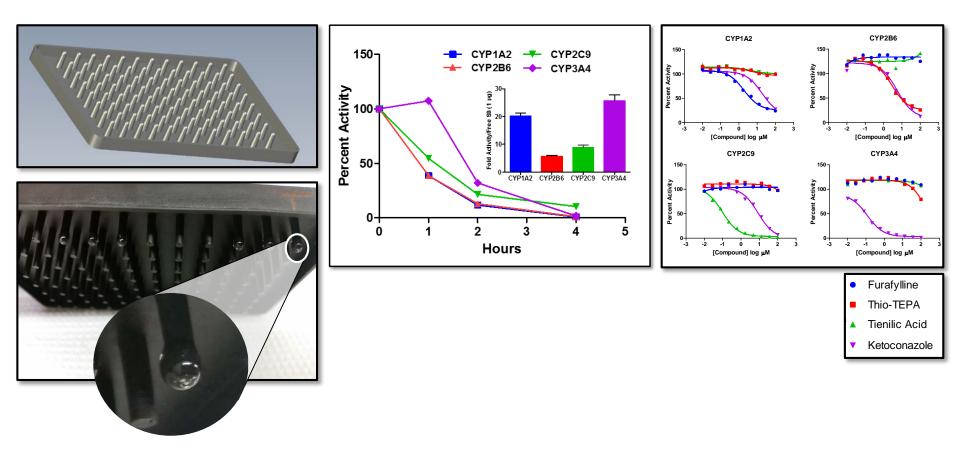


Comparing Sequencing Platforms and Developing Analysis Approach



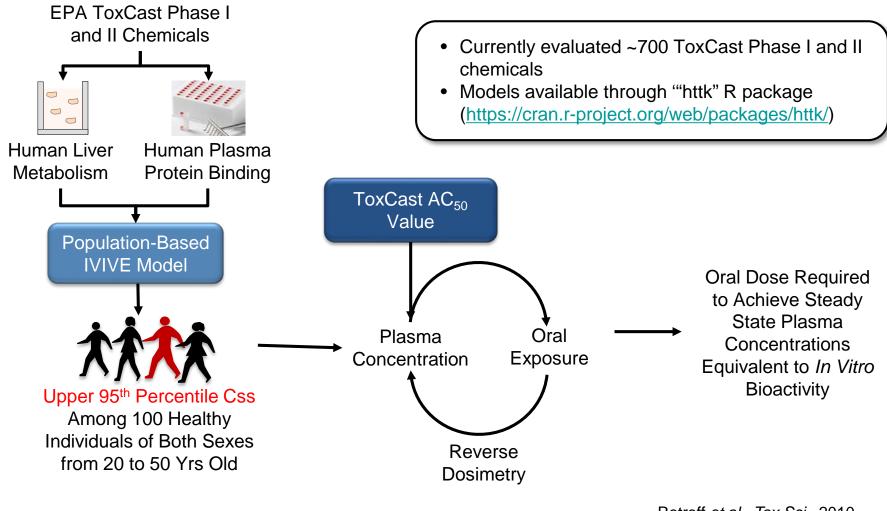


Beginning to Address Metabolic Competence





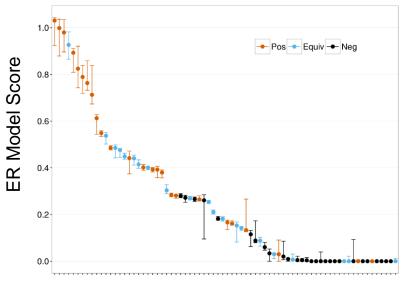
Adding the High-Throughput Toxicokinetic Component





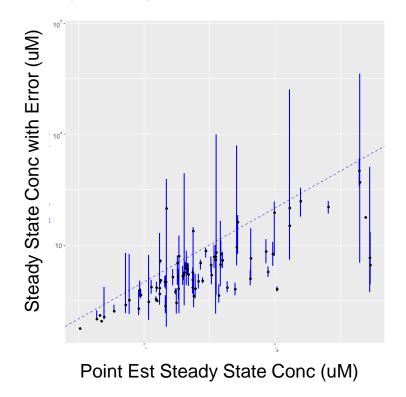
Adding in Chemical-Specific Uncertainty

Propagation of Experimental Uncertainty in Models of ER Potency



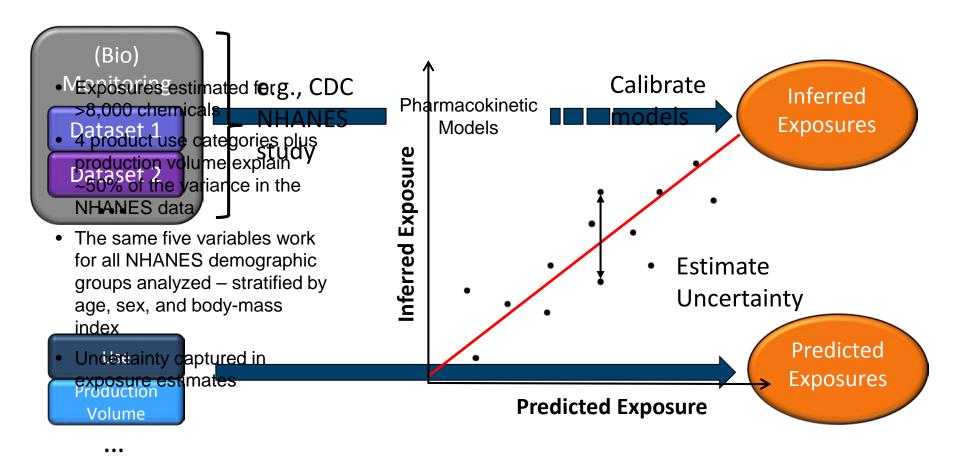
Chemical Rank

Propagation of Experimental Uncertainty in High-Throughput Toxicokinetic Estimates



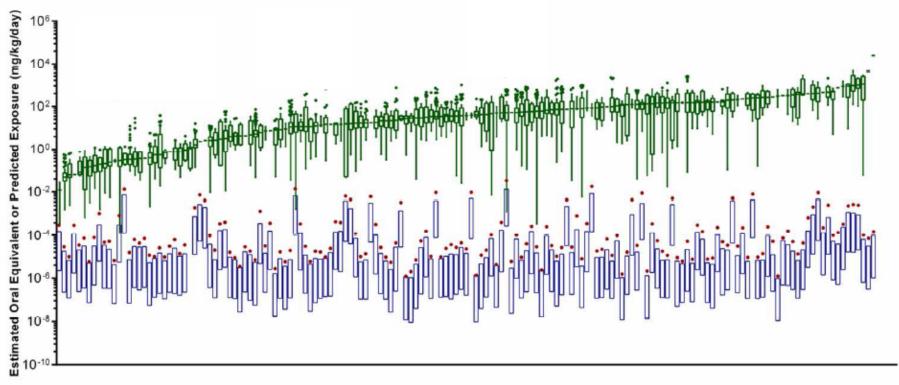


Adding the High-Throughput Exposure Component





Comparing Bioactivity with Exposure Predictions for Risk Context

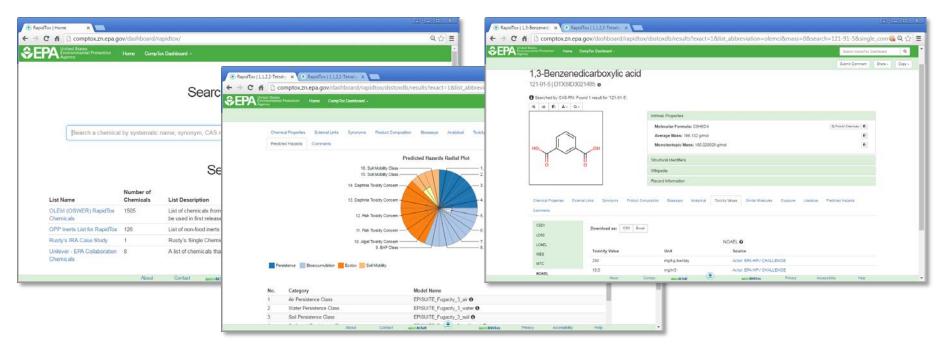


Chemicals

Wetmore et al., Tox Sci., 2015



RapidTox Dashboard as a Focal Point for Integrating Components



- 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



Thank You for Your Attention!

Tox21 Colleagues: NTP Crew FDA Collaborators NCATS Collaborators

EPA Colleagues: NERL NHEERL NCEA

