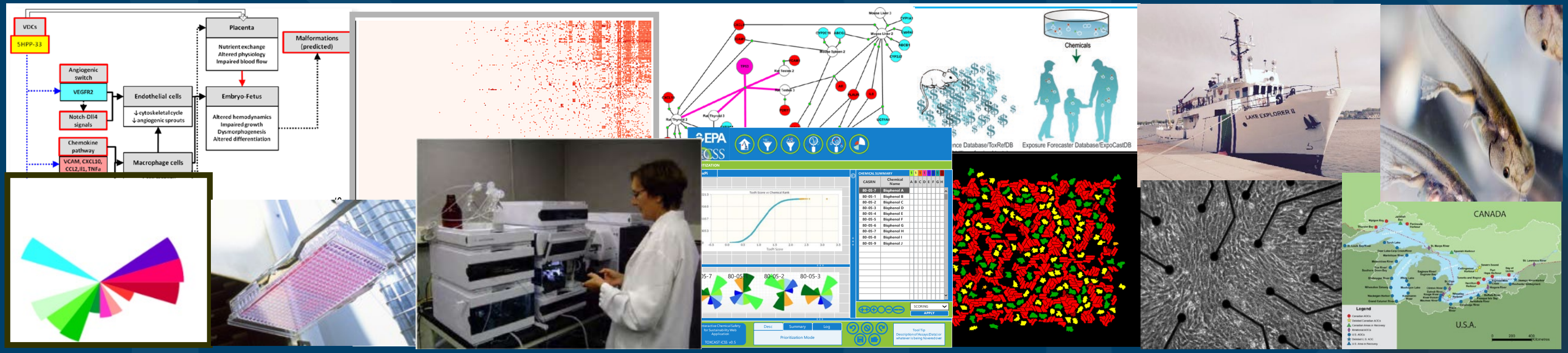
Seeing the Future of Chemical Safety with 2020 Vision



Health Canada/University of Ottawa Webinar

December 10, 2020

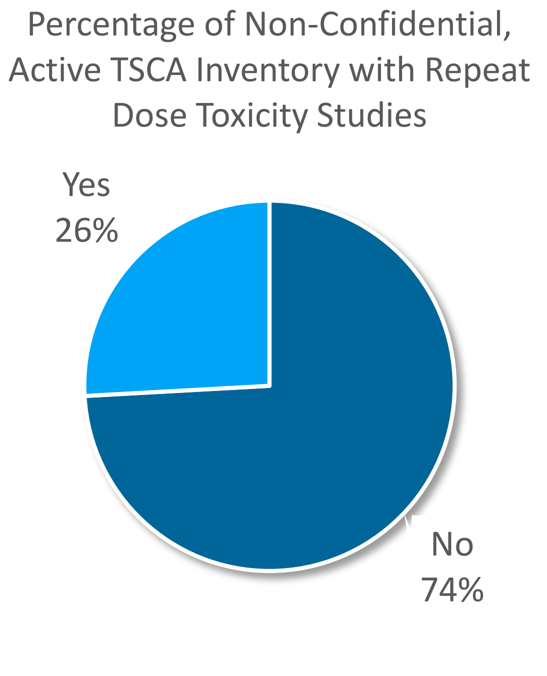
Rusty Thomas
Director
Center for Computational Toxicology and Exposure

United States Environmental Protection Agency

The Primary Issues Surrounding Chemical Safety Have Not Changed

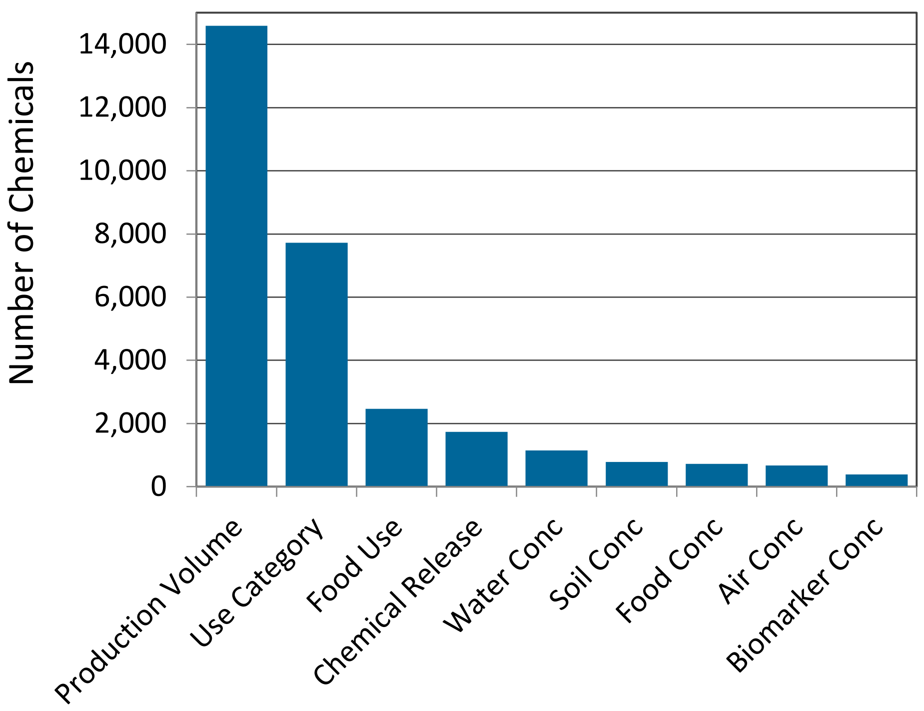
There is a Lack of Data on Hazard, Toxicokinetics, and Exposure for Most Chemicals

Hazard



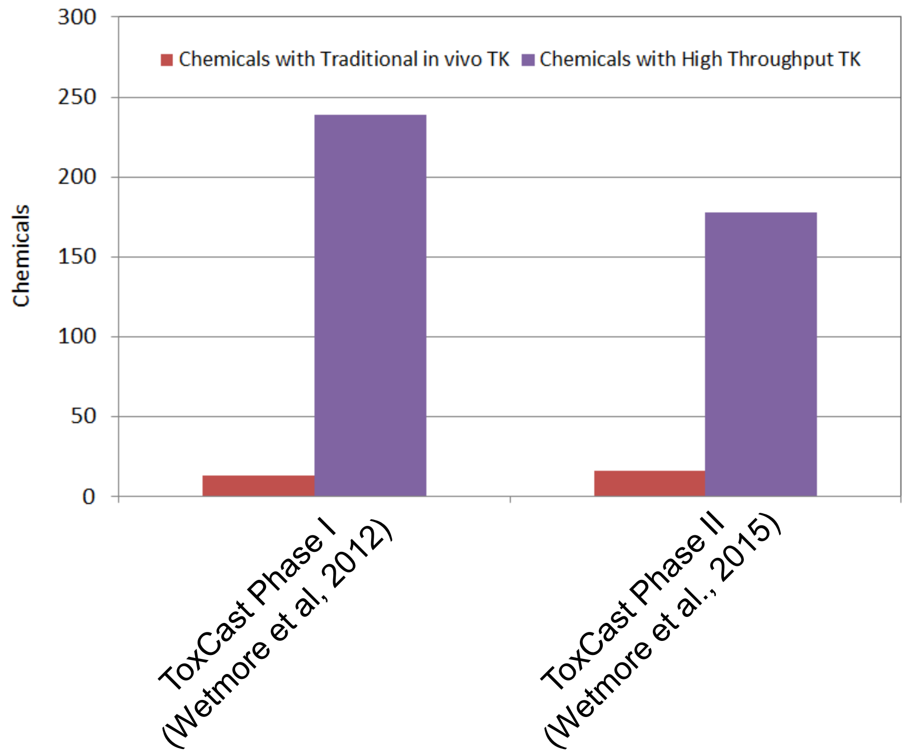
Data from ToxValDB (Dec 2019)

Exposure

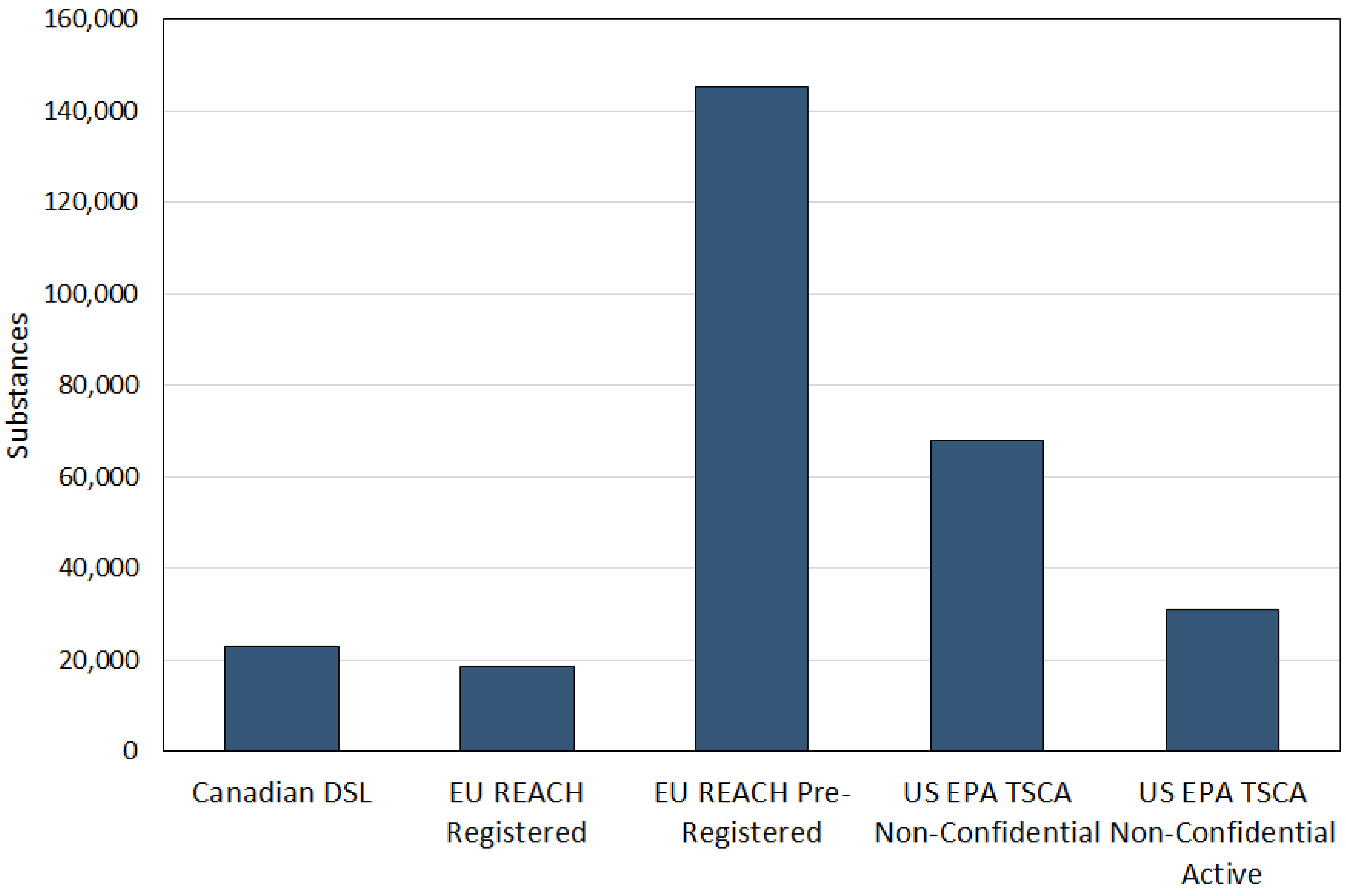


Egeghy et al., Science of the Total Environment, 2012

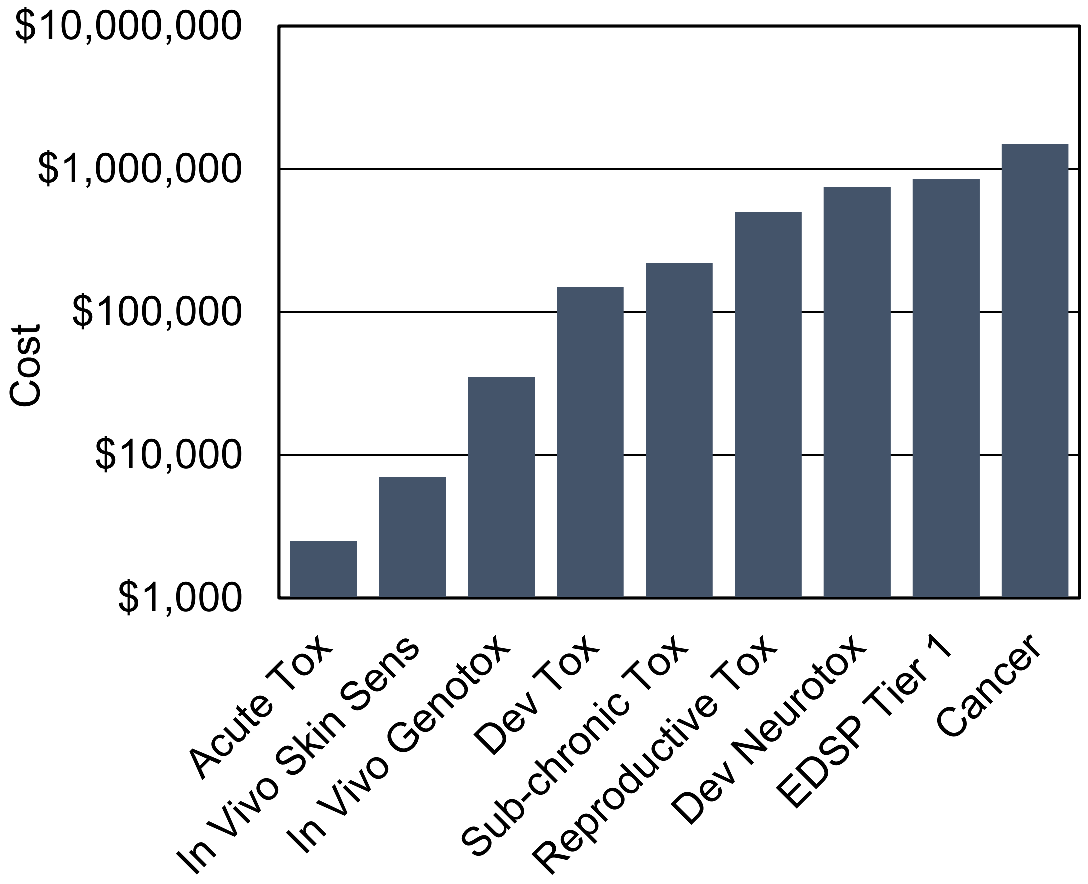
Toxicokinetics

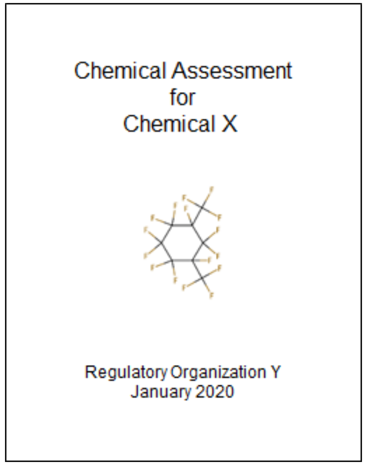


There are Large Numbers of Chemicals on Various National Inventories



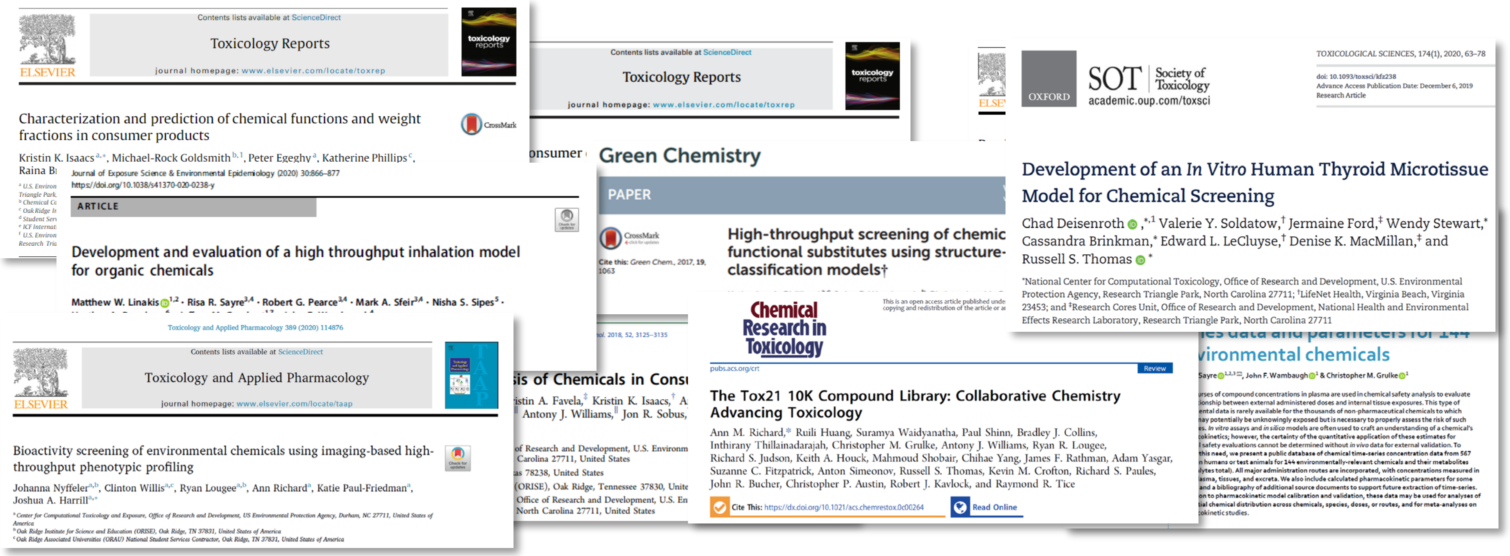
The Costs and Time Associated with Traditional Testing and Assessment are Extensive





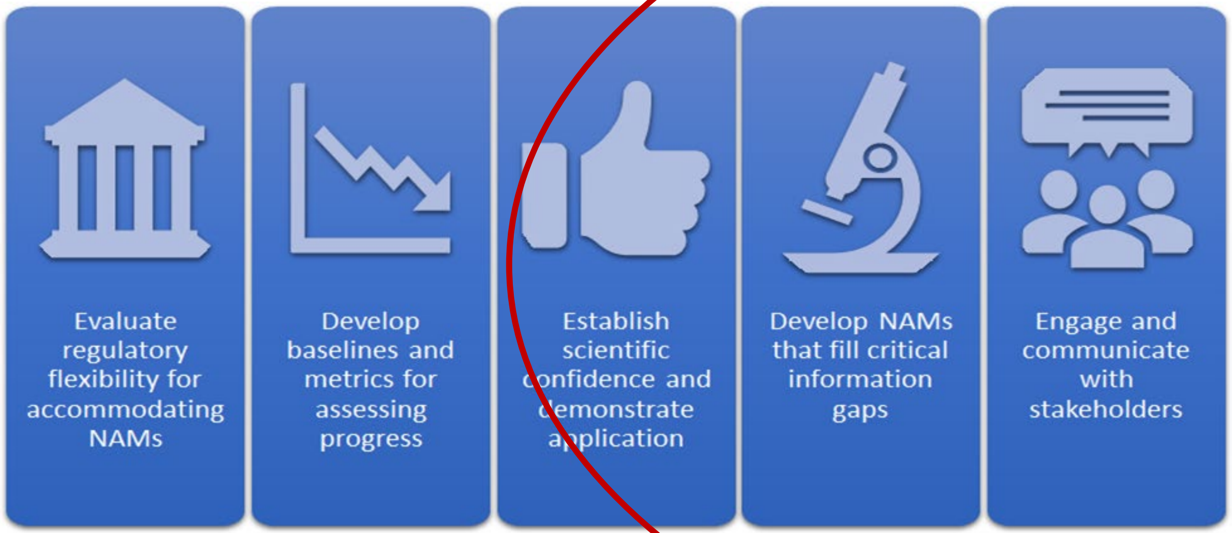
- Time from chemical selection to completion of subchronic and chronic tox studies requires 2+ years
- Time to perform a typical chemical assessment is 4+ years (Krewski et al., 2020)

Solving these Issues in Chemical Safety Requires a Clear Vision of Both the Forest and the Trees…

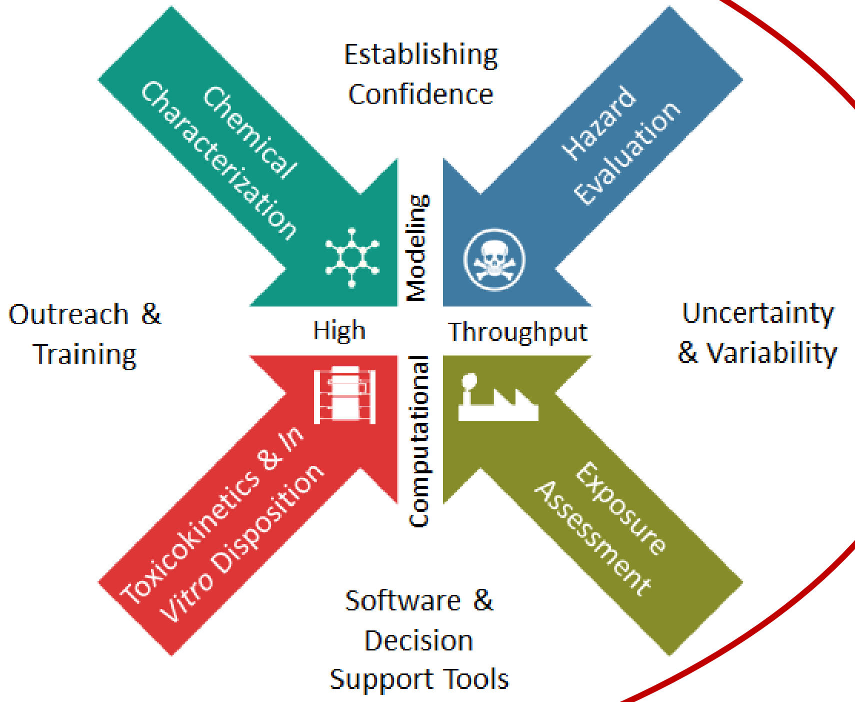


There is a Significant Overlap Between Elements of the EPA Big Picture Visions for Chemical Safety

EPA NAMs Work Plan



EPA CompTox Blueprint



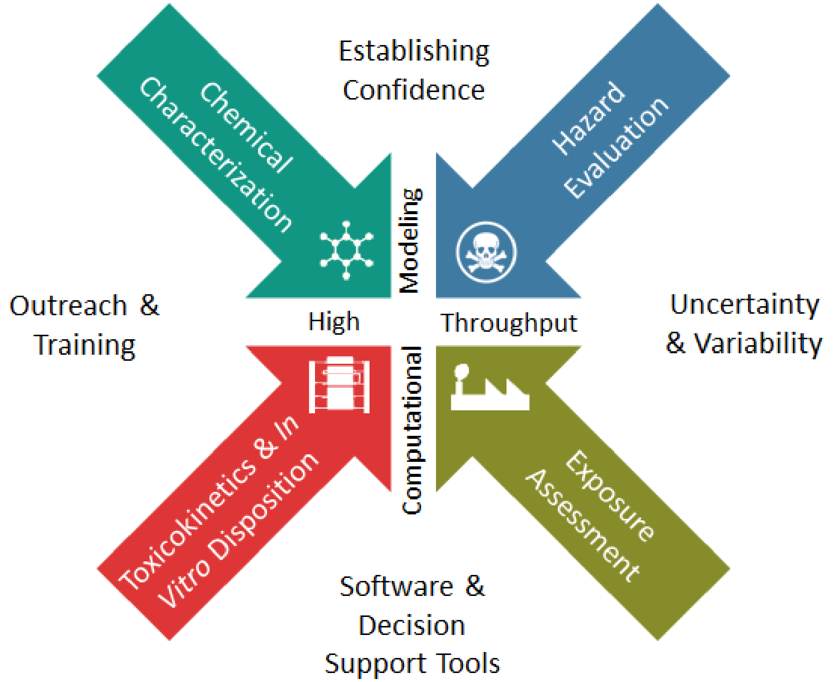
Mapping the Trees to the Forest Highlights a Complex, Multi-Disciplinary Research Program

- DSSTox
- Chemical library
- Read across
- SAR/QSAR modeling
- Chemotypes
- TTC

- OECD/ APCRA Case Studies
- NAM Work Plan
- Reference Materials
- Reporting Templates

- Eco/HH HTS (HTTr, HTPP, ToxCast)
- Tiered testing
- Organotypic models
- Addressing limitations (metabolism, chemical space)
- Statistical and Biologically-based Modeling
- AOPs

- Communities of Practice
- ToxCast Owners Manual
- Training courses/ videos



- SEEM
- ToxBoot
- HTTK
- ToxRefDB

- HTTK assays (metabolism, bioavailability, binding)
- Partition coefficients
- HTTK R package
- Multi-route models
- Model verification (e.g., CvT)
- In vitro disposition

- CompTox Chemicals Dashboard
- RapidTox
- Factotum
- ECOTOX
- SeqAPASS
- CEA and VOI Frameworks

- ExpoCast
- NTA/SSA
- ENTACT
- Product emissivity

With Multiple Areas of Active Collaboration with HC and ECCC (🇨🇦)

- OECD/ APCRA Case Studies
- NAM Work Plan
- Reference Materials
- Reporting Templates

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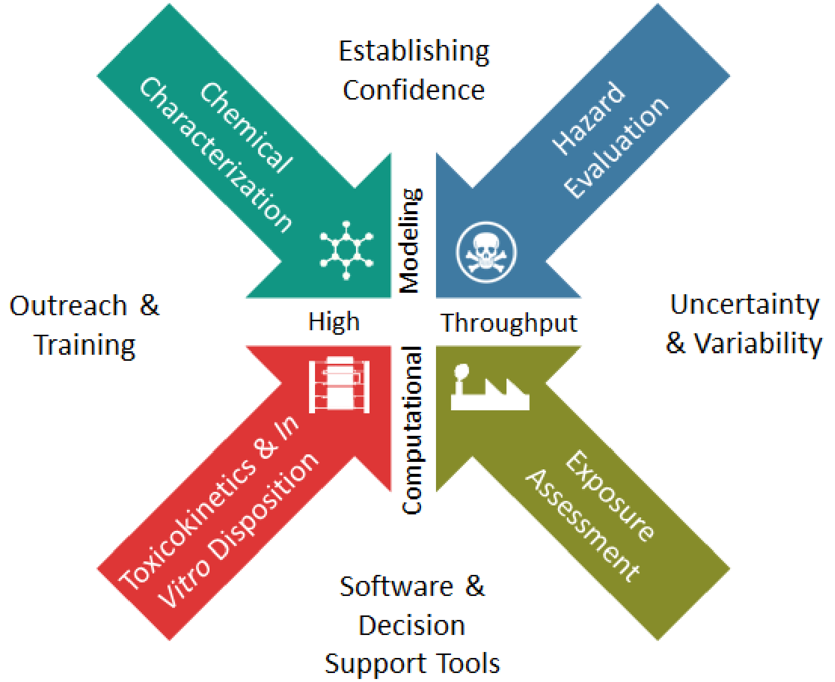

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United States Environmental Protection Agency

Today, I'm Going to Highlight a Few Areas of Progress and Show How They May Fit Together…

- DSSTox
- Chemical library
- Read across
- SAR/QSAR modeling
- Chemotypes
- TTC

- OECD/ APCRA Case Studies
- NAM Work Plan
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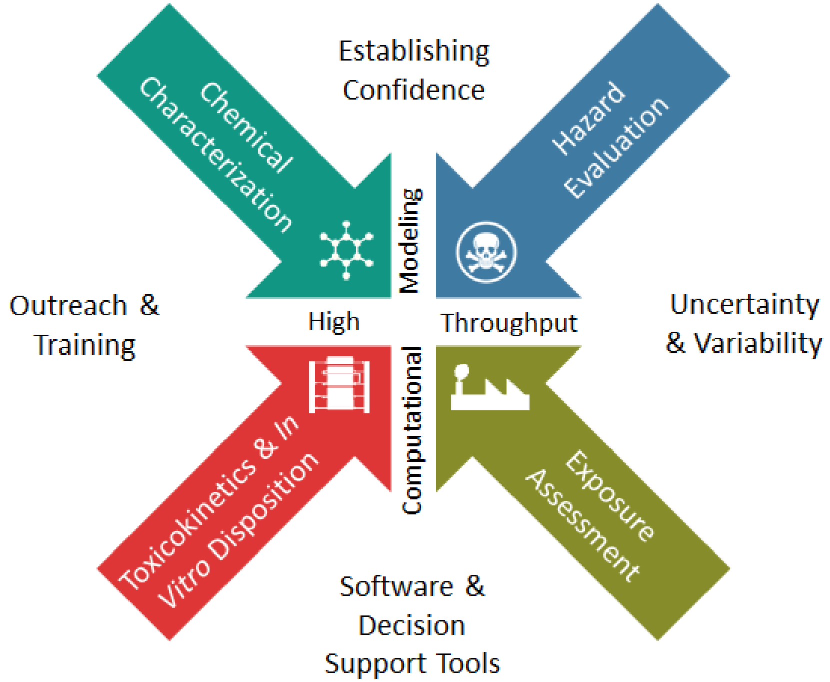

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United States Environmental Protection Agency

A Tiered Testing Approach is an Important Component in the Blueprint

TOXICOLOGICAL SCIENCES, 169(2), 2019, 317–332

doi: 10.1093/toxsci/kfz058
Advance Access Publication Date: March 5, 2019
Forum

OXFORD SOT Society of Toxicology
www.toxsci.oxfordjournals.org

FORUM

The Next Generation Blueprint of Computational Toxicology at the U.S. Environmental Protection Agency

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Disclaimer: The U.S. Environmental Protection Agency has provided administrative review and has approved this article for publication. The views expressed in this article are those of the authors and do not necessarily reflect the views of the U.S. Environmental Protection Agency.

ABSTRACT

The U.S. Environmental Protection Agency (EPA) is faced with the challenge of efficiently and credibly evaluating chemical safety often with limited or no available toxicity data. The expanding number of chemicals found in commerce and the environment, coupled with time and resource requirements for traditional toxicity testing and exposure characterization,

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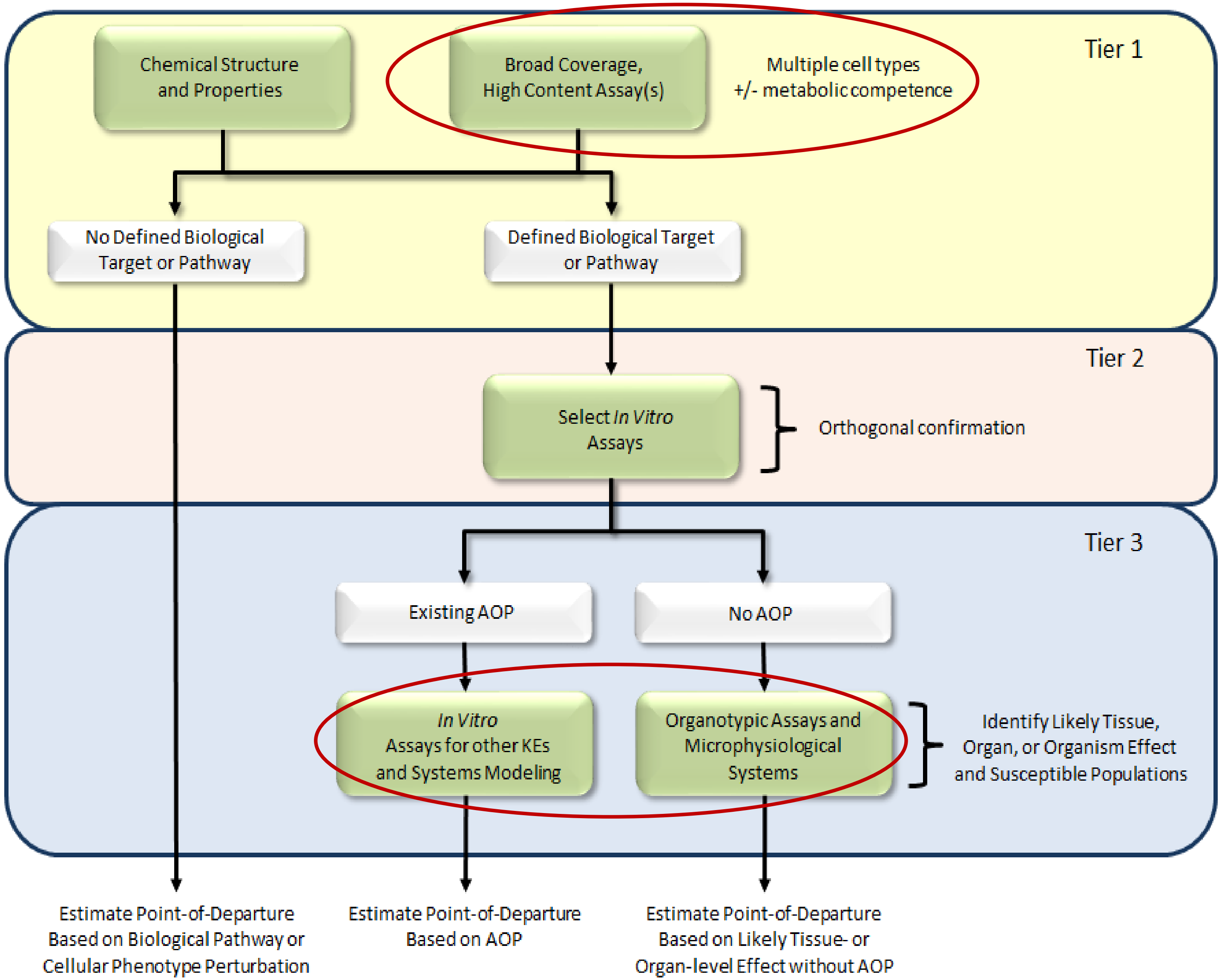
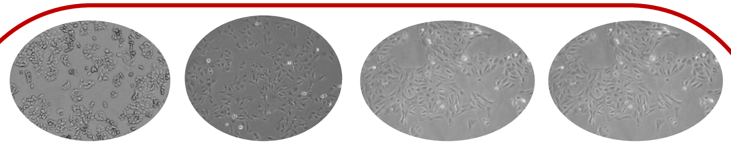
317



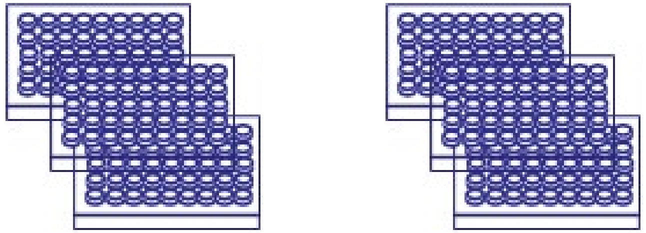
Center for Computational Toxicology & Exposure

High-Content Screening Being Perform Across Diverse Cell Types, Chemistry, and Taxa

Human Health Focus



MCF7 U2O2 HepaRG Cell Type X



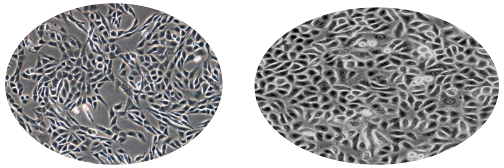
>1000 chemicals
Conc response
6, 24 hr exposure

~300 reference chemicals
Conc response
6, 24 hr exposure

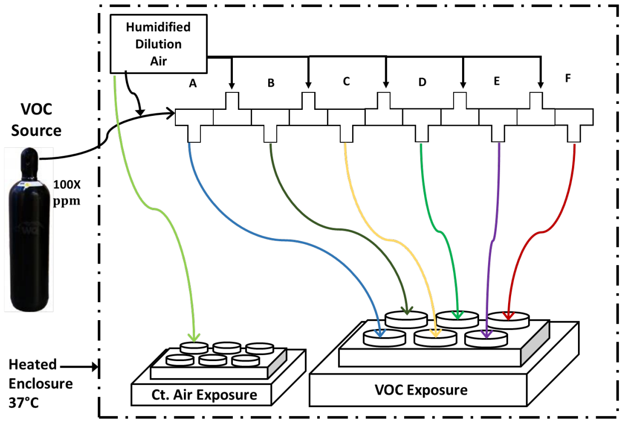
Phenotypic Profiling

TempOSeq

Human Health with Volatiles



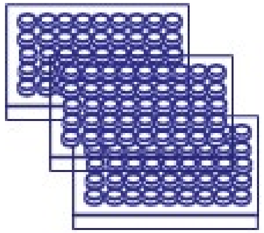
BEAS2B HBEpC



TempOSeq

Ecological Focus

Daphnia magna
Pimephales promelas
Chironomus dilutus
Raphidocelis subcapitata

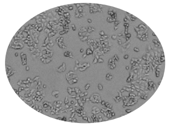


~100 chemicals
Conc response
24 hr exposure

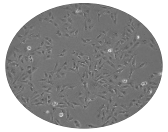
RNAseq

Phenotypic Responses

Using High-Throughput Transcriptomics to Screen Multiple Human Cell Types

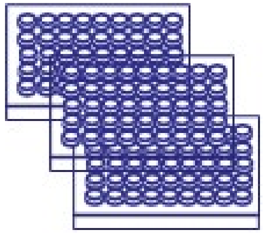


MCF7



U2O2

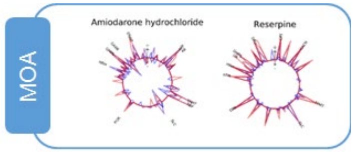
HepaRG



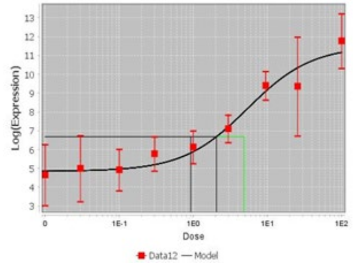
>1000 chemicals
Conc response
6, 24 hr exposure

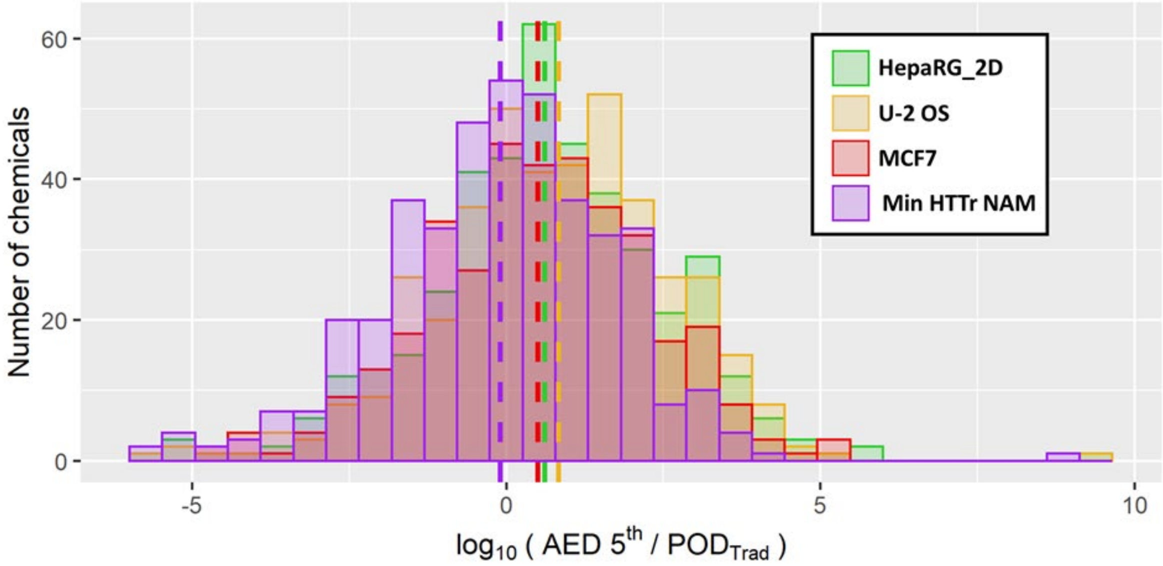
TempOSeq

Mode-of-Action Identification

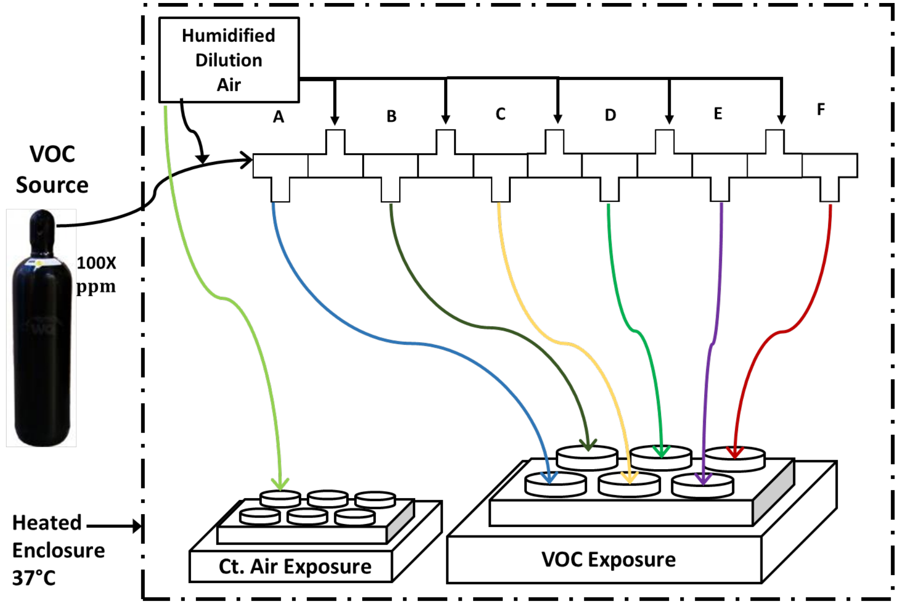


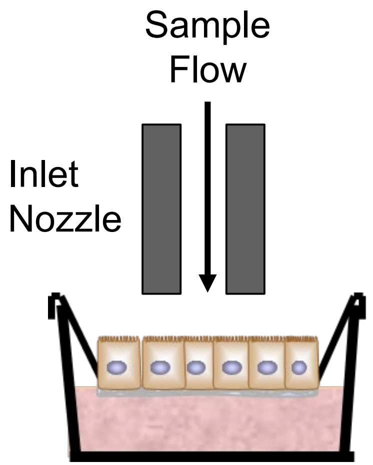
Concentration Response Modeling



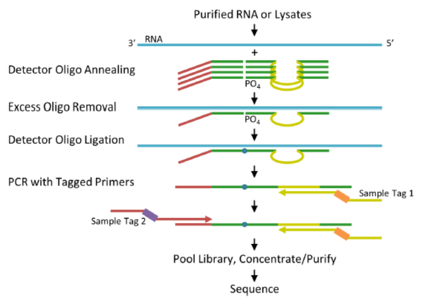


Using High-Throughput Transcriptomics to Screen Volatile Chemicals





Whole Genome Transcriptomics (HTTr)



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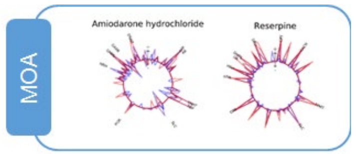
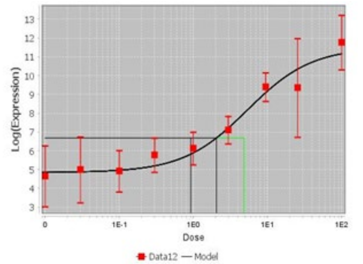


Concentration Response Modeling



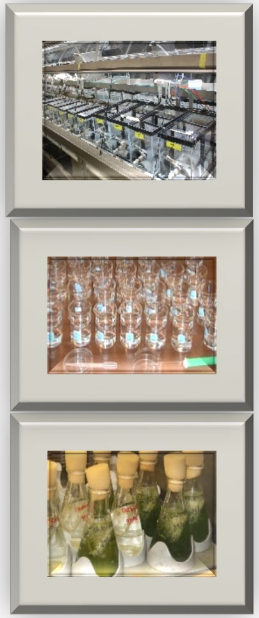
	ACGIH TLV-TWA (ppm)	BEAS-2B HTTr POD (ppm)	HBEC HTTr POD (ppm)
Acrolein	0.1	0.58	--
Formaldehyde	0.3	NA	--
1,3-Butadiene	10	13.98	--
Acetaldehyde	25	NA	--
1-Bromopropane	0.1 *	2.25	NA
Carbon Tetrachloride	10	9.56	NA
Trichloroethylene	50	44.8	28.1
Dichloromethane	100	142.13	266.7

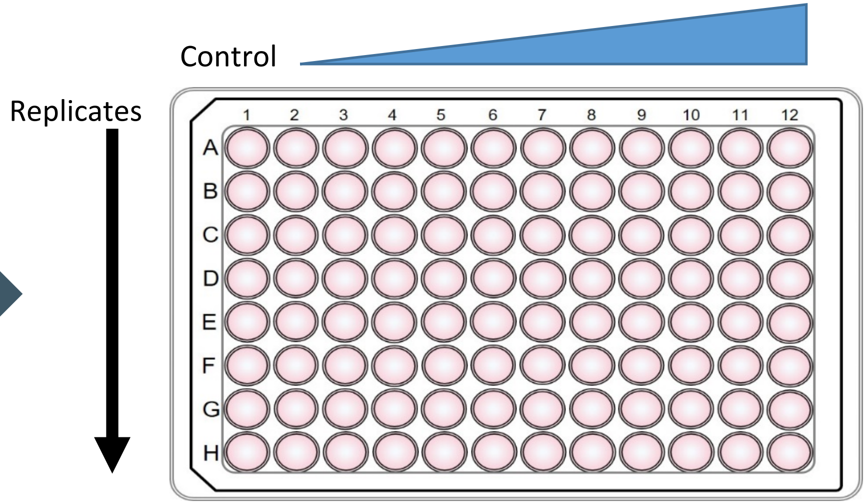
* The ACGIH TLV TWA for 1-bromopropane was updated to 0.1 ppm in 2012. Prior to that the TLV-TWA for 1-bromopropane was 10 ppm.

A.Speen (CPHEA), M. Higuchi (CPHEA), and J. Harrill, Unpublished

EPA United States Environmental Protection Agency

Using High-Throughput Transcriptomics Evaluate Responses Across Taxa

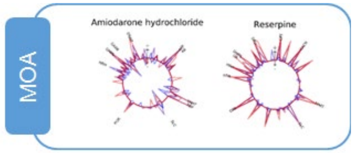




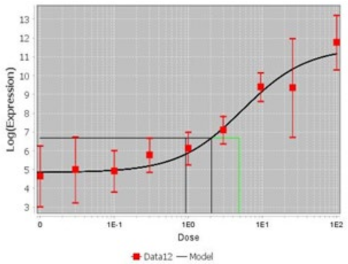
Whole Genome Transcriptomics (HTTr)

Phenotypic Responses

Mode-of-Action Identification



Concentration Response Modeling



Preliminary Results from Initial Subset of Chemicals

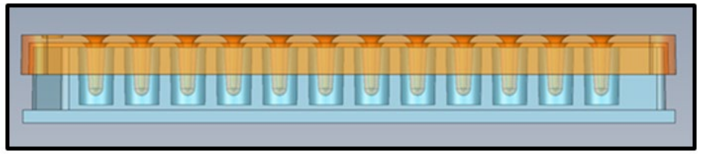
Chemical	Transcriptomic POD	Mortality-based POD
CuSO4	0.03 mg/L	0.2 mg/L
ZnSO4	0.00023 mg/L	3.2 mg/L
NiSO4	0.33 mg/L	3.9 mg/L
Imidacloprid	8.8 mg/L	> 10 mg/L
Flupyradifurone	1.3 mg/L	> 10 mg/L
Clothianidin	8.1 mg/L	> 10 mg/L
Thiacloprid	57.2 mg/L	85 mg/L
Sertraline	0.6 mg/L	0.9 mg/L
Fluoxetine	0.02 mg/L	0.8 mg/L
Paroxetine	1.0 mg/L	1.1 mg/L

K. Flynn, A. Biales, D. Bencic, R. Flick, J. Martinson, D. Villeneuve, K. Jensen, J. Cavallin, R. Hockett, T. Norberg-King, M. Le, K. Santana-Rodriguez, and K. Bush, Unpublished

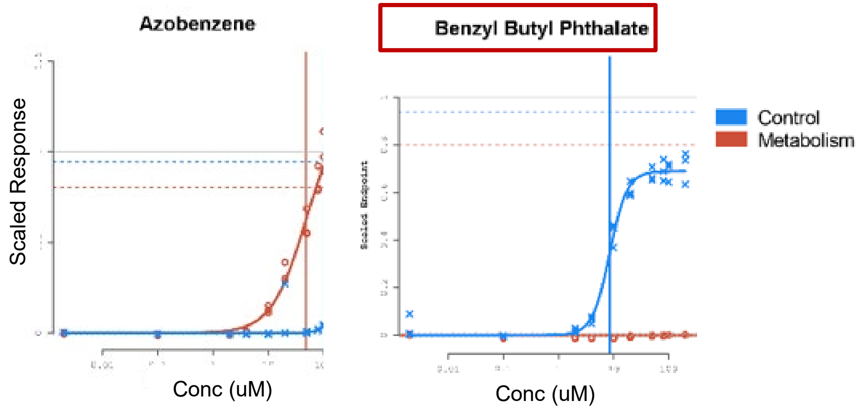
Incorporating Xenobiotic Metabolism Into *In Vitro* Assays

United States Environmental Protection Agency

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

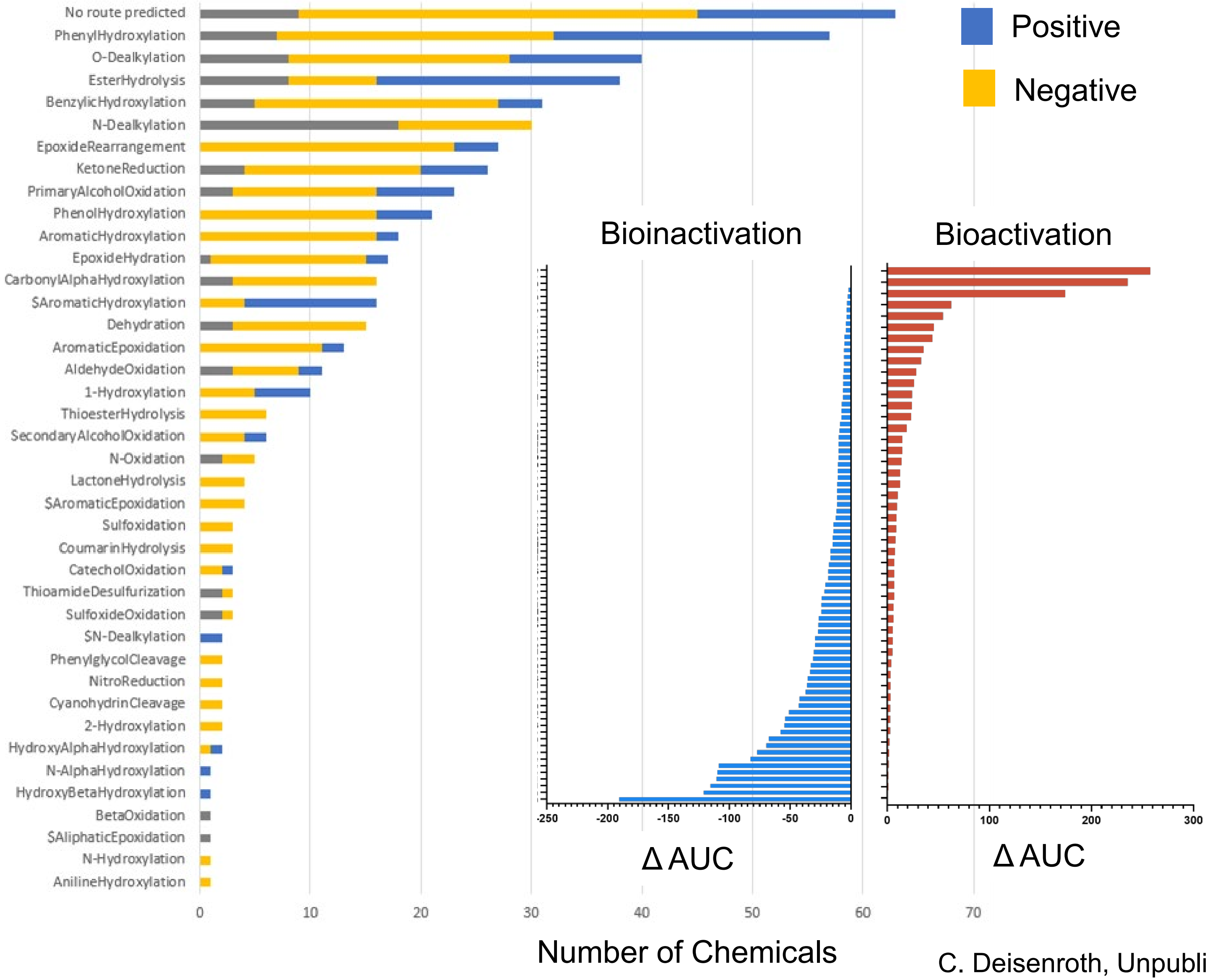


Application to ER Transactivation Assay (ERTA)
Pilot Screening Results of Pinto et al., 2016 Library



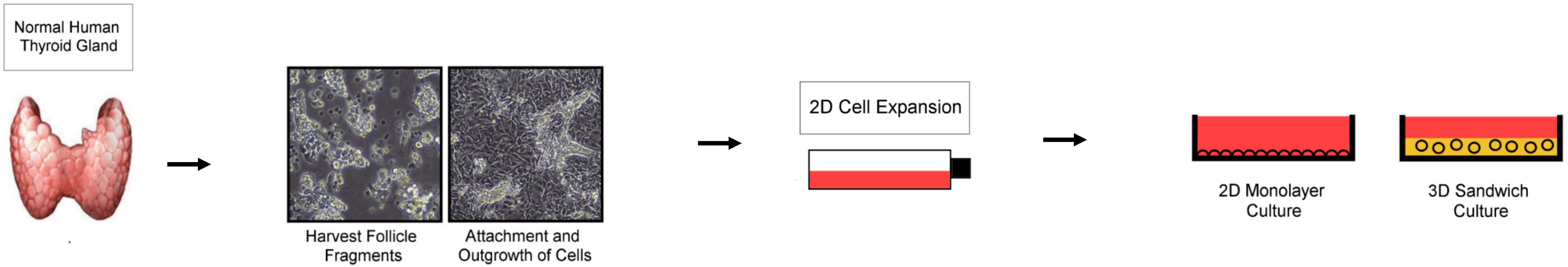
Deisenroth et al., Tox Sci, 2020

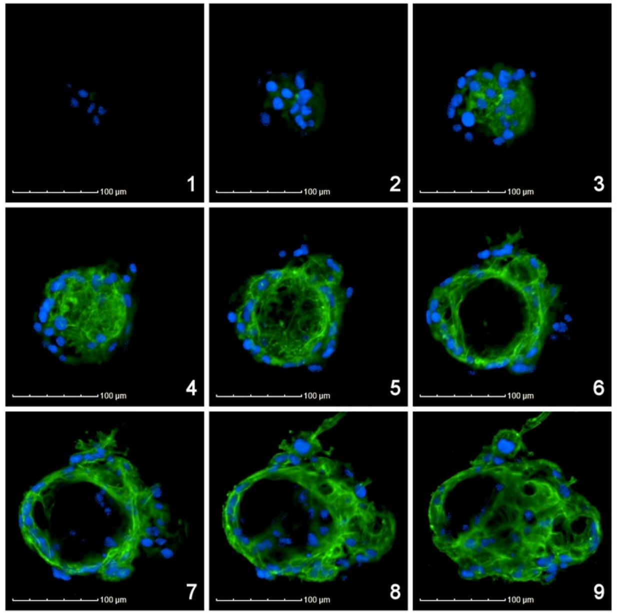
Preliminary Analysis of 768 ToxCast Chemical Screen



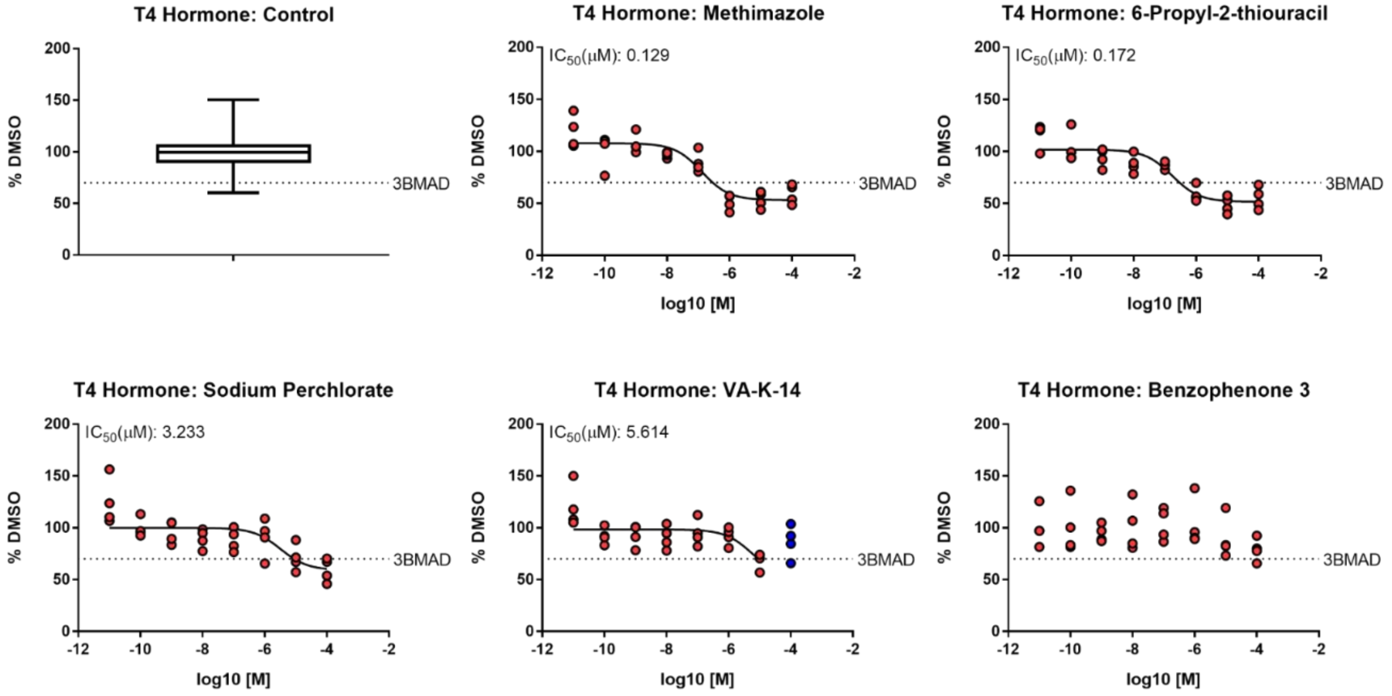
C. Deisenroth, Unpublished

Developing Organotypic Culture Models to Identify Tissue/Organ Effects



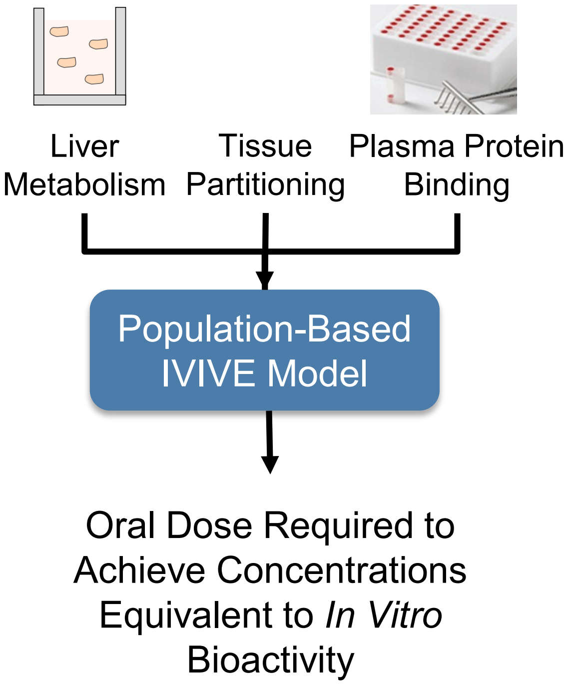


Blue, Hoechst 33342 /DNA
Green, Phalloidin/Actin

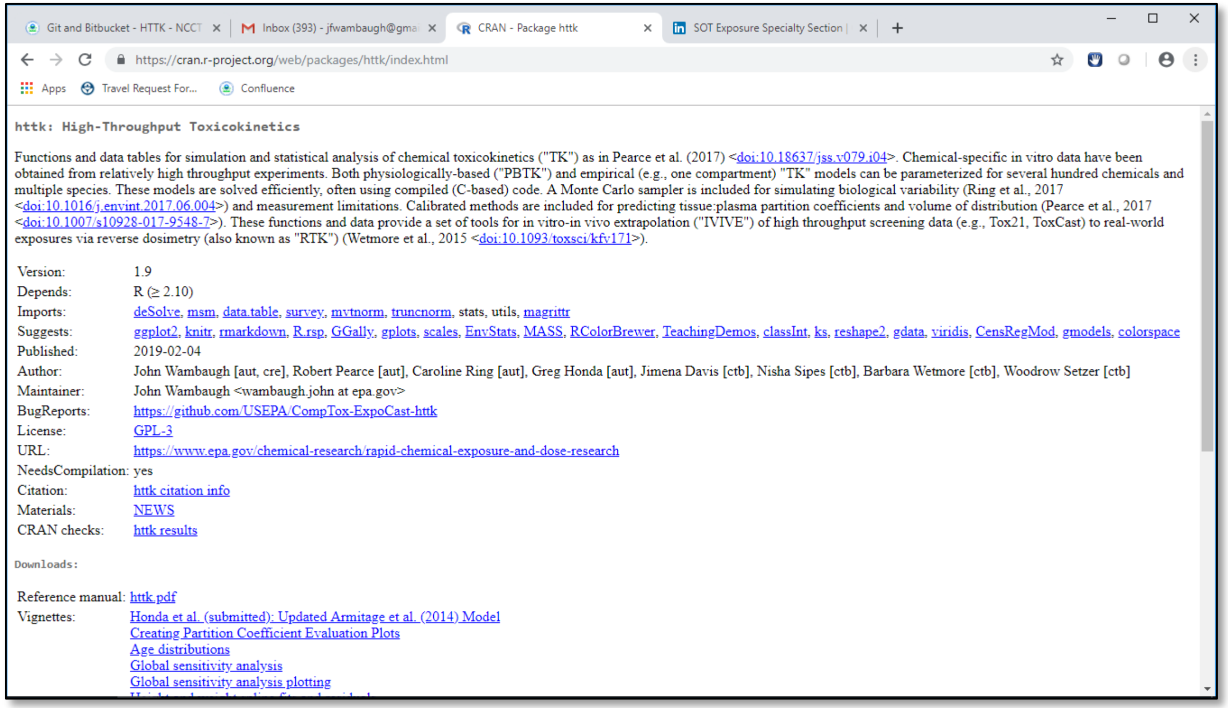


Deisenroth *et al.*, *Toxicol Sci*, 2020

Expanding Toxicokinetic Data Availability Using High-Throughput *In Vitro* Data and Modeling



Rotroff *et al.*, *Tox Sci.*, 2010
Wetmore *et al.*, *Tox Sci.*, 2012
Wetmore *et al.*, *Tox Sci.*, 2015
Wambaugh *et al.*, *J Stat Softw.*, 2017
Wambaugh et al., *Tox Sci.*, 2018
Wambaugh et al., *Tox Sci.*, 2019



Git and Bitbucket - HTTK - NCCT | Inbox (393) - jfwambaugh@gma | CRAN - Package httk | SOT Exposure Specialty Section |

https://cran.r-project.org/web/packages/httk/index.html

Apps | Travel Request For... | Confluence

httk: High-Throughput Toxicokinetics

Functions and data tables for simulation and statistical analysis of chemical toxicokinetics ("TK") as in Pearce et al. (2017) <doi:10.18637/jss.v079.i04>. Chemical-specific in vitro data have been obtained from relatively high throughput experiments. Both physiologically-based ("PBTK") and empirical (e.g., one compartment) "TK" models can be parameterized for several hundred chemicals and multiple species. These models are solved efficiently, often using compiled (C-based) code. A Monte Carlo sampler is included for simulating biological variability (Ring et al., 2017 <doi:10.1016/j.envint.2017.06.004>) and measurement limitations. Calibrated methods are included for predicting tissue:plasma partition coefficients and volume of distribution (Pearce et al., 2017 <doi:10.1007/s10928-017-9548-7>). These functions and data provide a set of tools for in vitro-in vivo extrapolation ("IVIVE") of high throughput screening data (e.g., Tox21, ToxCast) to real-world exposures via reverse dosimetry (also known as "RTK") (Wetmore et al., 2015 <doi:10.1093/toxsci/kfv171>).

Version:	1.9
Depends:	R (≥ 2.10)
Imports:	deSolve, msm, data.table, survey, mvtnorm, truncnorm, stats, utils, magrittr
Suggests:	ggplot2, knitr, rmarkdown, R.rsp, GGally, gplots, scales, EnvStats, MASS, RColorBrewer, TeachingDemos, classInt, ks, reshape2, gdata, viridis, CensRegMod, gmodels, colorspace
Published:	2019-02-04
Author:	John Wambaugh [aut, cre], Robert Pearce [aut], Caroline Ring [aut], Greg Honda [aut], Jimena Davis [ctb], Nisha Sipes [ctb], Barbara Wetmore [ctb], Woodrow Setzer [ctb]
Maintainer:	John Wambaugh <wambaugh.john at epa.gov>
BugReports:	https://github.com/USEPA/CompTox-ExpoCast-httk
License:	GPL-3
URL:	https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research
NeedsCompilation:	yes
Citation:	httk citation info
Materials:	NEWS
CRAN checks:	httk results

Downloads:

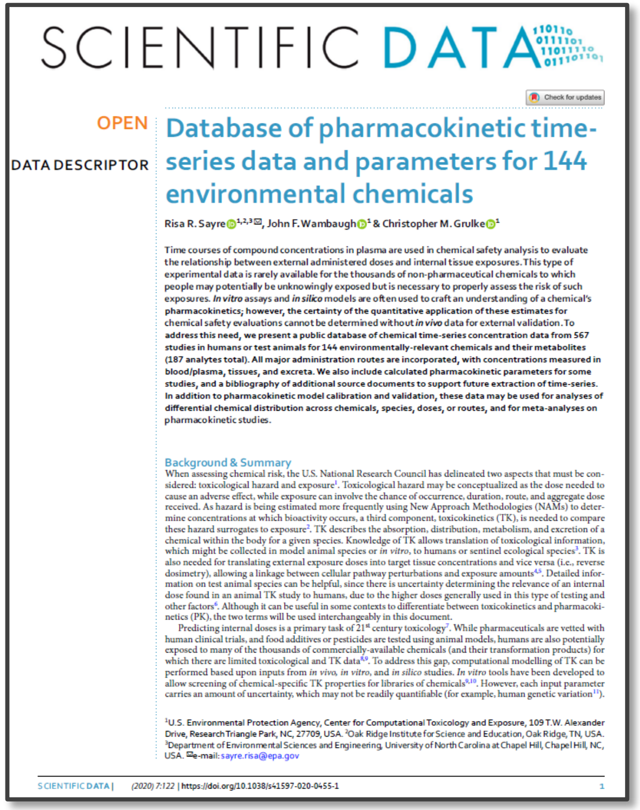
Reference manual:	httk.pdf
Vignettes:	Honda et al. (submitted): Updated Armitage et al. (2014) Model Creating Partition Coefficient Evaluation Plots Age distributions Global sensitivity analysis Global sensitivity analysis plotting

R package "httk"

- Open source, transparent, and peer-reviewed tools and data for **high throughput toxicokinetics (httk)**
- Allows *in vitro-in vivo* extrapolation (IVIVE) and physiologically-based toxicokinetics (PBTK)
- v1.10 features **942 total chemicals**
- Now allows propagation of uncertainty

United States Environmental Protection Agency

Extending High-Throughput Toxicokinetic Models to Inhalation Route



SCIENTIFIC DATA

Check for updates

OPEN

DATA DESCRIPTOR

Database of pharmacokinetic time-series data and parameters for 144 environmental chemicals

Risa R. Sayre[1,2,3], John F. Wambaugh[1] & Christopher M. Grulke[1]

Time courses of compound concentrations in plasma are used in chemical safety analysis to evaluate the relationship between external administered doses and internal tissue exposures. This type of experimental data is rarely available for the thousands of non-pharmaceutical chemicals to which people may potentially be unknowingly exposed but is necessary to properly assess the risk of such exposures. *In vitro* assays and *in silico* models are often used to craft an understanding of a chemical's pharmacokinetics; however, the certainty of the quantitative application of these estimates for chemical safety evaluations cannot be determined without *in vivo* data for external validation. To address this need, we present a public database of chemical time-series concentration data from 567 studies in humans or test animals for 144 environmentally-relevant chemicals and their metabolites (187 analytes total). All major administration routes are incorporated, with concentrations measured in blood/plasma, tissues, and excreta. We also include calculated pharmacokinetic parameters for some studies, and a bibliography of additional source documents to support future extraction of time-series. In addition to pharmacokinetic model calibration and validation, these data may be used for analyses of differential chemical distribution across chemicals, species, doses, or routes, and for meta-analyses on pharmacokinetic studies.

Background & Summary

When assessing chemical risk, the U.S. National Research Council has delineated two aspects that must be considered: toxicological hazard and exposure[1]. Toxicological hazard may be conceptualized as the dose needed to cause an adverse effect, while exposure can involve the chance of occurrence, duration, route, and aggregate dose received. As hazard is being estimated more frequently using New Approach Methodologies (NAMs) to determine concentrations at which bioactivity occurs, a third component, toxicokinetics (TK), is needed to compare these hazard surrogates to exposure[2]. TK describes the absorption, distribution, metabolism, and excretion of a chemical within the body for a given species. Knowledge of TK allows translation of toxicological information, which might be collected in model animal species or *in vitro*, to humans or sentinel ecological species[3]. TK is also needed for translating external exposure doses into target tissue concentrations and vice versa (i.e., reverse dosimetry), allowing a linkage between cellular pathway perturbations and exposure amounts[4,5]. Detailed information on test animal species can be helpful, since there is uncertainty determining the relevance of an internal dose found in an animal TK study to humans, due to the higher doses generally used in this type of testing and other factors[6]. Although it can be useful in some contexts to differentiate between toxicokinetics and pharmacokinetics (PK), the two terms will be used interchangeably in this document.

Predicting internal doses is a primary task of 21st century toxicology[7]. While pharmaceuticals are vetted with human clinical trials, and food additives or pesticides are tested using animal models, humans are also potentially exposed to many of the thousands of commercially-available chemicals (and their transformation products) for which there are limited toxicological and TK data[8,9]. To address this gap, computational modelling of TK can be performed based upon inputs from *in vivo*, *in vitro*, and *in silico* studies. *In vitro* tools have been developed to allow screening of chemical-specific TK properties for libraries of chemicals[9,10]. However, each input parameter carries an amount of uncertainty, which may not be readily quantifiable (for example, human genetic variation[11]).

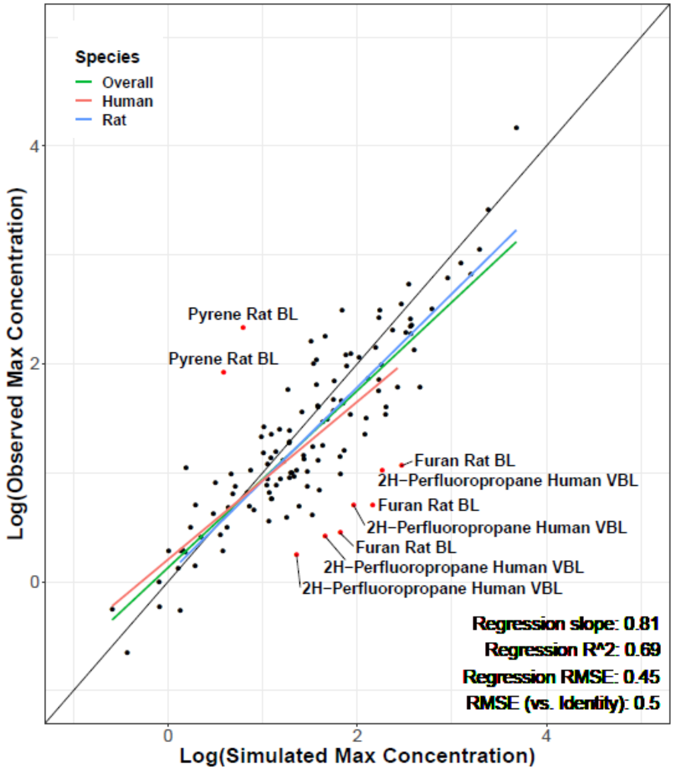
[1]U.S. Environmental Protection Agency, Center for Computational Toxicology and Exposure, 109 T.W. Alexander Drive, Research Triangle Park, NC, 27709, USA. [2]Oak Ridge Institute for Science and Education, Oak Ridge, TN, USA. [3]Department of Environmental Sciences and Engineering, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. e-mail: sayre.risa@epa.gov

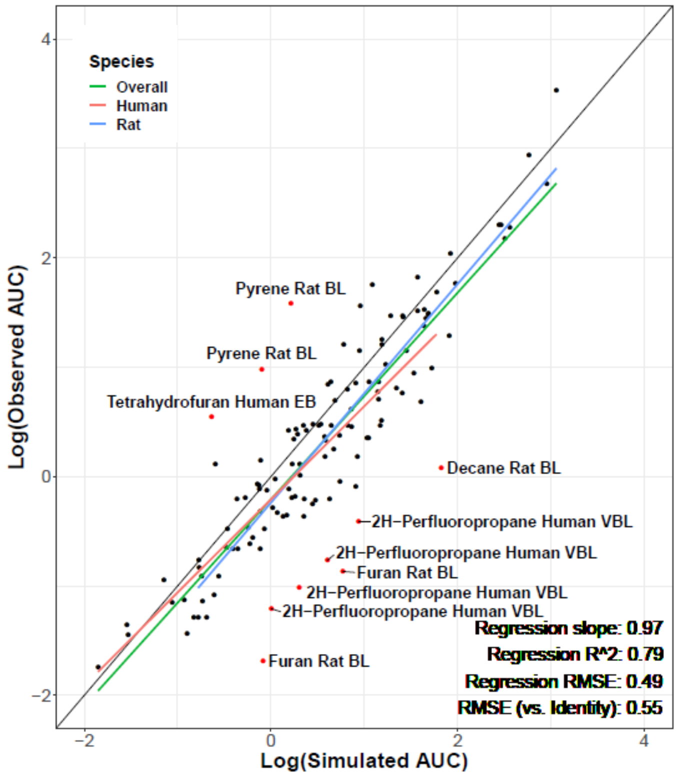
SCIENTIFIC DATA | (2020) 7:122 | https://doi.org/10.1038/s41597-020-0455-1 1

Sayre *et al.*, *Scientific Data.* 2020

142 Exposure Scenarios
41 VOCs

Evaluating Performance of Generic Inhalation PBTK Models

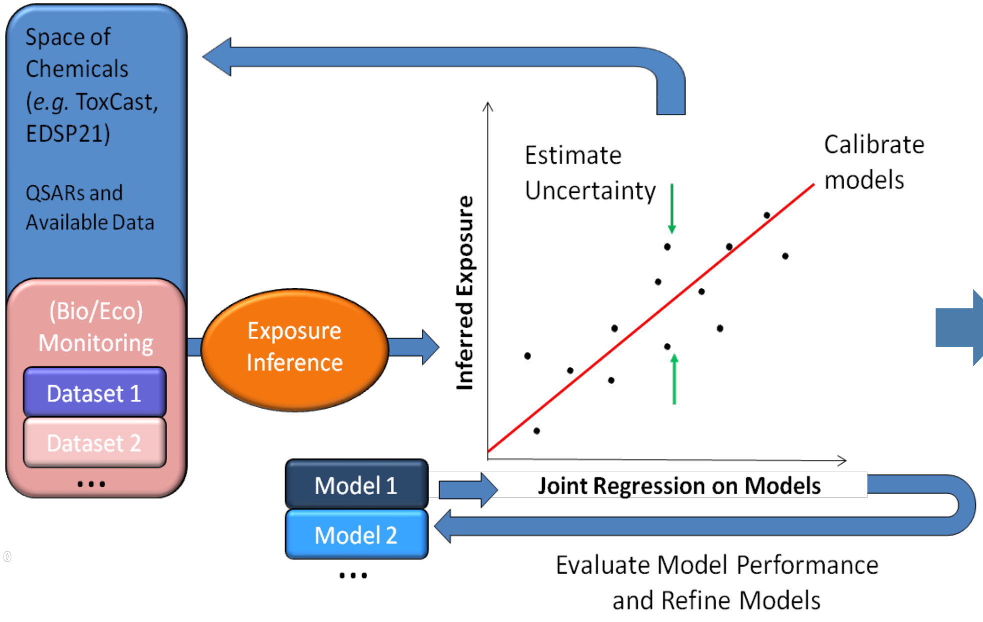


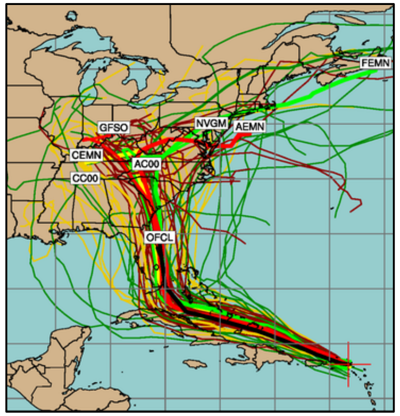


Linakis *et al.*, *J Expo Sci Environ Epidemiol.* 2020

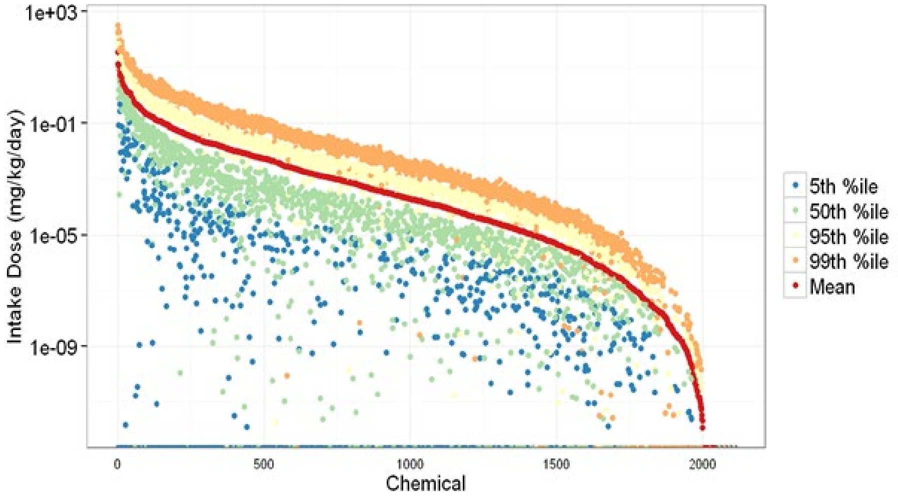
Consensus Exposure Predictions with the SEEM Framework

- Incorporate multiple models (simple heuristics, SHEDS-HT, USETox) into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM)** (Wambaugh et al., 2013, 2014; Ring, 2019)



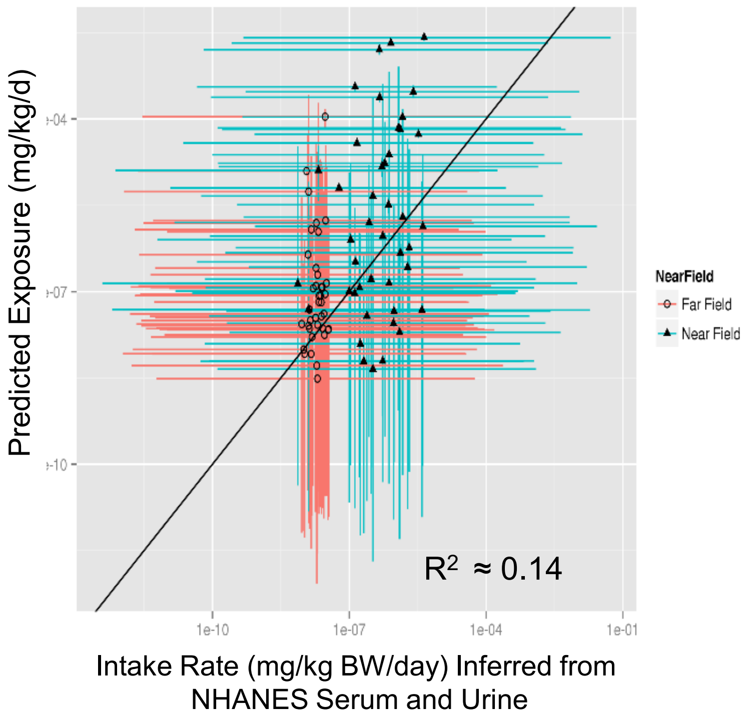


Hurricane Path Prediction is an Example of Integrating Multiple Models



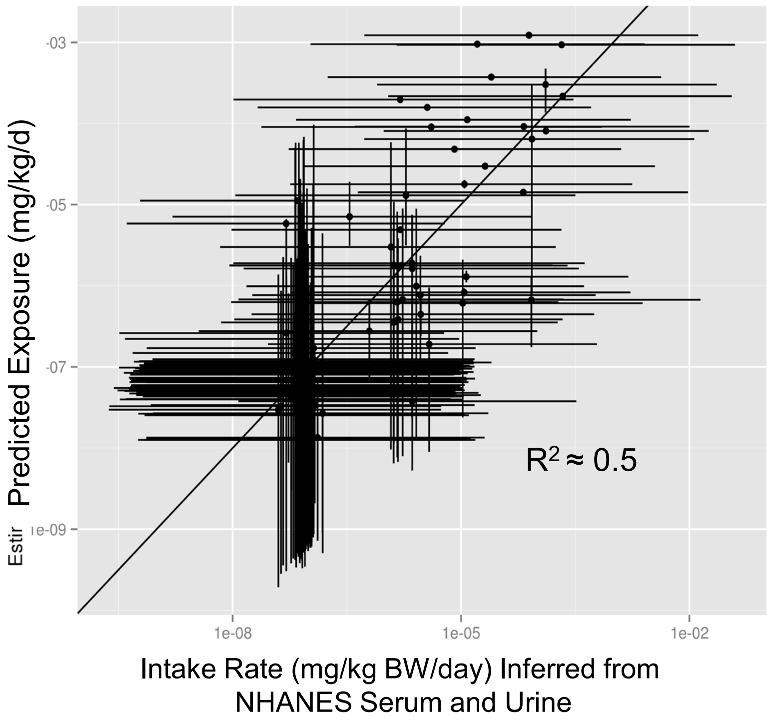
Development of First and Second Generation SEEM Models

Near-field
+
Far-Field



Wambaugh et al., 2013

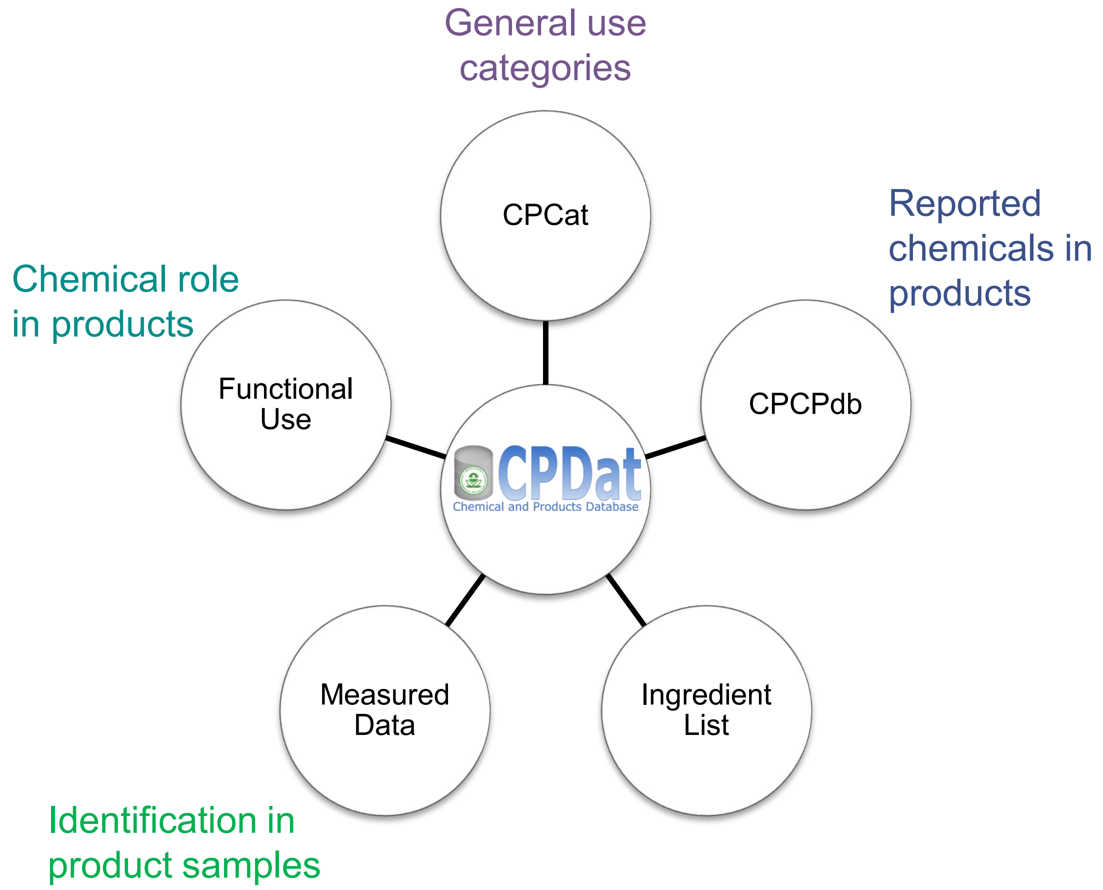
Production Volume
+
5 Functional Use
Heuristics



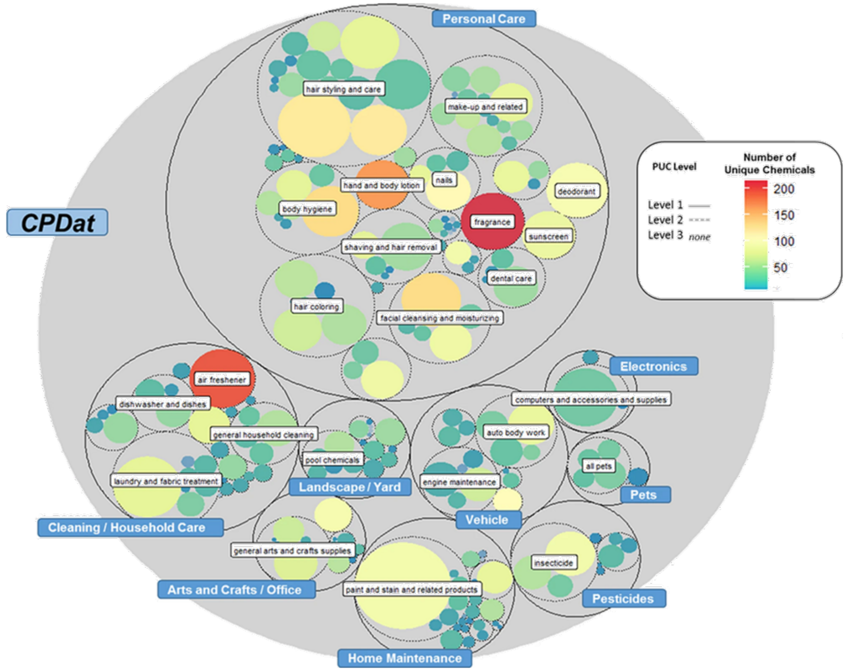
Wambaugh et al., 2014

United States Environmental Protection Agency

Curating the Data to Support Pathway-Based Exposure Models for 1000s of Chemicals



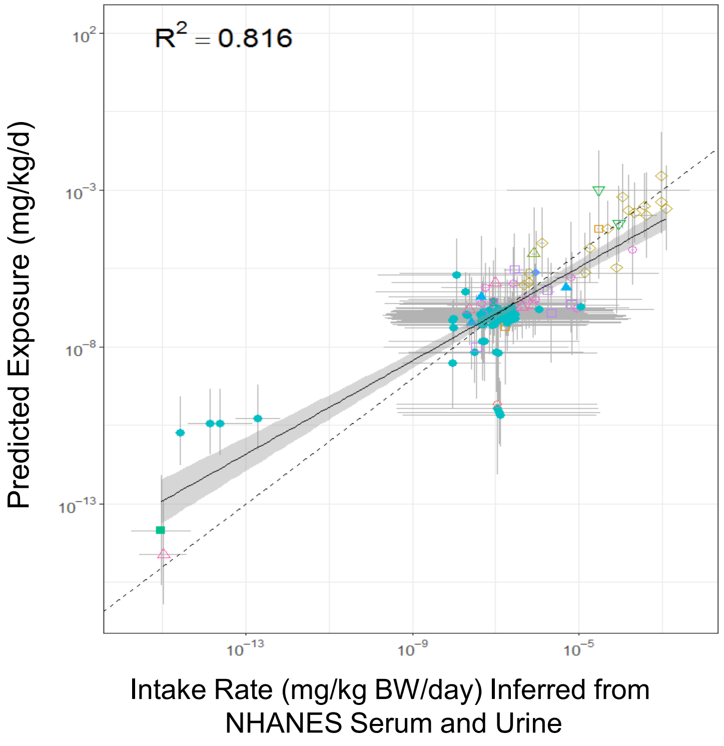
Dionisio et al., *Sci Data*. 2018



Group Type	Documents	Raw Chemical Records	Curated Chemical Records
Consumer Product Composition	473,271	3,738,350	1,791,250
Functional use	33,770	34,680	11,946
CPCat Categories (Public chemical lists)	2,088	117,231	68,133
Occupational exposure	1,304	4,825	1078
Literature monitoring	1,175	966	In process
Habits and practices (Consumer Product Use Patterns)	202	NA	NA

Integration of Twelve Exposure Pathway Models in the Third Generation SEEM Model

Predictor	Reference(s)	Chemicals Predicted	Pathways
EPA Inventory Update Reporting and Chemical Data Reporting (CDR) (2015)	US EPA (2018)	7856	All
Stockholm Convention of Banned Persistent Organic Pollutants (2017)	Lallas (2001)	248	Far-Field Industrial and Pesticide
EPA Pesticide Reregistration Eligibility Documents (REDs) Exposure Assessments (Through 2015)	Wetmore et al. (2012, 2015)	239	Far-Field Pesticide
United Nations Environment Program and Society for Environmental Toxicology and Chemistry toxicity model (USEtox) Industrial Scenario (2.0)	Rosenbaum et al. (2008)	8167	Far-Field Industrial
USEtox Pesticide Scenario (2.0)	Fantke et al. (2011, 2012, 2016)	940	Far-Field Pesticide
Risk Assessment IDentification And Ranking (RAIDAR) Far-Field (2.02)	Arnot et al. (2008)	8167	Far-Field Pesticide
EPA Stochastic Human Exposure Dose Simulator High Throughput (SHEDS-HT) Near-Field Direct (2017)	Isaacs (2017)	7511	Far-Field Industrial and Pesticide
SHEDS-HT Near-field Indirect (2017)	Isaacs (2017)	1119	Residential
Fugacity-based INdoor Exposure (FINE) (2017)	Bennett et al. (2004), Shin et al. (2012)	645	Residential
RAIDAR-ICE Near-Field (0.803)	Arnot et al., (2014), Zhang et al. (2014)	1221	Residential
USEtox Residential Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016,2017)	615	Residential
USEtox Dietary Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016), Ernstoff et al. (2017)	8167	Dietary



Ring et al., *Environ Sci Technol*. 2019

Initial Case Study on Evaluating NAMs for Screening Level Assessments


Bloomberg BNA Daily Environment Report™

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Practitioner Insights: Bringing New Methods for Chemical Safety into the Regulatory Toolbox; It is Time to Get Serious

Chemicals

The recently amended toxics law requires the EPA to take significant strides towards using non-animal safety tests for chemicals. EPA's Dr. Robert Kavlock explores this challenge and reports on a recent international ... work for tests that can reduce reli... information.

Chemical Research in Toxicology

Perspective

Accelerating the Pace of Chemical Risk Assessment

Robert J. Kavlock, Tina Bahadori, Tara S. Barton-Maclaren, Maureen R. Gwinn, Mike Rasenberg, and Russell S. Thomas

Accelerating the Pace of Chemical Risk Assessment

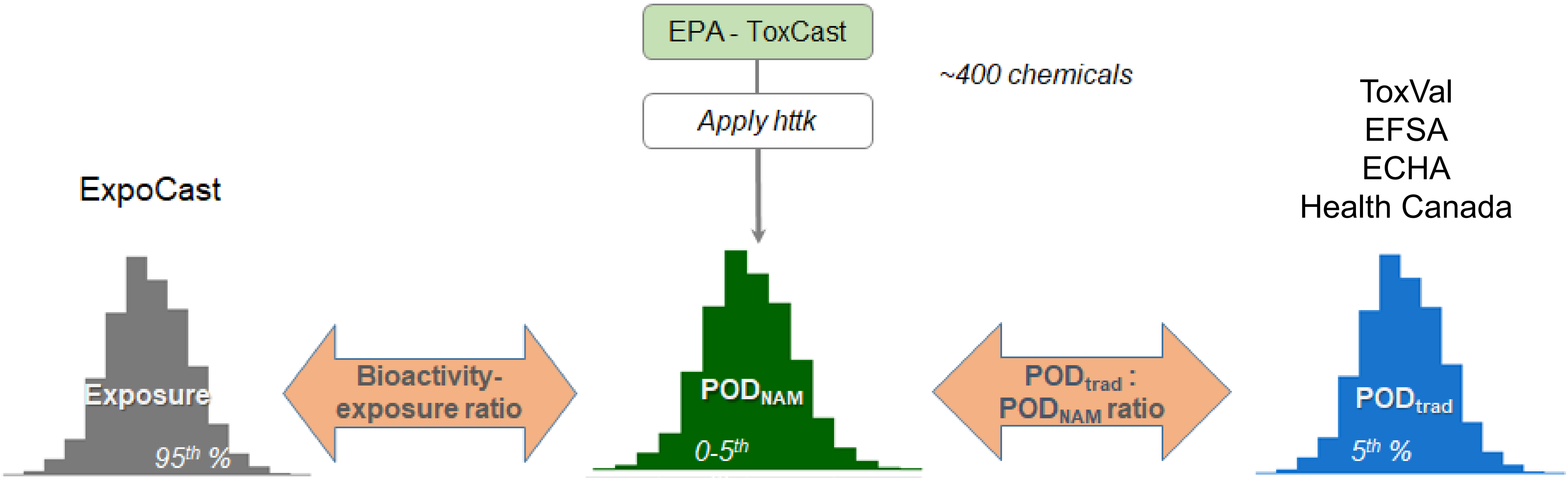
APCRA

CONTENTS

1. OVERVIEW

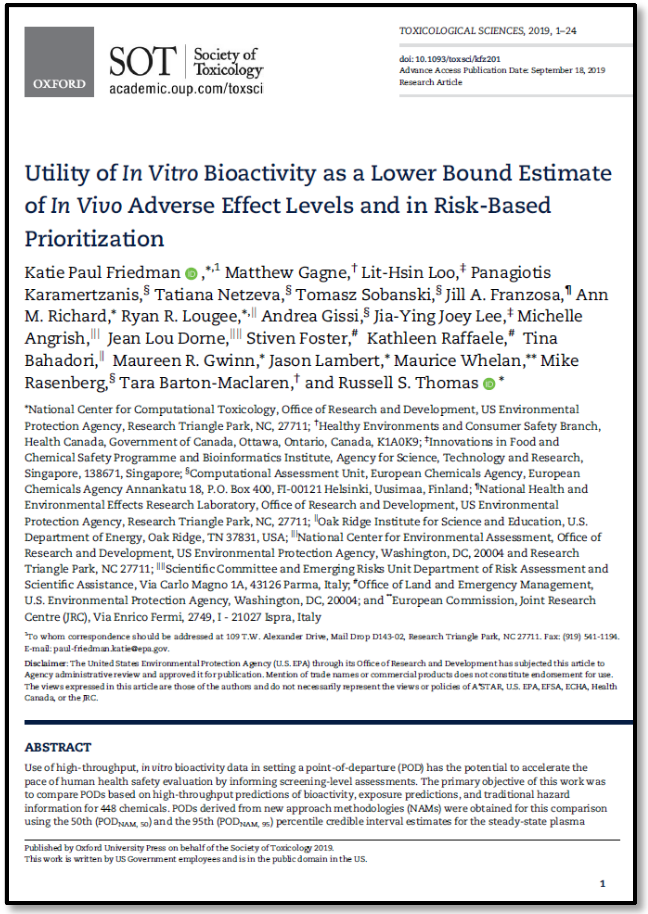
- Multiple international case studies stemming from 2016 inter-governmental workshop
- Example: *In Vitro* Bioactivity as a Conservative Point of Departure
- Participants include EPA, Health Canada, ECHA, EFSA, JRC, and A*STAR
- Goal: Determine whether *in vitro* bioactivity from broad high-throughput 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.

Case Study on Evaluating NAMs for Screening Level Assessments



- *NOEL, LOEL, NOAEL, or LOAEL*
- *Oral exposures*
- *Mg/kg-bw/day units*

Regulatory Focused Case Study on Evaluating NAMs for Screening Level Assessments



TOXICOLOGICAL SCIENCES, 2019, 1–24

doi: 10.1093/toxsci/kfz201
Advance Access Publication Date: September 18, 2019
Research Article

OXFORD SOT Society of Toxicology academic.oup.com/toxsci

Utility of *In Vitro* Bioactivity as a Lower Bound Estimate of *In Vivo* Adverse Effect Levels and in Risk-Based Prioritization

Katie Paul Friedman,[*,1] Matthew Gagne,[†] Lit-Hsin Loo,[‡] Panagiotis Karamertzanis,[§] Tatiana Netzeva,[§] Tomasz Sobanski,[§] Jill A. Franzosa,[¶] Ann M. Richard,[*] Ryan R. Lougee,[*,||] Andrea Gissi,[§] Jia-Ying Joey Lee,[‡] Michelle Angrish,[|||] Jean Lou Dorne,[||||] Stiven Foster,[#] Kathleen Raffaele,[#] Tina Bahadori,[||] Maureen R. Gwinn,[*] Jason Lambert,[*] Maurice Whelan,[**] Mike Rasenberg,[§] Tara Barton-Maclaren,[†] and Russell S. Thomas[*]

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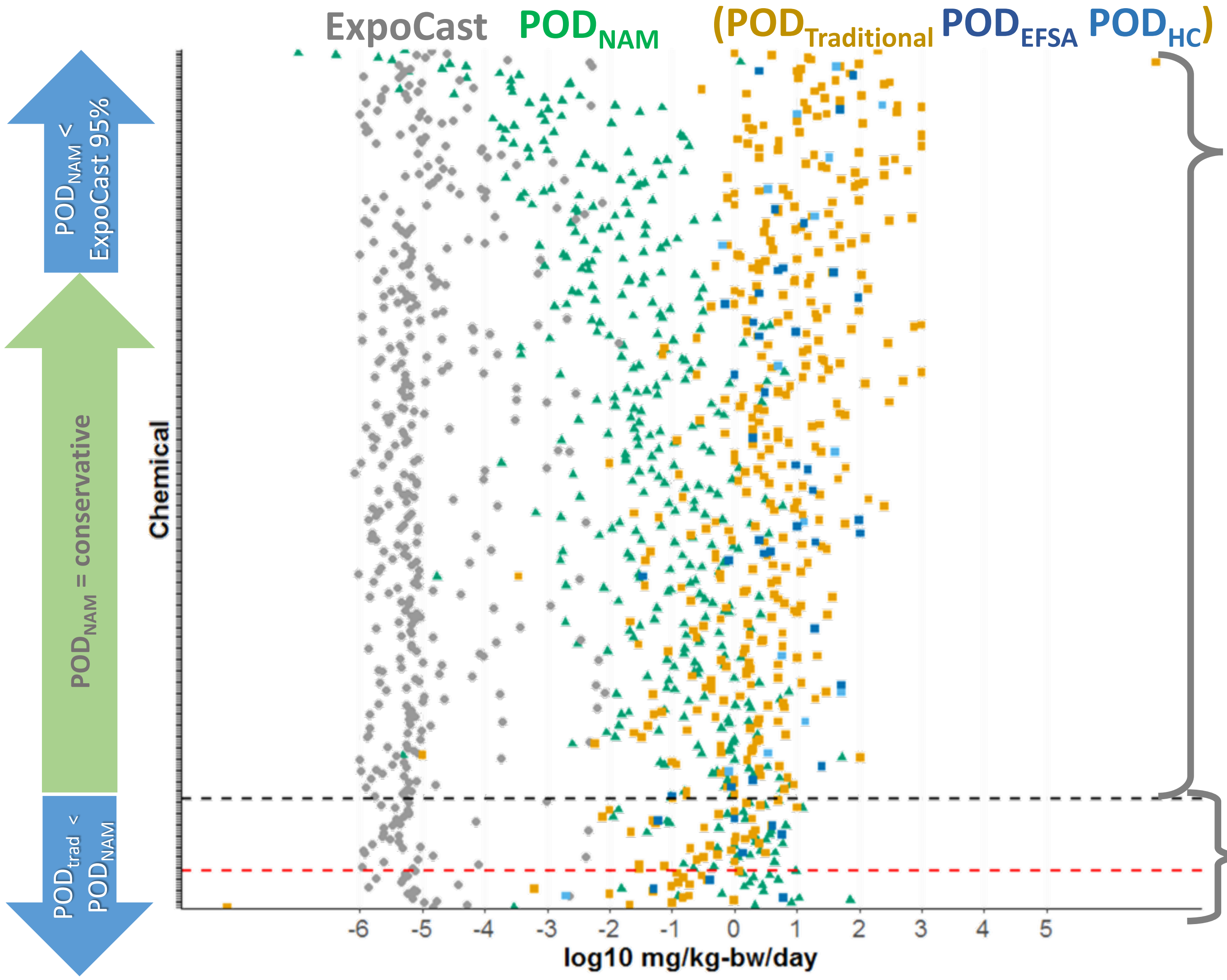
[1]To whom correspondence should be addressed at 109 T.W. Alexander Drive, Mail Drop D143-02, Research Triangle Park, NC 27711. Fax: (919) 541-1194. E-mail: paul-friedman.katie@epa.gov.

Disclaimer: The United States Environmental Protection Agency (U.S. EPA) through its Office of Research and Development has subjected this article to Agency administrative review and approved it for publication. Mention of trade names or commercial products does not constitute endorsement for use. The views expressed in this article are those of the authors and do not necessarily represent the views or policies of A*STAR, U.S. EPA, EFSA, ECHA, Health Canada, or the JRC.

ABSTRACT

Use of high-throughput, *in vitro* bioactivity data in setting a point-of-departure (POD) has the potential to accelerate the pace of human health safety evaluation by informing screening-level assessments. The primary objective of this work was to compare PODs based on high-throughput predictions of bioactivity, exposure predictions, and traditional hazard information for 448 chemicals. PODs derived from new approach methodologies (NAMs) were obtained for this comparison using the 50th ($POD_{NAM,50}$) and the 95th ($POD_{NAM,95}$) percentile credible interval estimates for the steady-state plasma

1

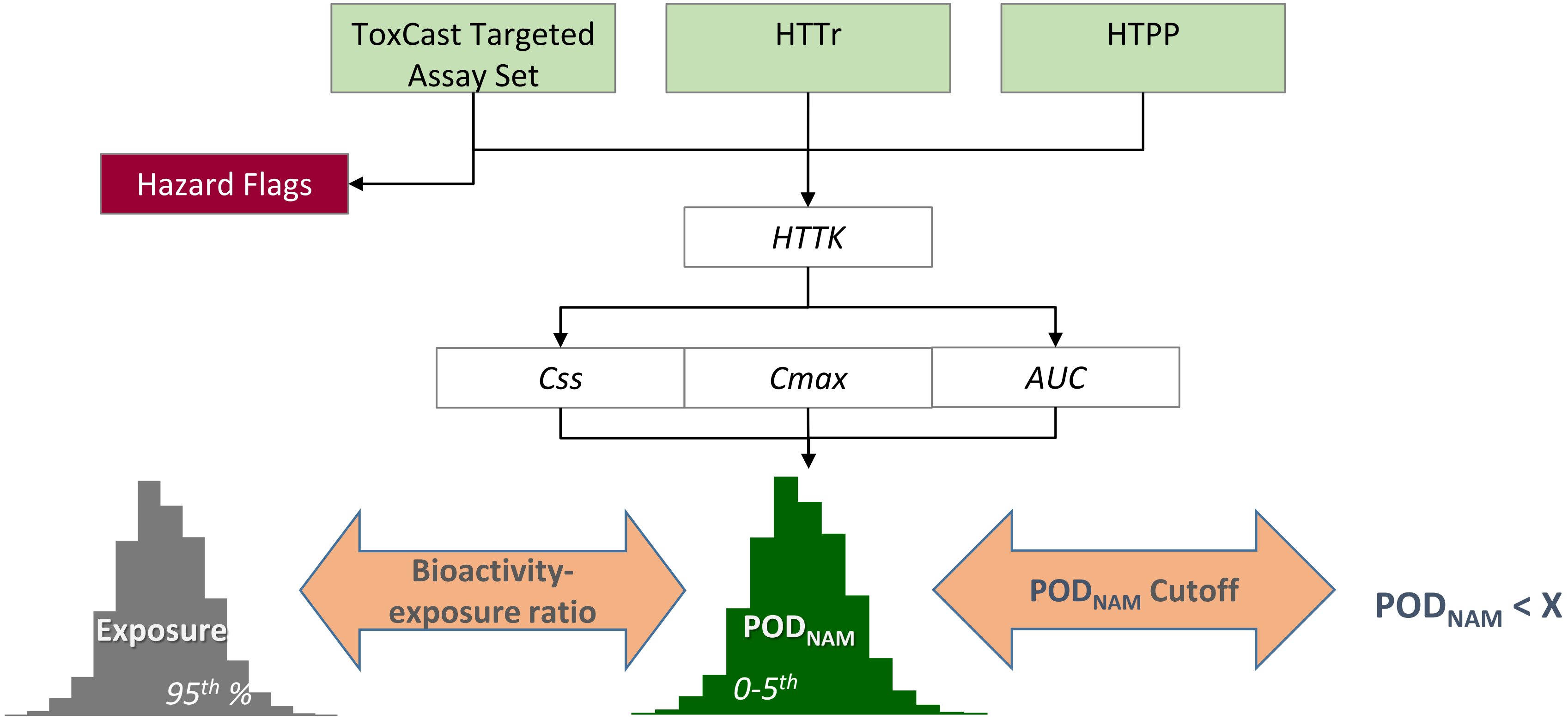


For ~89% of the chemicals, POD_{NAM} was conservative.

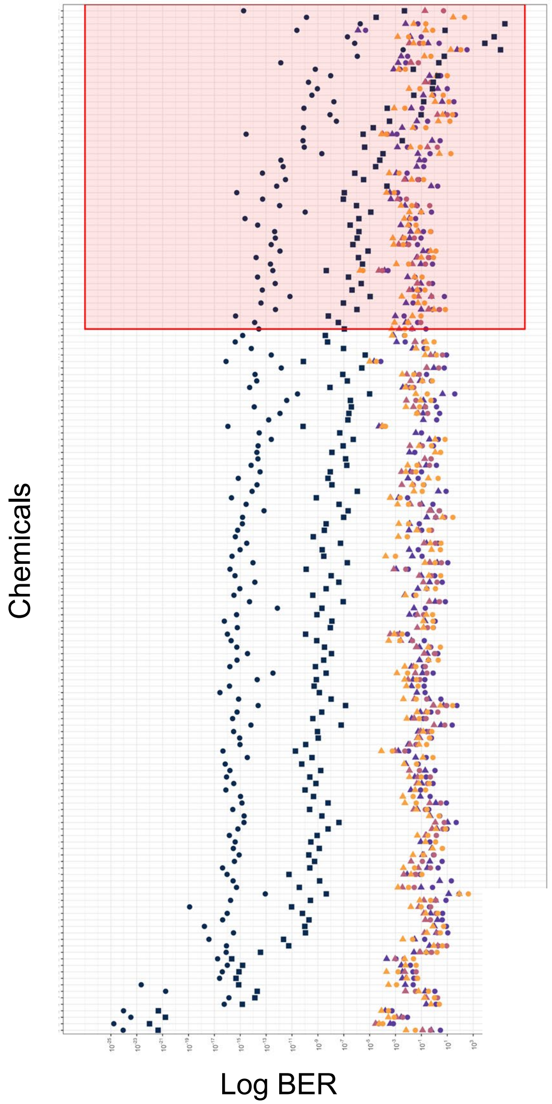
(~100-fold on average), but less conservative than a TTC

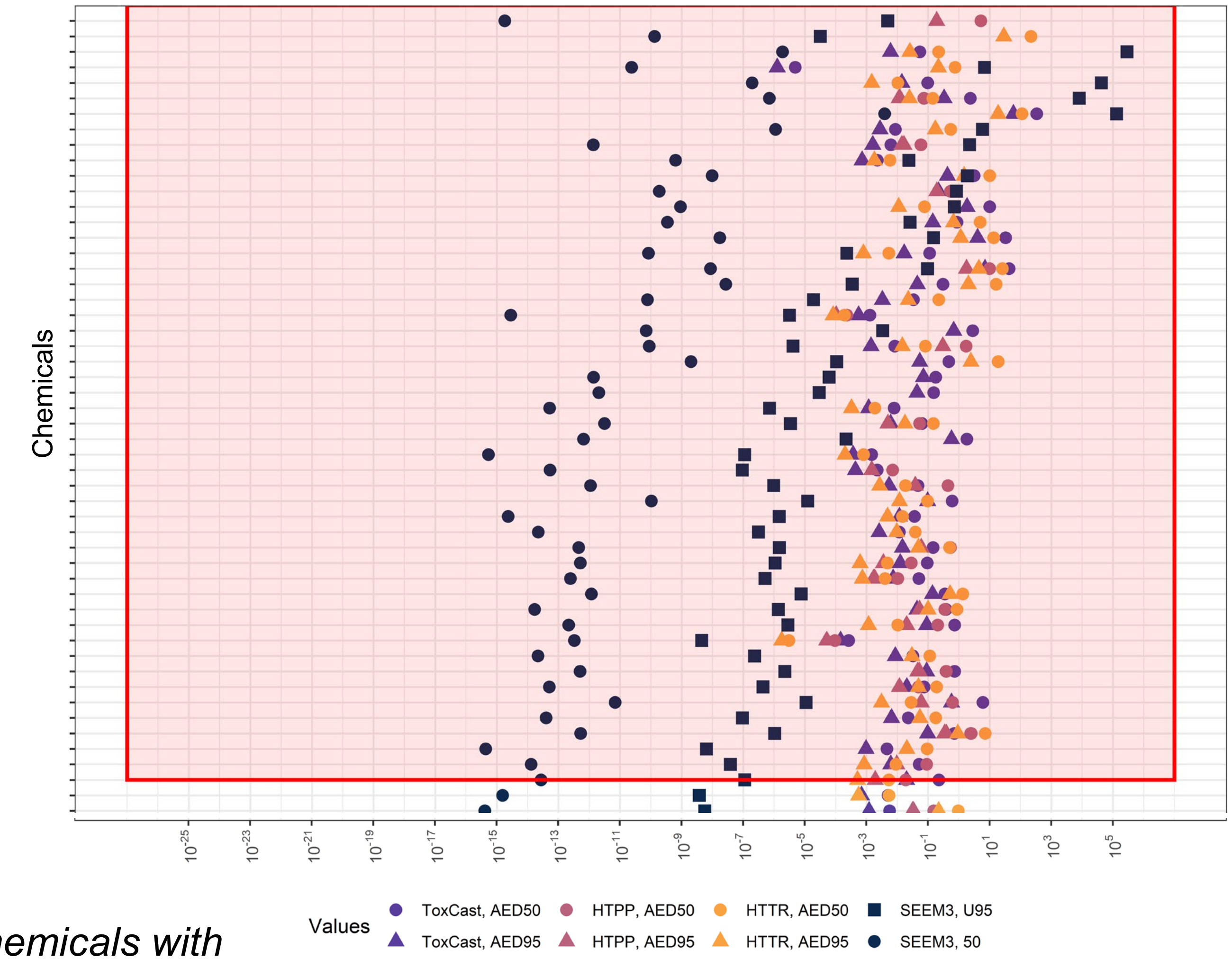
Chemicals where POD_{NAM} was not conservative enriched in OPs/carbamates

Follow-Up Prospective Case Study on Application To Data Poor Chemicals on National Inventories



Preliminary Analysis of Follow-Up Prospective Case Study on Application To Data Poor Chemicals

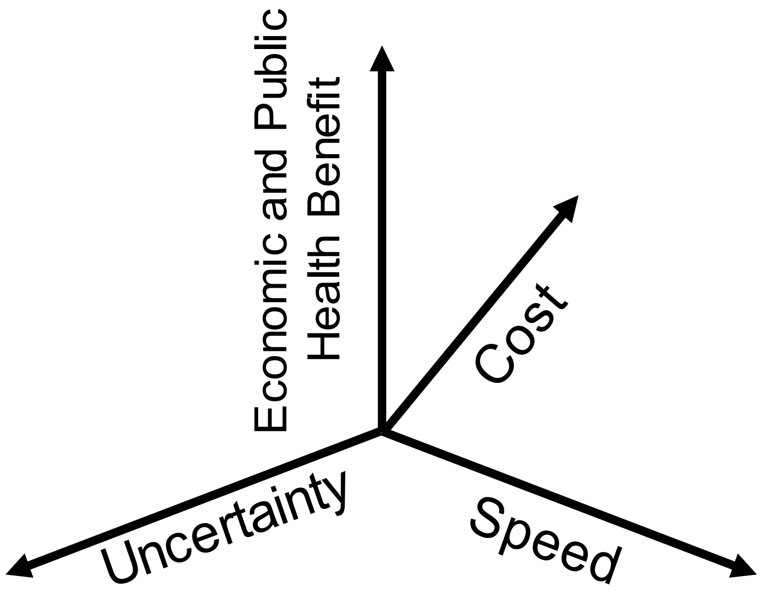




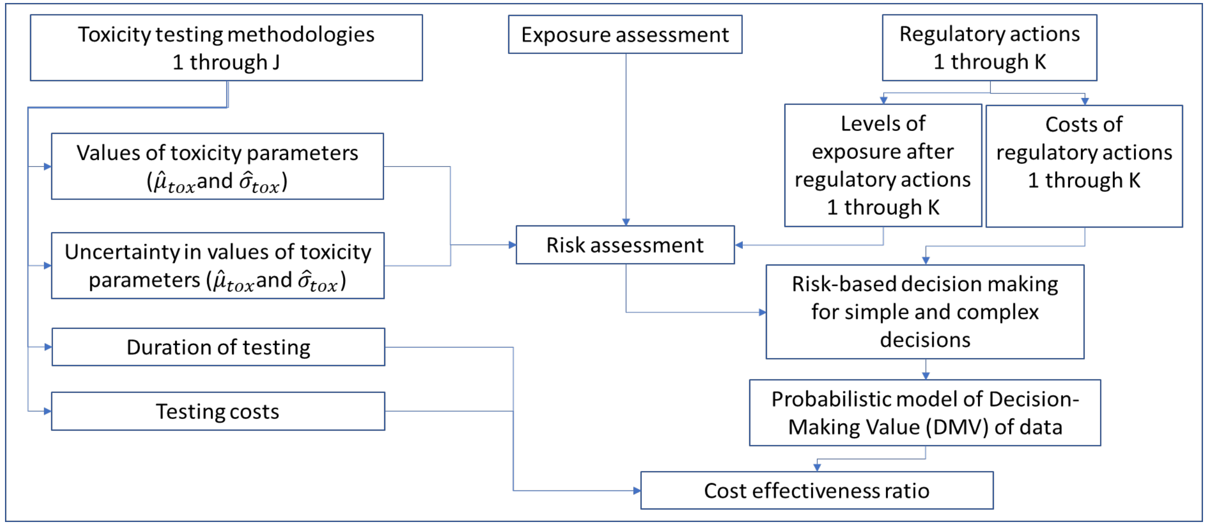
Red box is chemicals with BER ≤ 10,000

Incorporating Approaches into Decision Support Frameworks

Systematic Evaluation of Trade-offs of Speed, Cost, and Uncertainty



Components of a Cost Effectiveness Framework for Toxicity Testing Methods



$$CER^{j\,|l} = \frac{\sum_{y=1}^{y_{\mathrm{T},j}} \frac{C_y^j}{(1+r)^{y-1}}}{\sum_{y=y_{\mathrm{T},j}+y_{\mathrm{TA},j}}^{TH} \frac{DMV_y^{j\,|l}}{(1+r)^{y-1}}}$$

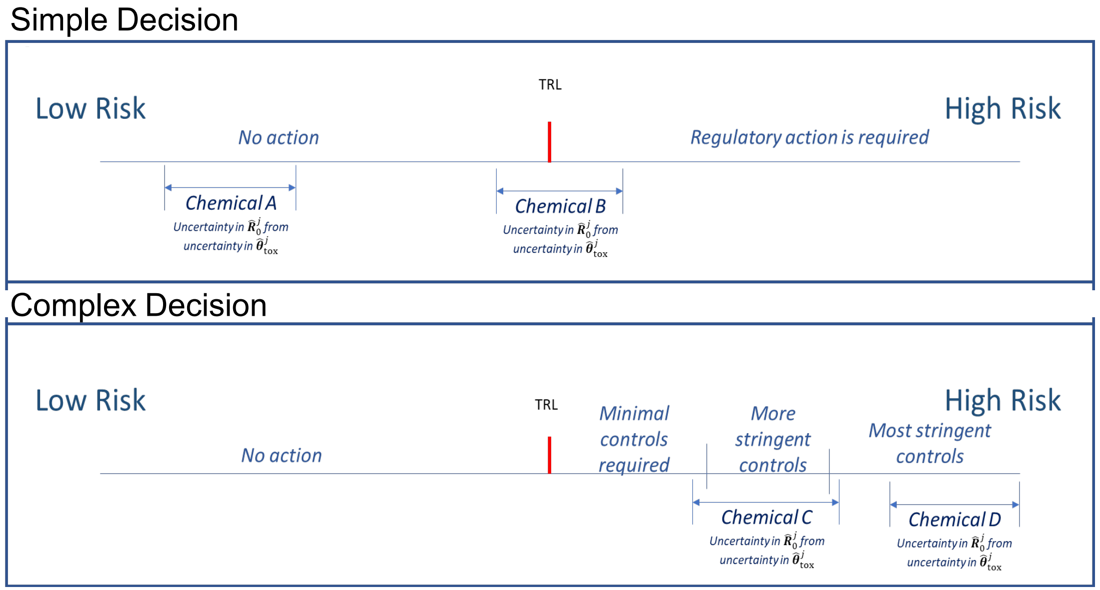
- C_y^j cost of performing the j^{th} testing methodology and interpreting results in the y^{th} year (millions of dollars)
- $DMV_y^{j|l}$(Decision Making Value) probability of correctly making the l^{th} type of regulatory decision given the findings of the j^{th} testing methodology in the y^{th} year (unitless)
- $y_{\mathrm{T},j}$ time it takes to perform the j^{th} method of toxicity testing (years)
- $y_{TA,j}$ time required to convert the findings of the j^{th} testing methodology into a toxicity assessment (years)
- y_{TH} time horizon of the analysis where y_{TH} must be greater than the sum of $y_{TA,j}$ and $y_{T,j}$ (years)
- y time since the beginning of the toxicity testing (years)
- r annual discount rate (fraction per year)

EPA United States Environmental Protection Agency

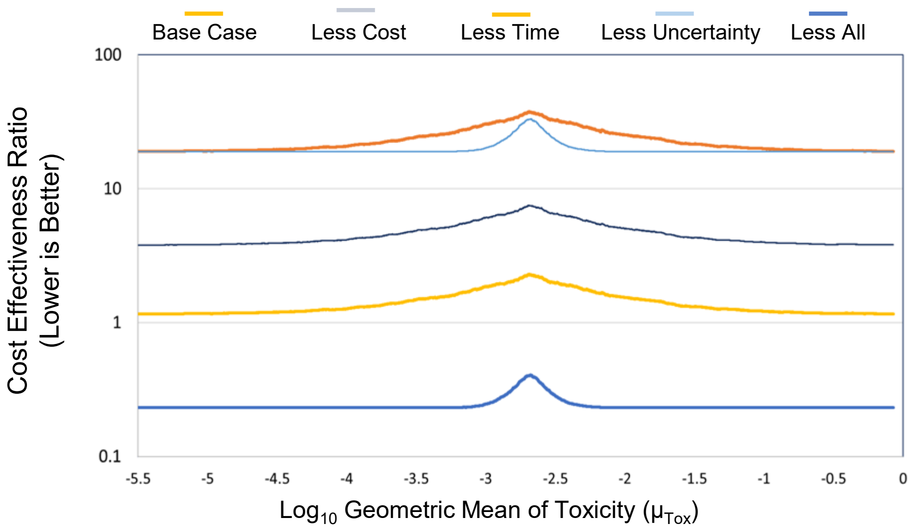
Incorporating Approaches into Decision Support Frameworks

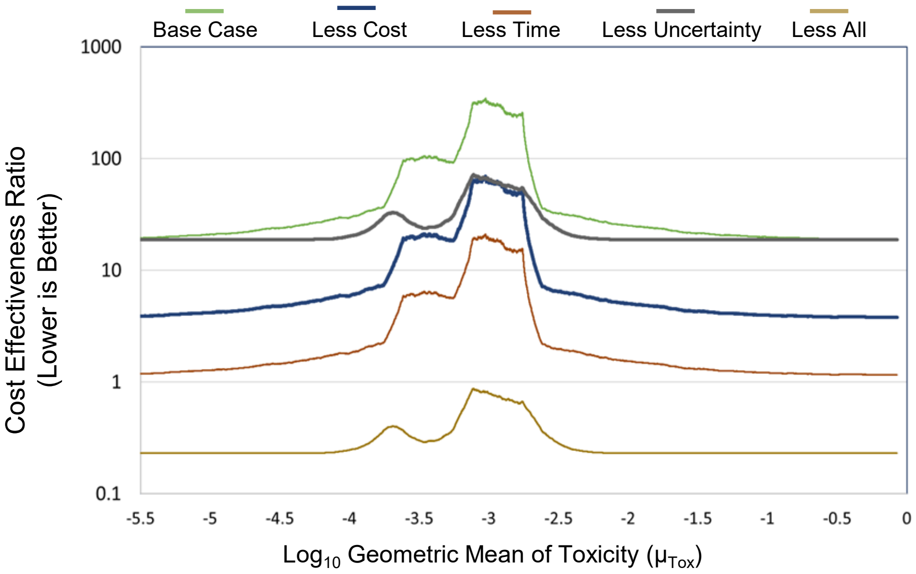
			Toxicity Testing Methodology				
			1	2	3	4	5
Parameter	Description	Units	Base case	Less cost	Less time	Less uncertainty	Less all three
$y_{T,j}$	Duration of toxicity testing	Years	10	10	2	10	2
C^j	The total cost of toxicity testing one chemical	Millions $	5	1	5	5	1
$\sigma(\hat{\mu}_{tox})$	Uncertainty in the geometric mean of toxicity	Unitless	1	1	1	0.2	0.2

			Regulatory actions					
Parameter	Description	Units	No action	1	2	3	4	5
$\hat{\mu}_{k,exp}$	Log_{10} of geometric mean of exposure in the population	Log_{10} (mg/kg/d)	-8	-8	-8	-8.5	-9	-14
$\hat{\sigma}_{k,exp}$	Log_{10} of geometric standard deviation of exposure in the population	Log_{10} (mg/kg/d)	0.5	0.4	0.3	0.5	0.5	0.1



Incorporating Approaches into Decision Support Frameworks





	Average value of CER across all values of μ_{tox}		Value of CER for the value of μ_{tox} most impacted by uncertainty	
	Simple decision	Complex decision	Simple decision	Complex decision
Toxicity Testing Methodology #1 (Base case)	22	45	38	350
Toxicity Testing Methodology #2 (Less cost)	4.4	9.1	7.5	70
Toxicity Testing Methodology #3 (Less time) - maximum impact	1.4	2.8	2.3	21
Toxicity Testing Methodology #4 (Less uncertainty)	20	23	33	72
Toxicity Testing Methodology #5 (Less cost, less time - min, less uncertainty)	0.24	0.28	0.41	0.88
	Ratios of CER values for Toxicity Testing Methodologies			
Impact of less cost	5.0	5.0	5.0	5.0
Maximum impact of less time	16.4	16.4	16.4	16.4
Impact of less uncertainty	1.1	2.0	1.5[1]	5.2[1]
Combined impact of less of cost, minimum impact of less time and less uncertainty	92.8	160.3	125.7	425.3

[1]*Values are determined based on the set of data with the largest difference between Toxicity Testing Methodologies #1 and #4.*

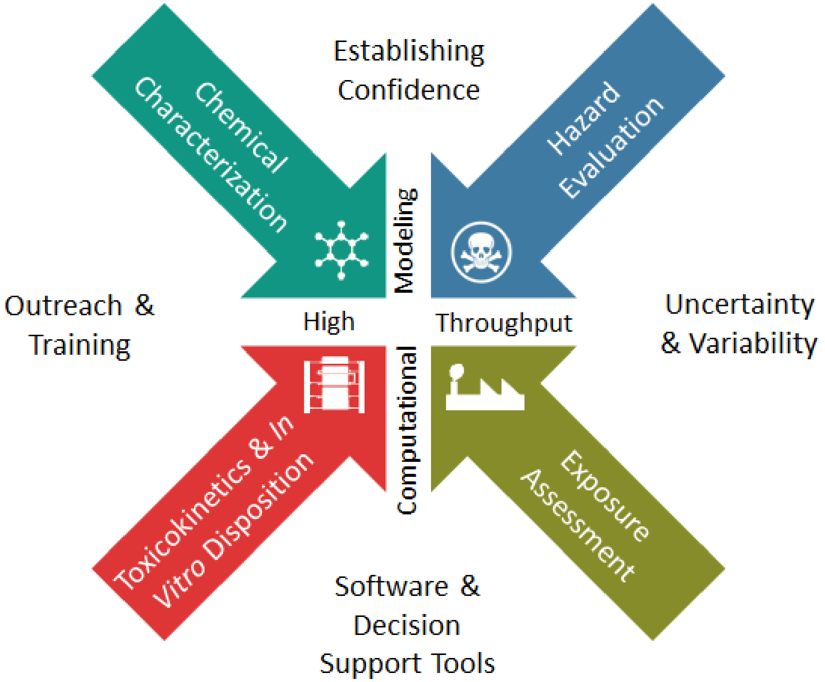
To Succeed it will Take a Complex, Multi-Disciplinary Research Program, but…

- DSSTox
- Chemical library
- Read across
- SAR/QSAR modeling
- Chemotypes
- TTC

- OECD/ APCRA Case Studies
- NAM Work Plan
- Reference Materials
- Reporting Templates

- Eco/HH HTS (HTTr, HTPP, ToxCast)
- Tiered testing
- Organotypic models
- Addressing limitations (metabolism, chemical space)
- Statistical and Biologically-based Modeling
- AOPs

- Communities of Practice
- ToxCast Owners Manual
- Training courses/ videos



- SEEM
- ToxBoot
- HTTK
- ToxRefDB

- HTTK assays (metabolism, bioavailability, binding)
- Partition coefficients
- HTTK R package
- Multi-route models
- Model verification (e.g., CvT)
- In vitro disposition

- CompTox Chemicals Dashboard
- RapidTox
- Factotum
- ECOTOX
- SeqAPASS
- CEA and VOI Frameworks

- ExpoCast
- NTA/SSA
- ENTACT
- Product emissivity

The Chemical Safety Groundhog Day is Coming to a Close…