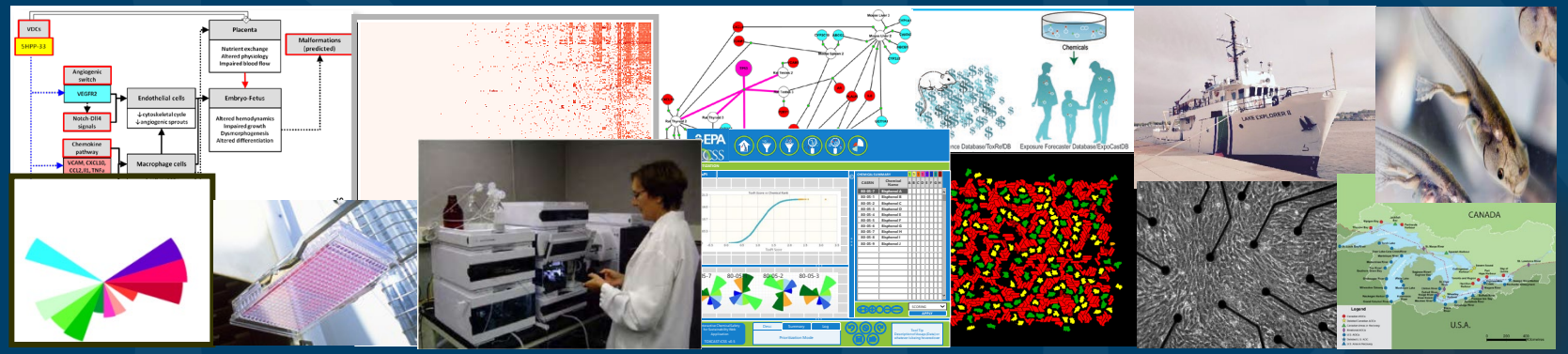
Application of New Approach Methods for Hazard Characterization of Chemicals



German MAK Commission

May 19, 2021

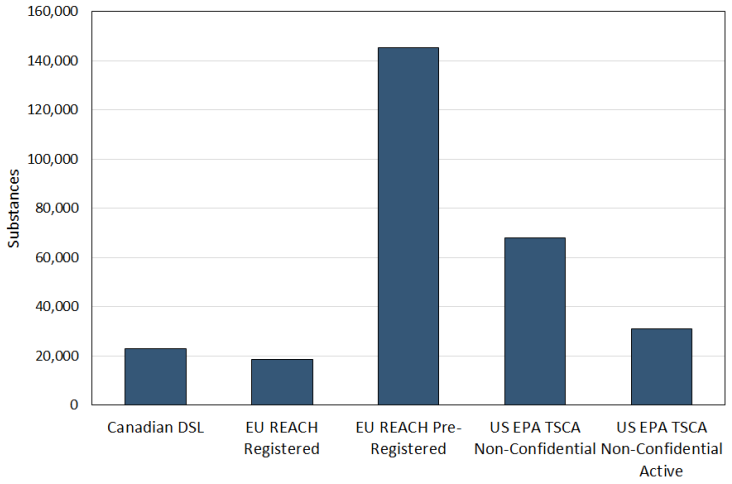
Rusty Thomas
Director
Center for Computational Toxicology and Exposure

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

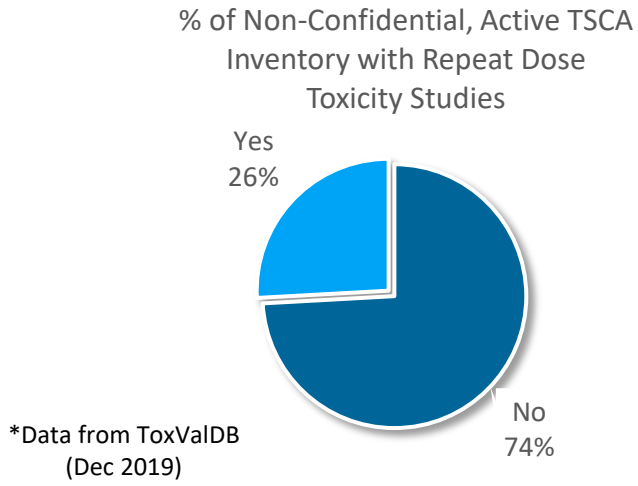
Toxicology and Risk Assessment Face Many Challenges

United States Environmental Protection Agency

Number of Substances

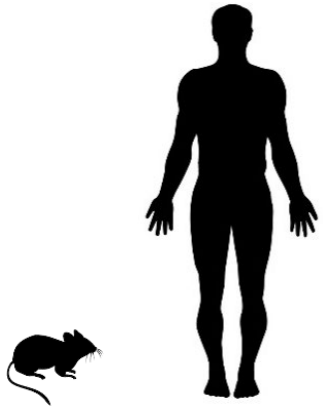


Amount of Data

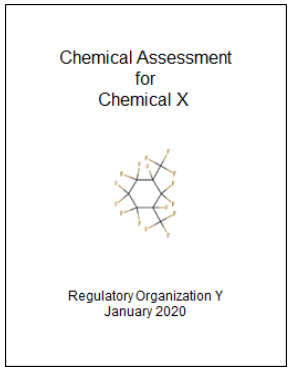


*Data from ToxValDB (Dec 2019)

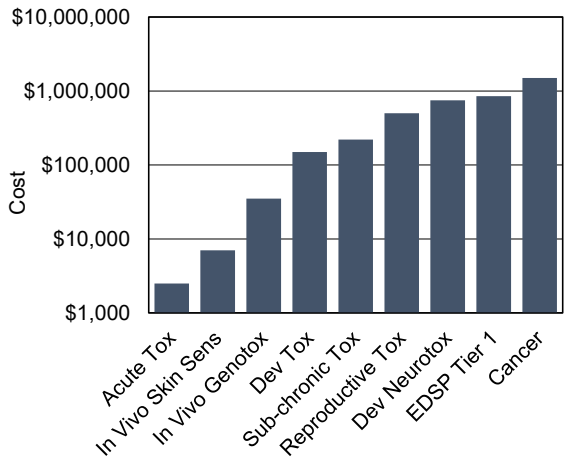
Reliability/Relevance/Ethics



Time



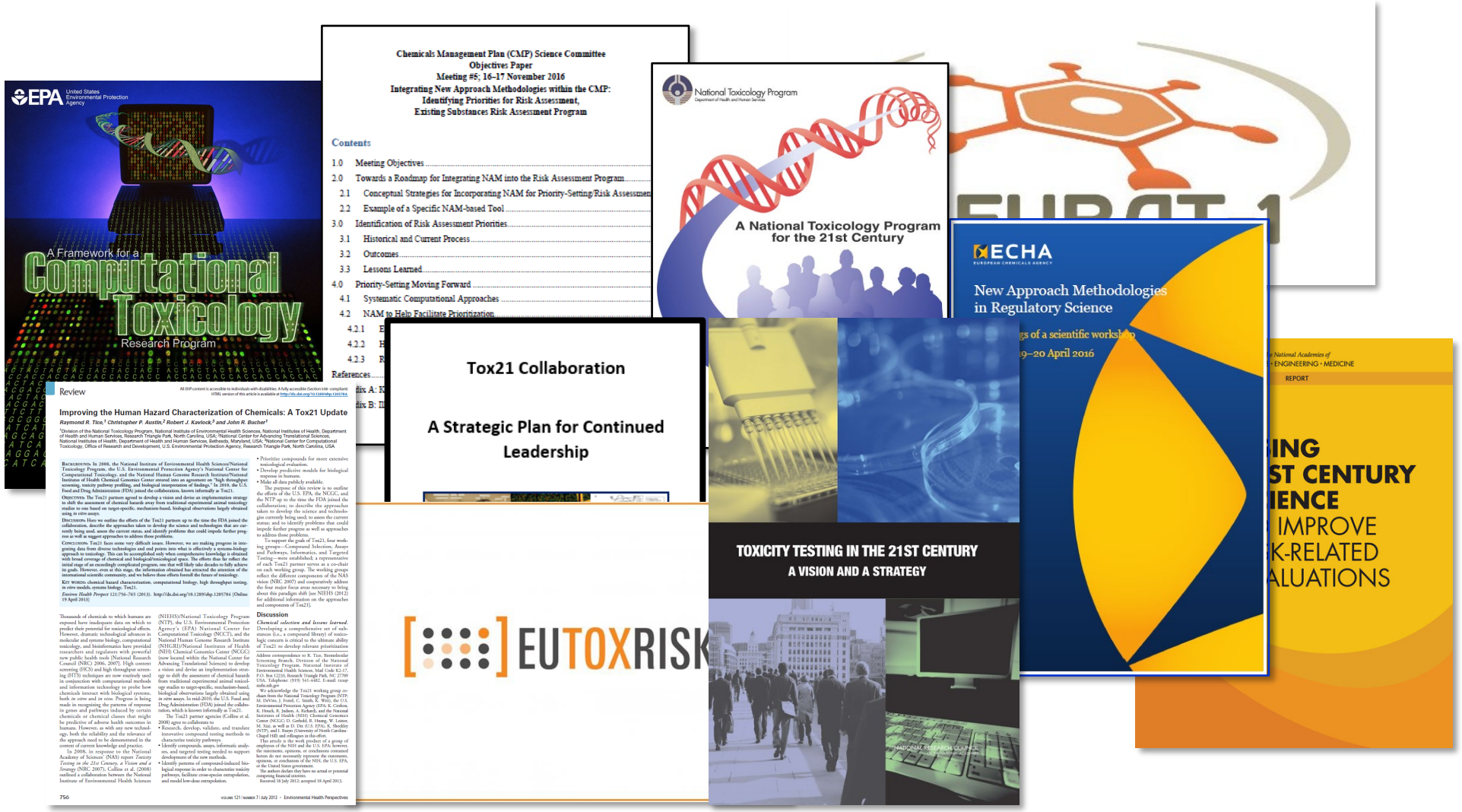
Economics



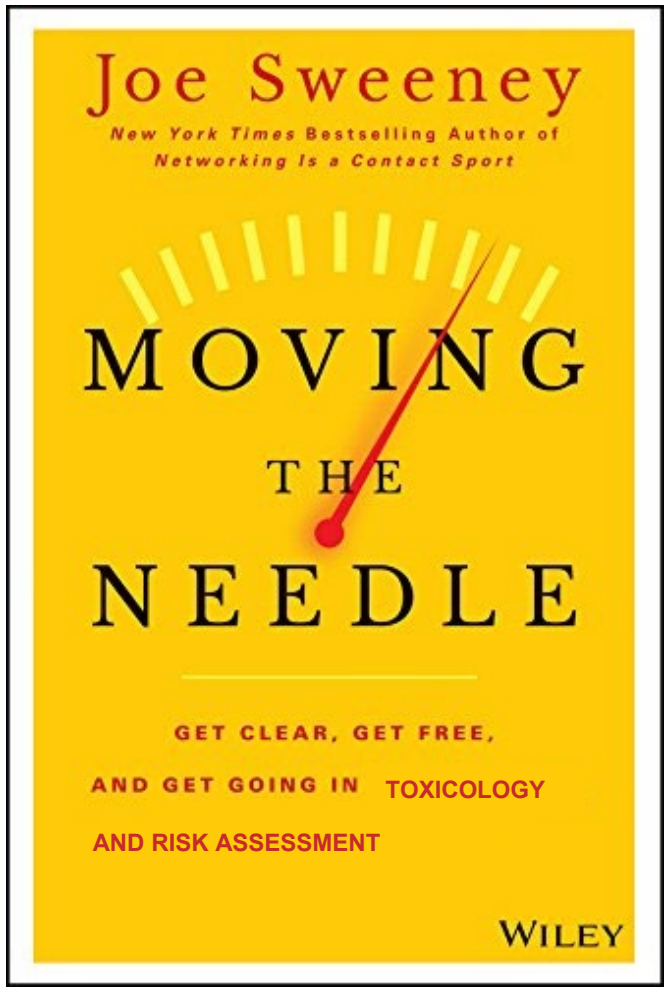
Broad Range of Decision Contexts

Multiple Initiatives Have Attempted to Address One or More of the Challenges

- *In silico* modeling
- *In vitro assays*
- Analog approaches
- IATA
- …



But, "Moving the Needle" Has Been Difficult…



Frequent Criticisms Against Broader Application

- Limited coverage of important cellular and intracellular processes
- Relatively short duration exposures
- Endpoints with indirect connection to adverse responses in organs and tissues
- Limited metabolic capacity
- Reduced biological complexity
- "Black box" predictions
- Limited chemical domain of applicability
- Lack of familiarity and training
- Complex data interpretation
- Lengthy validation process

EPA Developed an Operational Blueprint to Focus and Facilitate Progress

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

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

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

FORUM

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

Russell S. Thomas,*,1 Tina Bahadori,† Timothy J. Buckley,‡ John Cowden,* Chad Deisenroth,* Kathie L. Dionisio,‡ Jeffrey B. Frithsen,§ Christopher M. Grulke,* Maureen R. Gwinn,* Joshua A. Harrill,* Mark Higuchi,¶ Keith A. Houck,* Michael F. Hughes,¶ E. Sidney Hunter, III,¶ Kristin K. Isaacs,‡ Richard S. Judson,* Thomas B. Knudsen,* Jason C. Lambert,‖ Monica Linnenbrink,* Todd M. Martin,‖ Seth R. Newton,‡ Stephanie Padilla,¶ Grace Patlewicz,* Katie Paul-Friedman,* Katherine A. Phillips,‡ Ann M. Richard,* Reeder Sams,* Timothy J. Shafer,¶ R. Woodrow Setzer,* Imran Shah,* Jane E. Simmons,¶ Steven O. Simmons,* Amar Singh,* Jon R. Sobus,‡ Mark Strynar,‡ Adam Swank,‡ Rogelio Tornero-Valez,‡ Elin M. Ulrich,‡ Daniel L. Villeneuve,‖ John F. Wambaugh,* Barbara A. Wetmore,‡ and Antony J. Williams*

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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

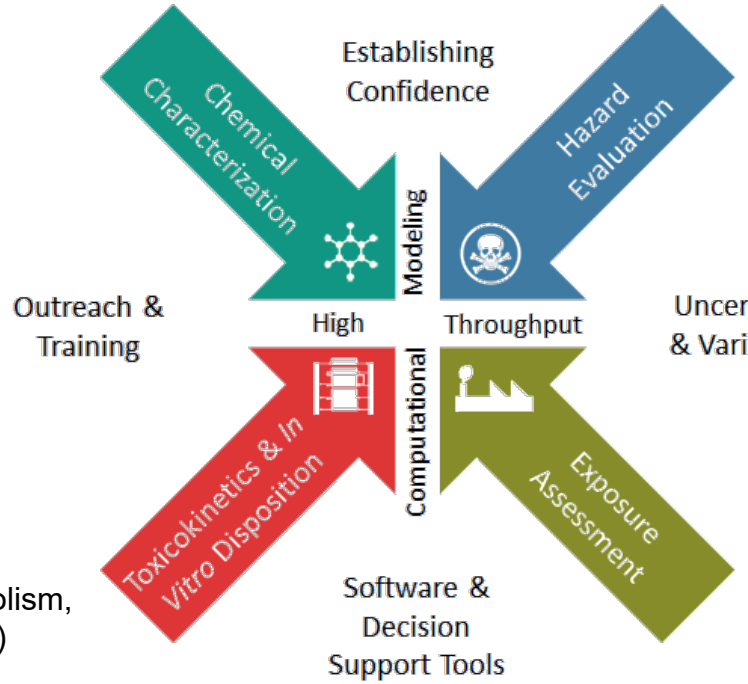
The U.S. Environmental Protection Agency (EPA) is faced with the challenge of efficiently and credibly evaluating chemical safety often with limited or no available toxicity data. The expanding number of chemicals found in commerce and the environment, coupled with time and resource requirements for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

Published by Oxford University Press on behalf of the Society of Toxicology 2019.

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

- Case Studies
- Reference Materials
- Reporting Templates

- In Vitro Assays (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

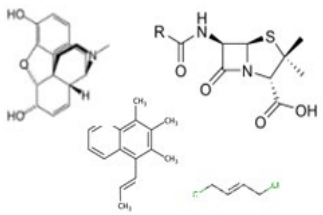
- SEEM
- ToxBoot
- HTTK
- ENTACT
- ToxRefDB

- 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

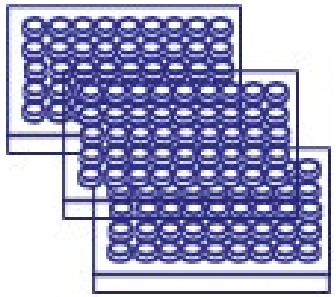
- ExpoCast
- NTA/SSA
- CPDat/CPCat
- Product emissivity

Application of High-Throughput Assays to Test Thousands of Chemicals



Thousands of Chemicals

Concentration Response Screening

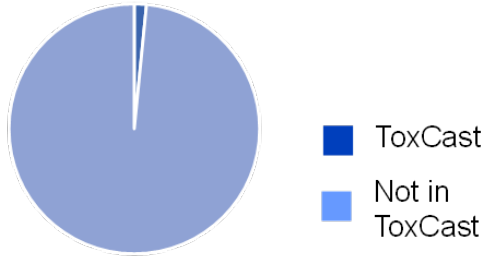


ToxCast Assays

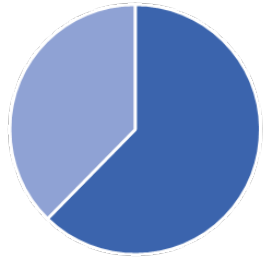
Transcription Factors
Transporter
Cytokines
Kinases
Nuclear Receptors
CYP450 / ADME
Cholinesterase
Phosphatases
Proteases
XME metabolism
GPCRs
Ion channels

~700 Assay Endpoints

Gene Coverage

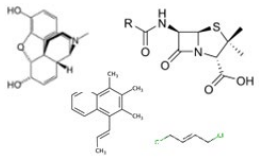


Pathway Coverage*

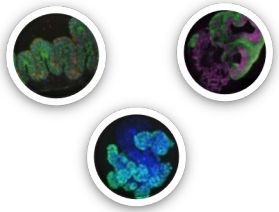


*At least one gene from pathway represented

Incorporating High-Content Technologies to Increase Biological Coverage

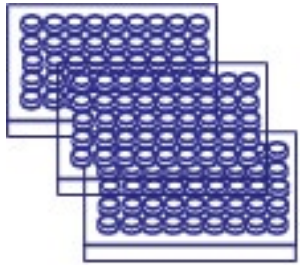


Thousands of Chemicals

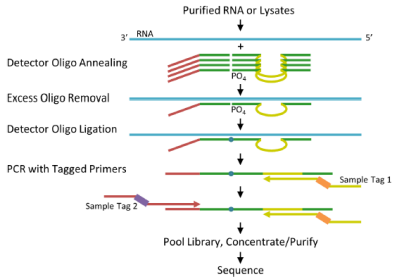


Multiple Cell Types

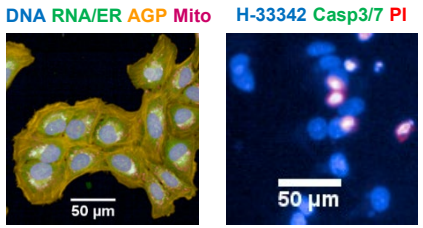
Concentration Response Screening



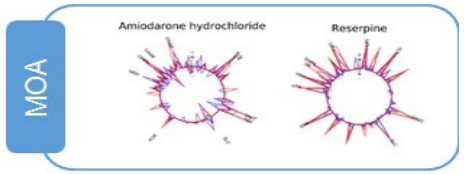
Whole Genome Transcriptomics



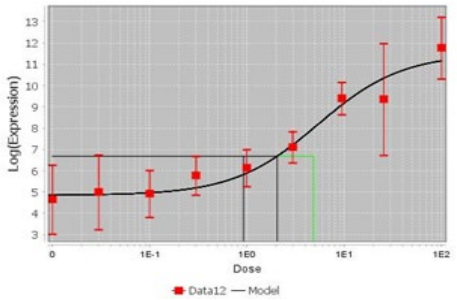
Multi-Parameter Cellular Phenotypic Profiling



Mode-of-Action Identification

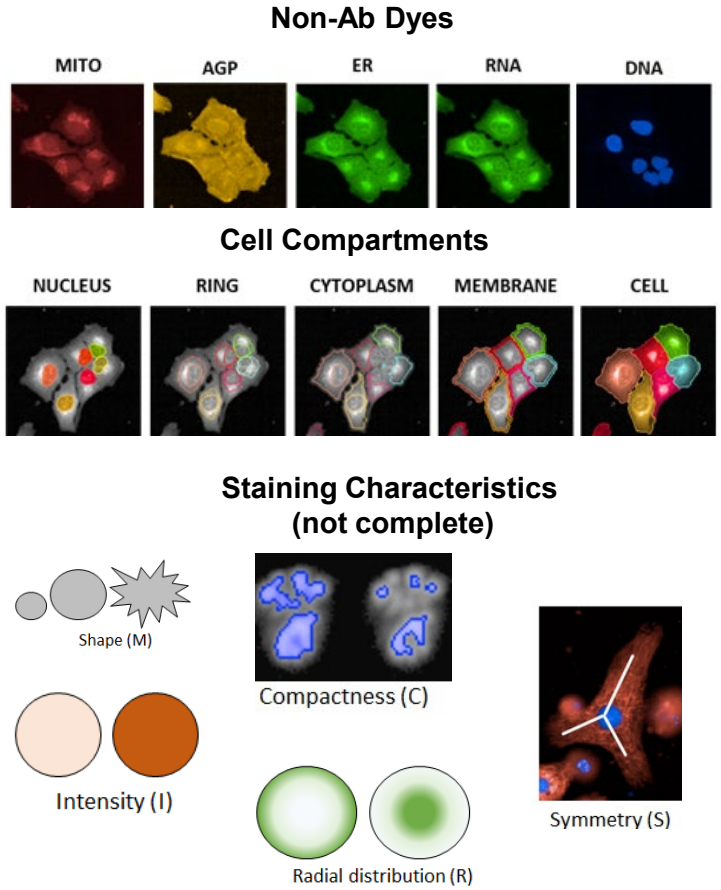


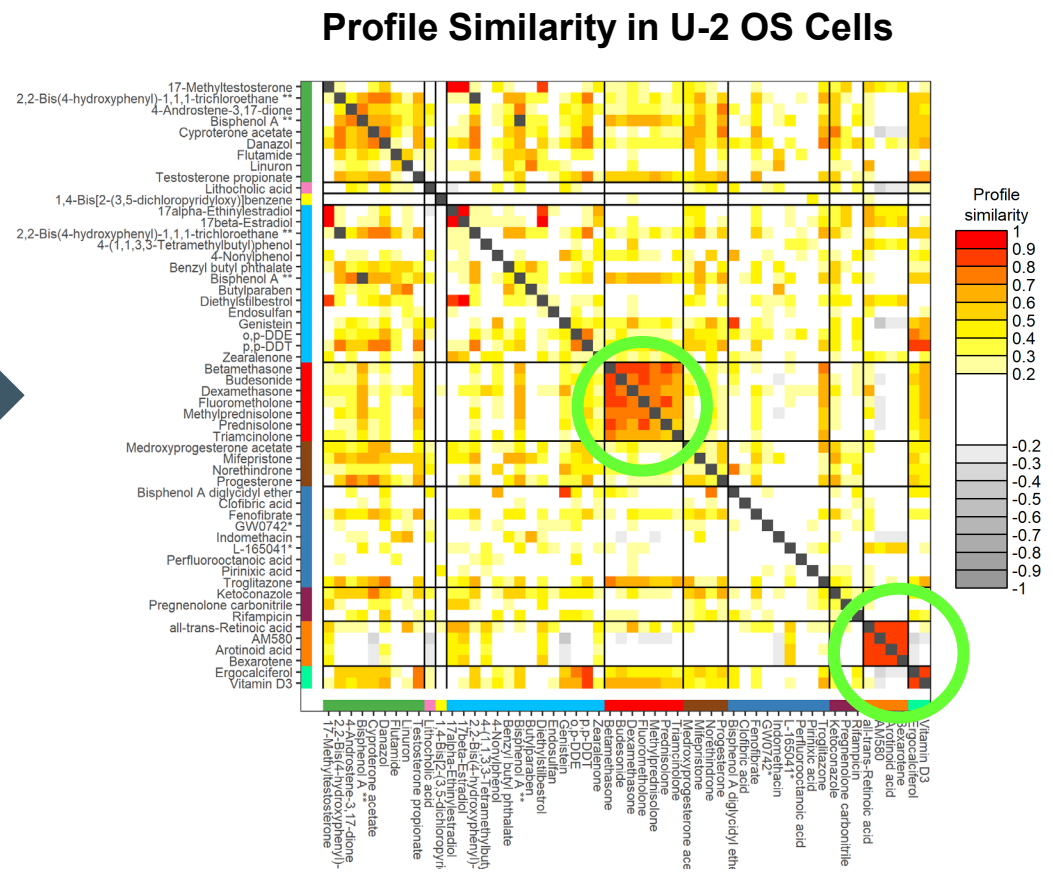
Concentration Response Modeling

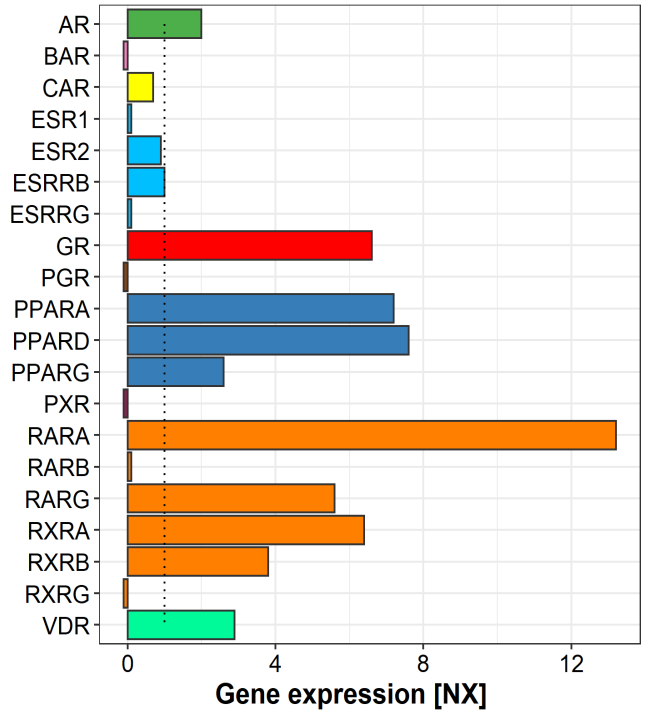


Increased Coverage of Important Pathways and Processes

Cellular Phenotypic Profiles Reflect Similarity in Molecular Mecanisms



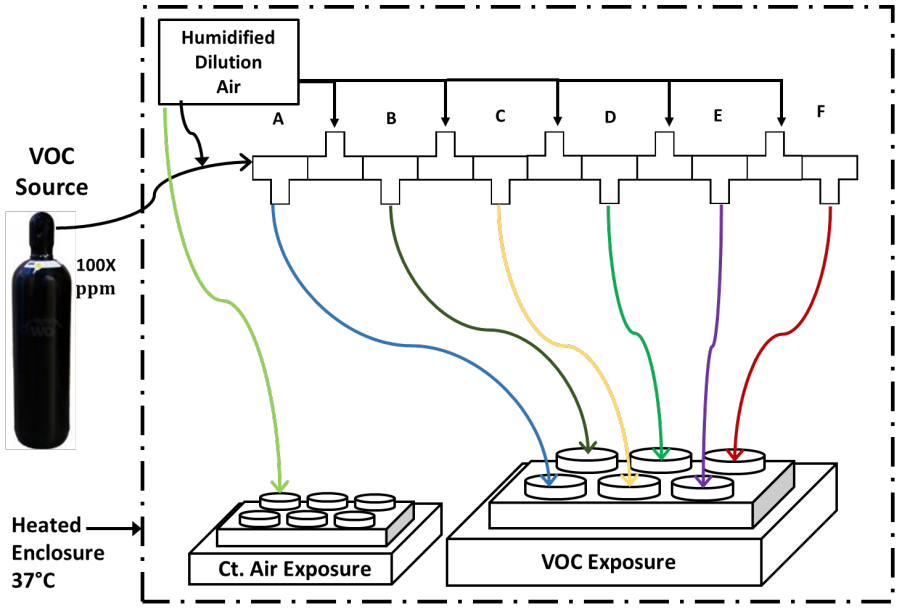


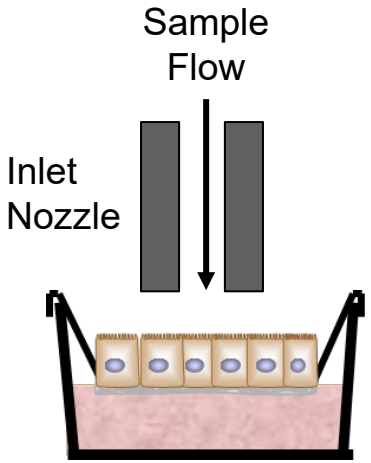


~1,300 total phenotypic endpoints

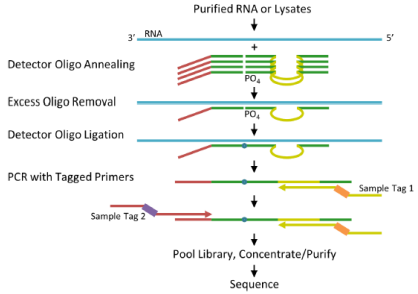
Nyffeler and Harrill, Unpublished

In Vitro Transcriptomic Points of Departure for Volatile Chemicals are Similar to Occupational Exposure Limits

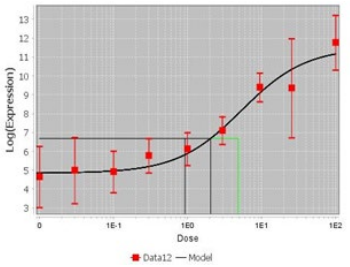




Whole Genome Transcriptomics (HTTr)



Concentration Response Modeling



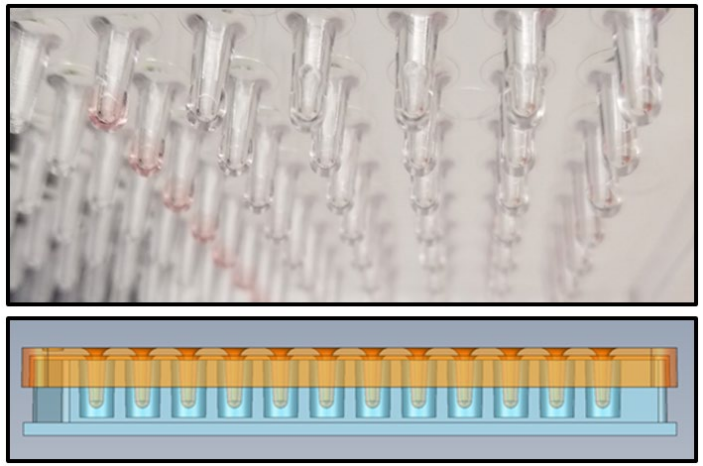
	ACGIH TLV-TWA (ppm)	BEAS-2B HTTr POD (ppm)	HBEC HTTr POD (ppm)
Acrolein	0.1	0.58	--
Formaldehyde	0.3	NA	--
1,3-Butadiene	10	13.98	--
Acetaldehyde	25	NA	--
1-Bromopropane	0.1 *	2.25	NA
Carbon Tetrachloride	10	9.56	NA
Trichloroethylene	50	44.8	28.1
Dichloromethane	100	142.13	266.7

* 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.

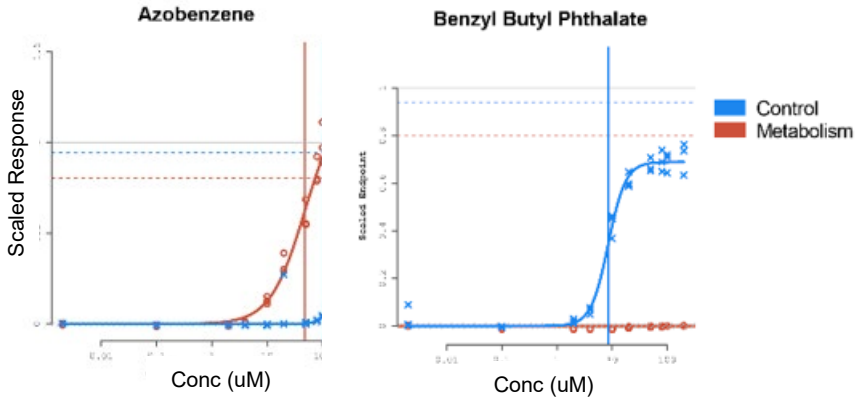
A.Speen (CPHEA), M. Higuchi (CPHEA), and J. Harrill, Unpublished

Retrofitting *In Vitro* Assays with Xenobiotic Enables Identification of Bio(in)activated Chemicals

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

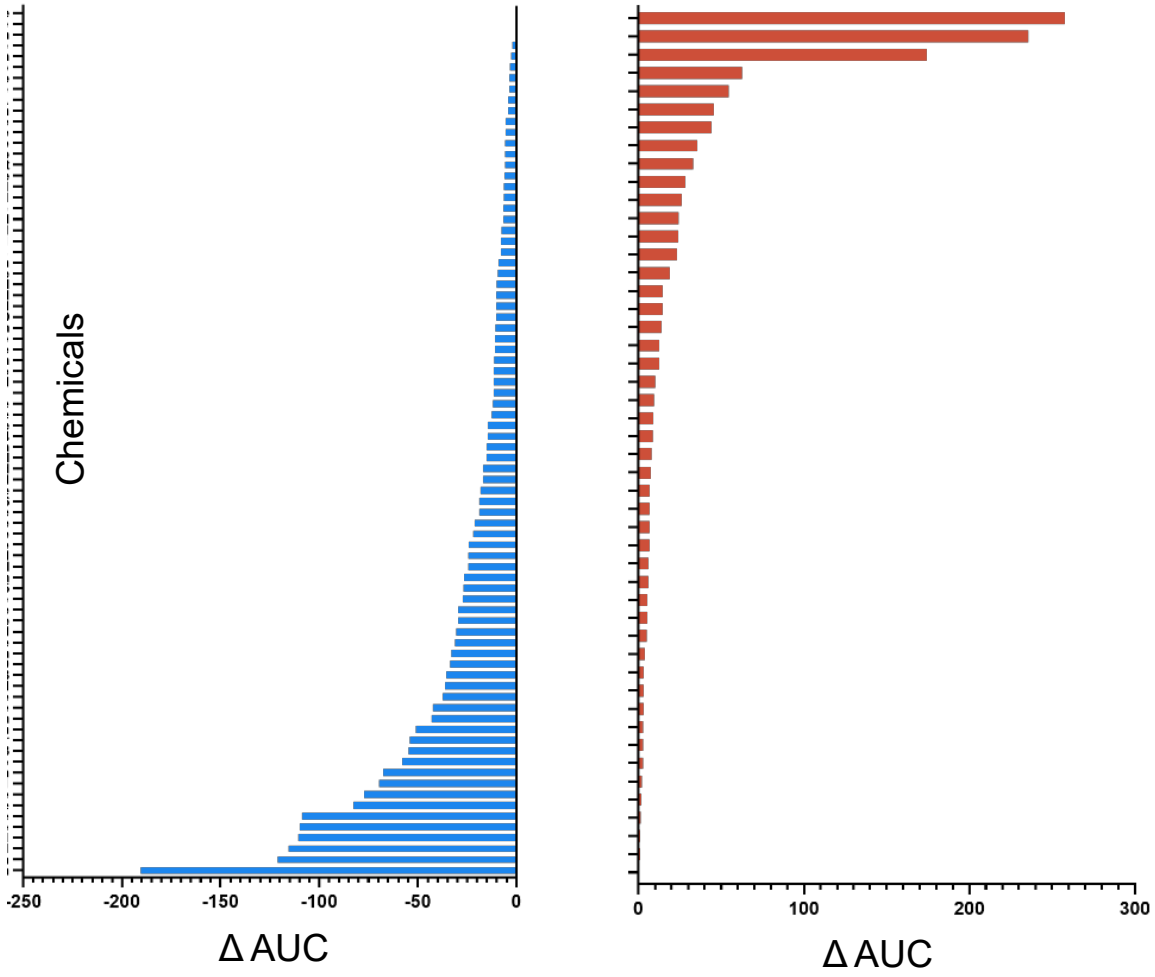


Application to ER Transactivation Assay (ERTA)
Pilot Screening Results of Pinto et al., 2016 Library



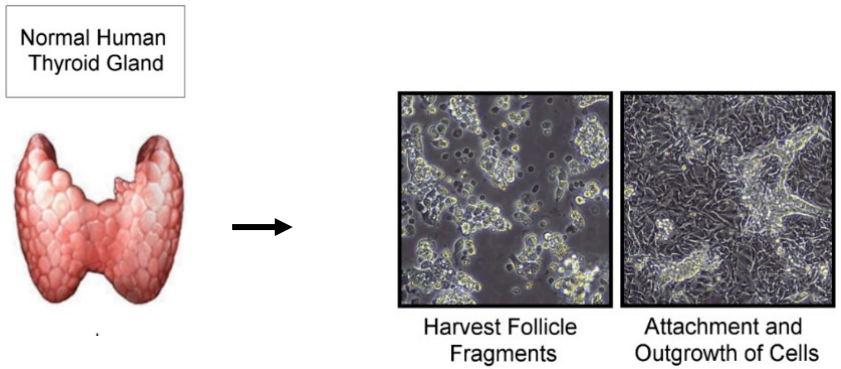
Deisenroth et al., Tox Sci, 2020

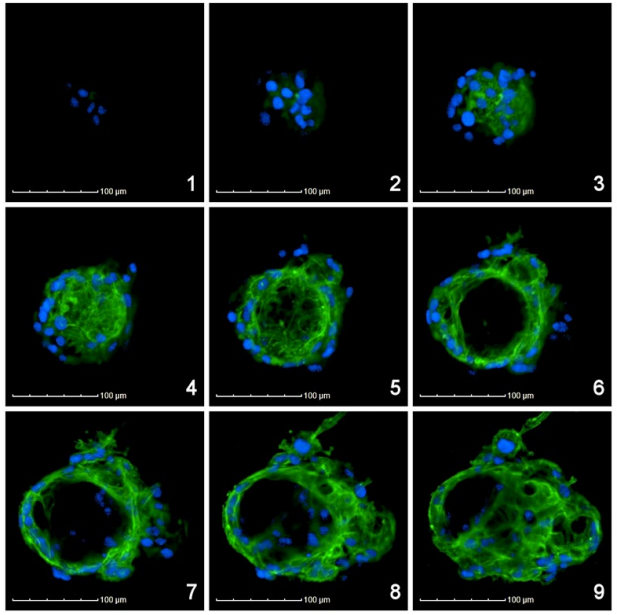
Preliminary Analysis of 768 ToxCast Chemical Screen



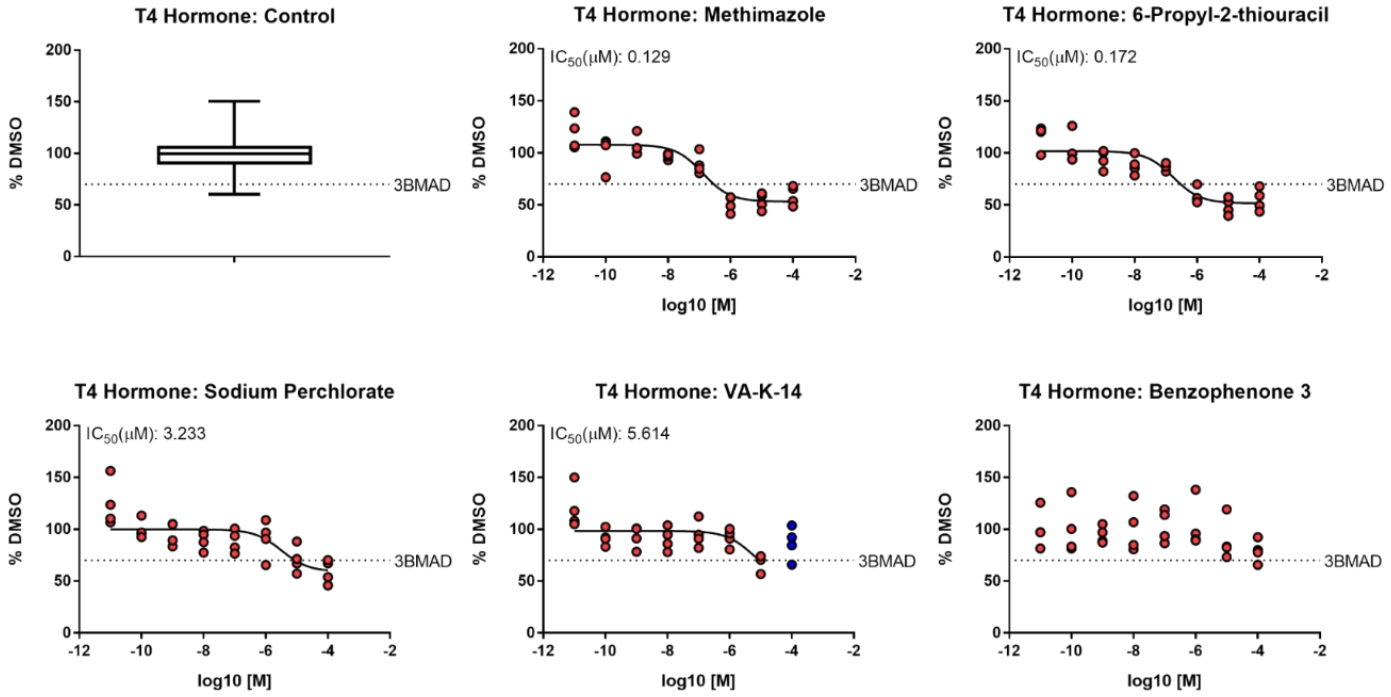
C. Deisenroth, Unpublished

Complex Organotypic Culture Models Enable Evaluation of Tissue/Organ Effects



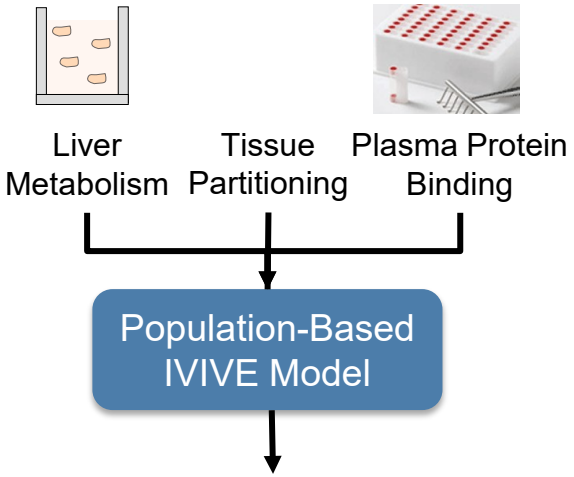


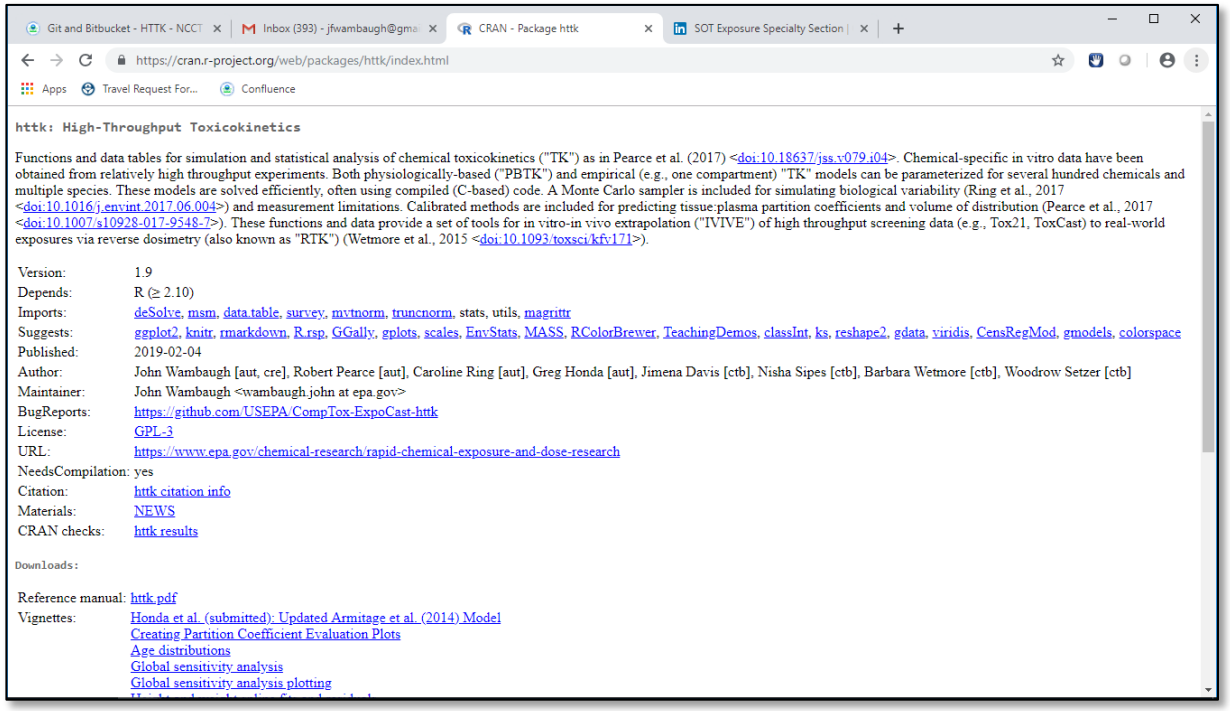
Blue, Hoechst 33342 /DNA
Green, Phalloidin/Actin



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

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





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:

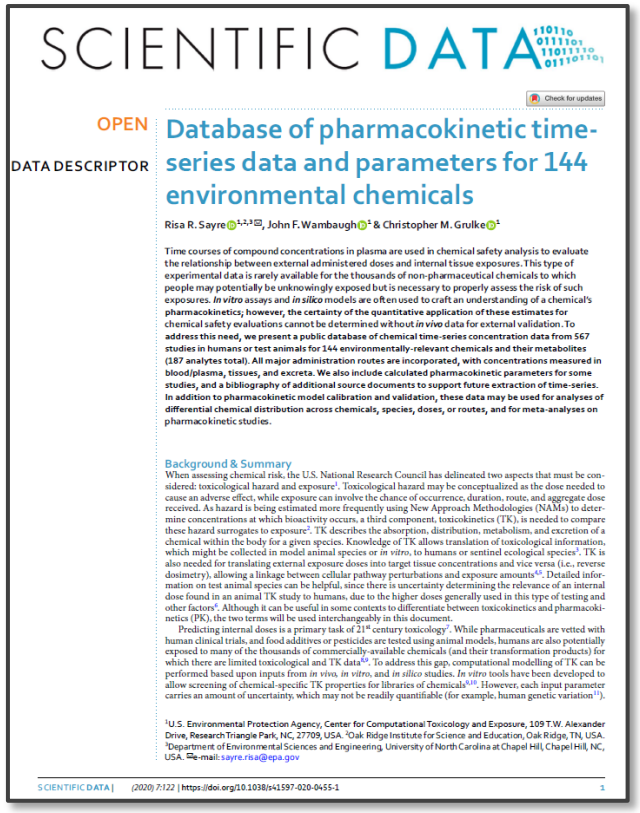
Reference manual:	httk.pdf
Vignettes:	Honda et al. (submitted): Updated Armitage et al. (2014) Model Creating Partition Coefficient Evaluation Plots Age distributions Global sensitivity analysis Global sensitivity analysis plotting

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

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

Extending High-Throughput Toxicokinetic Models to Inhalation Route



SCIENTIFIC DATA

OPEN

DATA DESCRIPTOR

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

Risa R. Sayre, John F. Wambaugh & Christopher M. Grulke

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[8,10]. However, each input parameter carries an amount of uncertainty, which may not be readily quantifiable (for example, human genetic variation[11]).

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Sayre *et al., Scientific Data.* 2020

142 Exposure Scenarios
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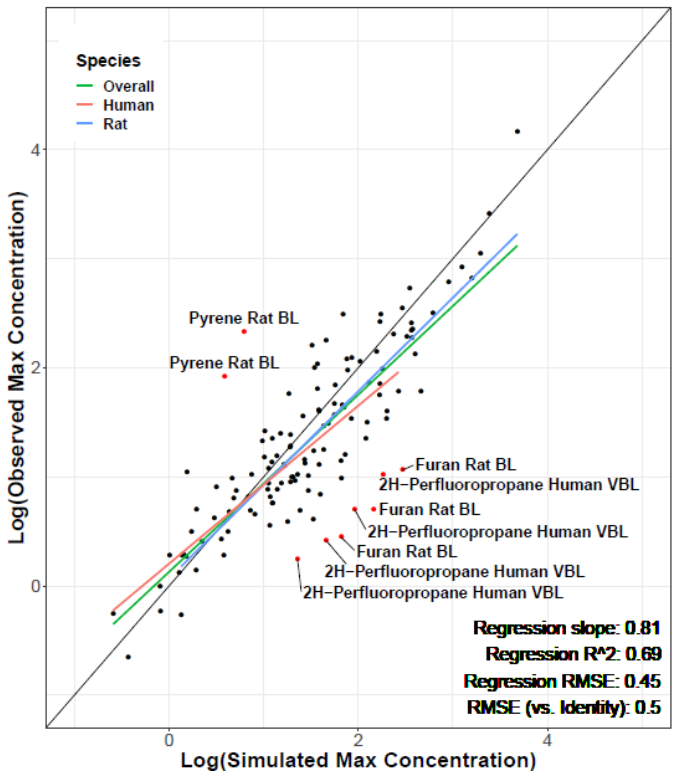

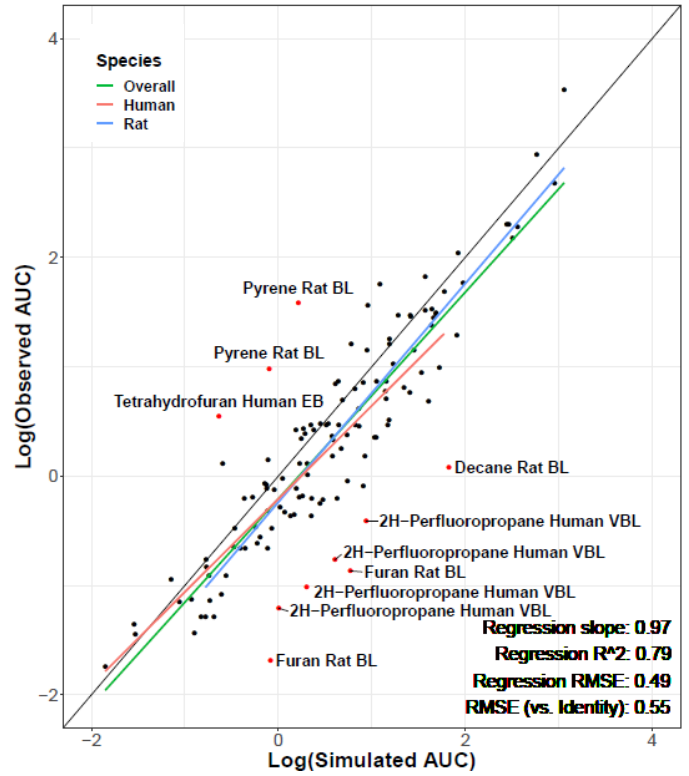

Linakis *et al., J Expo Sci Environ Epidemiol.* 2020

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