EPA
United States
Environmental Protection
Agency

Coming to Terms with the State of the Science in Environmental Toxicology and Defining a Path for the Future

NVT Annual Meeting

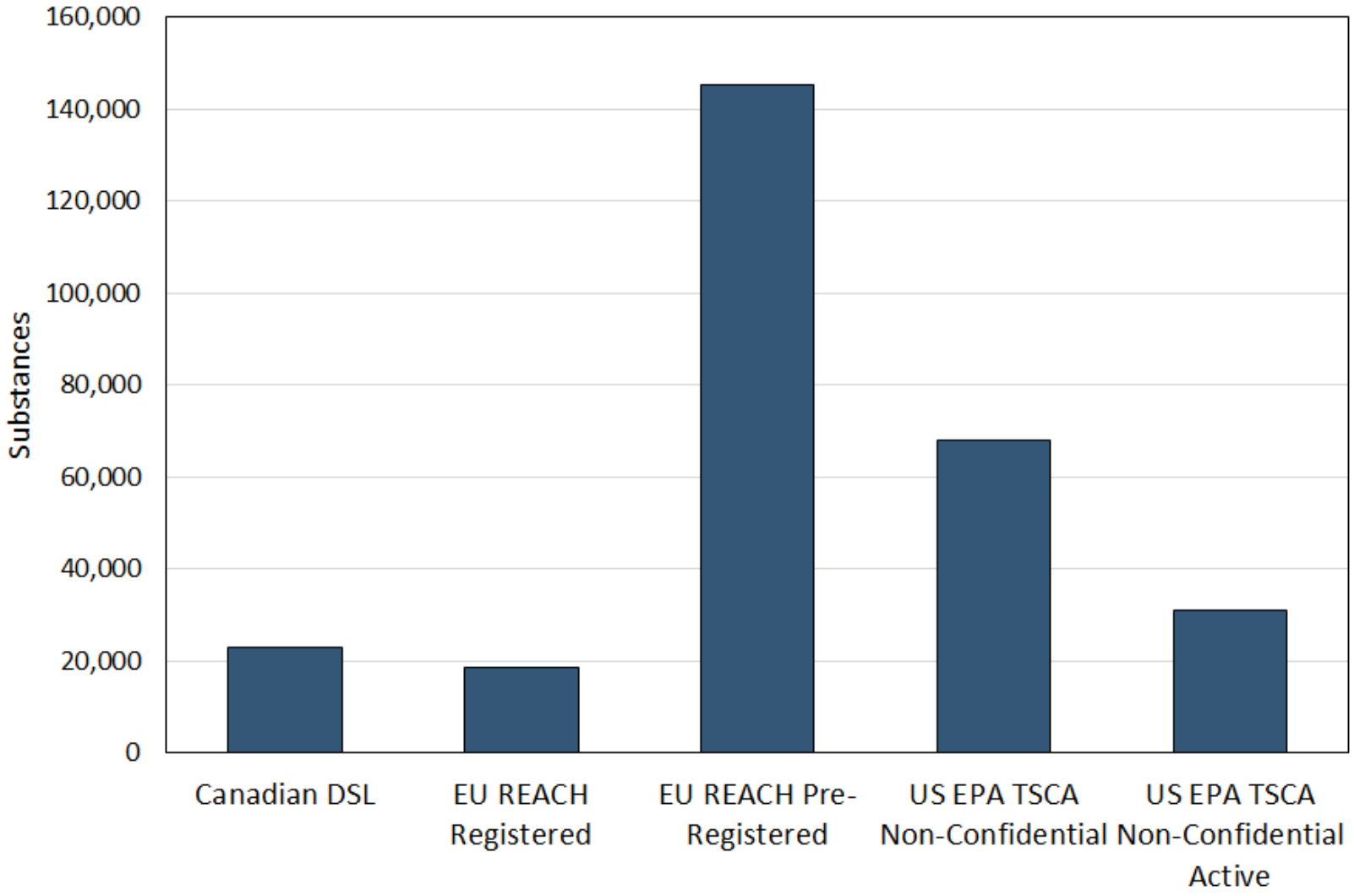
June 12, 2019

Rusty Thomas
Director
National Center for Computational Toxicology

On Milestone Birthdays, It is a Tradition to Examine Where We Are and Chart a Path for the Future…

EPA United States Environmental Protection Agency

Large Numbers of Chemicals in Commerce



Lack of Toxicity Data

Toxicity Testing

Strategies to Determine Needs and Priorities

Steering Committee on Identification of Toxic and Potentially Toxic Chemicals for Consideration by the National Toxicology Program

Board on Toxicology and Environmental Health Hazards

Commission on Life Sciences

National Research Council

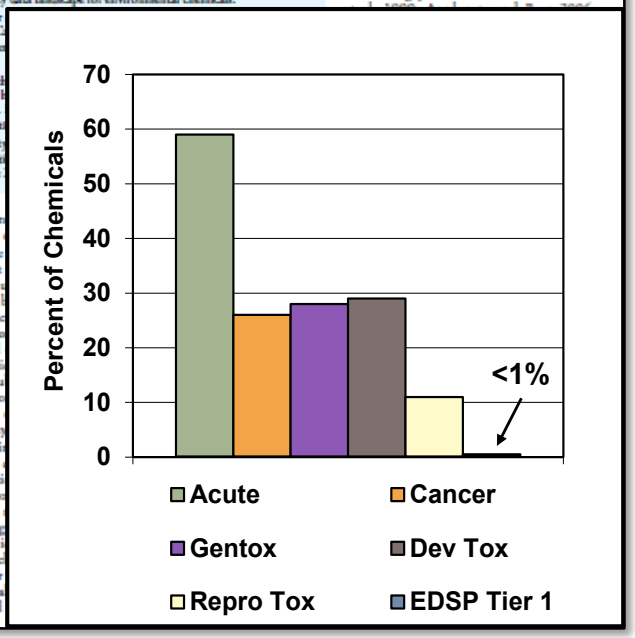
- Major challenge is too many chemicals and not enough data
- Total # chemicals = 65,725
- Chemicals with no toxicity data of any kind = ~46,000

NATIONAL ACADEMY PRESS
Washington, D.C. 1984

The Toxicity Data Landscape for Environmental Chemicals

Richard Judson,[1] Ann Richard,[1] David J. Dix,[1] Keith Houck,[1] Matthew Martin,[1] Robert Kavlock,[1] Vicki Dellarco,[2] Tala Henry,[3] Todd Holderman,[3] Philip Sayre,[3] Shirlee Tan,[4] Thomas Carpenter,[5] and Edwin Smith[6]

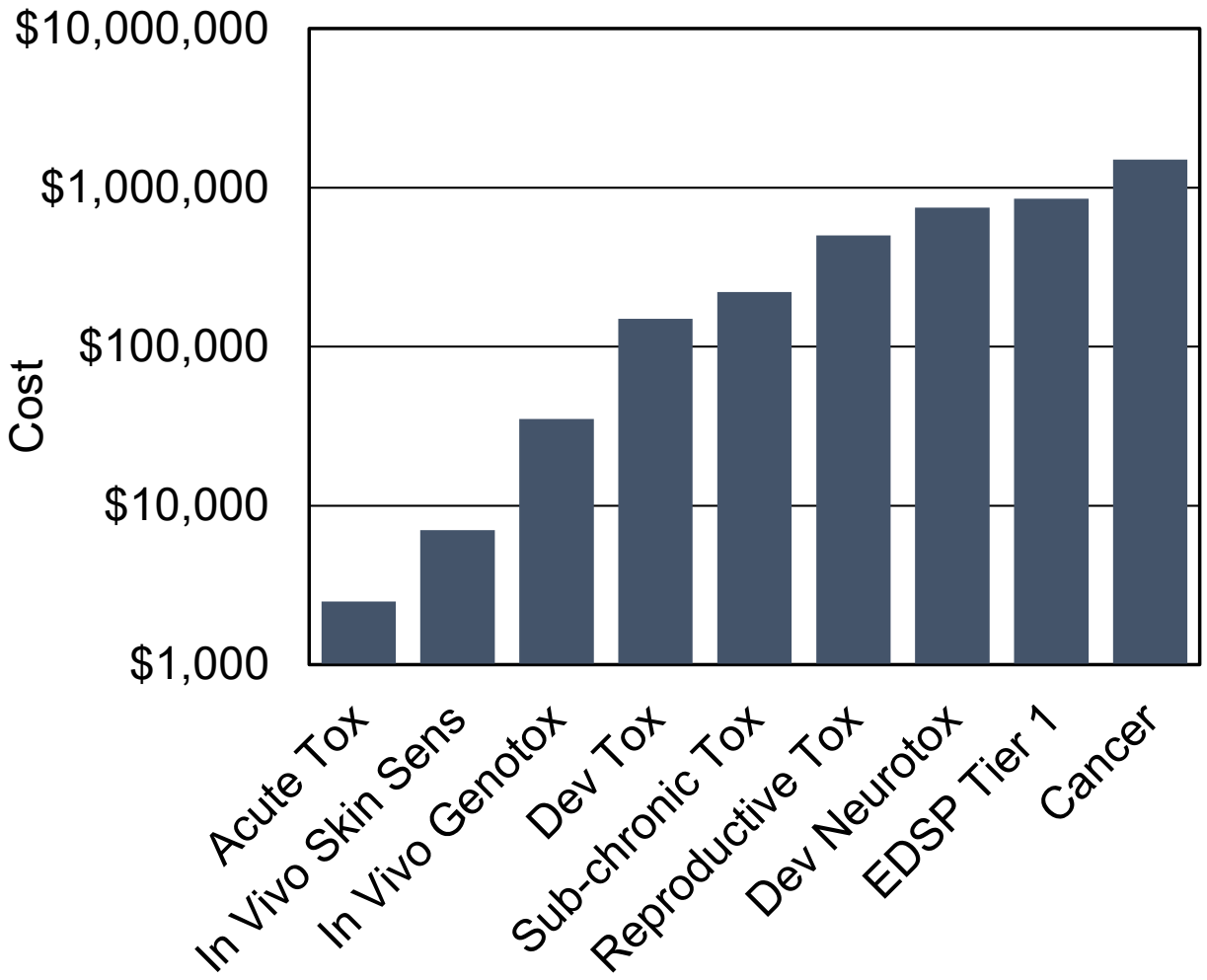
[1]National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA; [2]Office of Pesticide Programs, Office of Prevention, Pesticides, and Toxic Substances, U.S. Environmental Protection Agency, Arlington, Virginia, USA; [3]Office of Pollution Prevention and Toxics and [4]Office of Science Coordination and Policy, Office of Prevention, Pesticides, and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC, USA; [5]Office of Water, Office of Ground Water and Drinking Water, U.S. Environmental Protection Agency, Washington, DC, USA; [6]Great Lakes National Program Office, U.S. Environmental Protection Agency, Chicago, Illinois, USA



Modified from Judson *et al.*, EHP 2009

EPA
United States
Environmental Protection
Agency

Costs of Traditional Toxicity Testing



EPA
United States
Environmental Protection
Agency

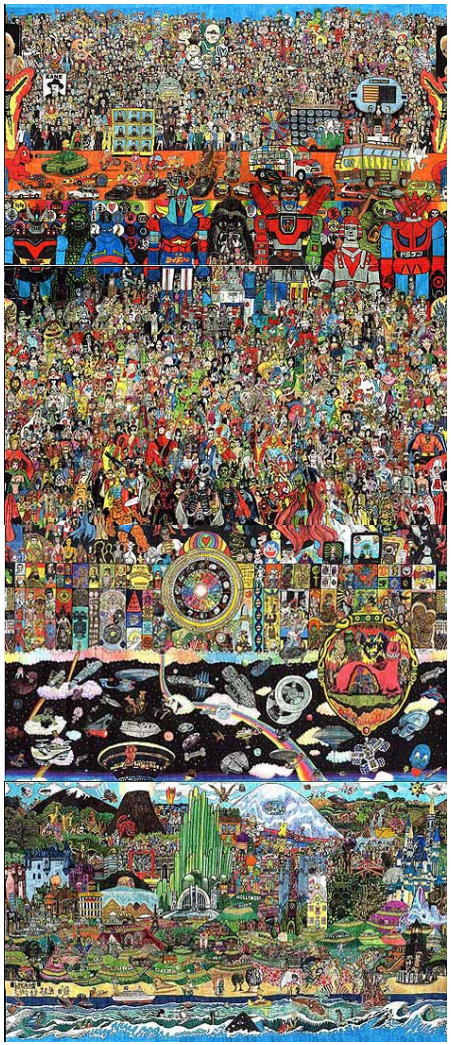
That Is Not a Great Way to Start a Birthday…

EPA United States Environmental Protection Agency

Charting a New Path for Toxicology

- Incorporate technological advances to evaluate large numbers of chemicals across toxicological space
- Systematically address limitations of *in vitro* test systems
- Put results in a dose and exposure context
- Characterize variability and relevance of current toxicological test systems
- Delivery of data and models through decision support tools
- Building confidence through regulatory focused case studies

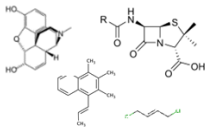
Toxicology is Analogous to Trying to Create a 'Picture of Everything'



Picture of Everything
Howard Hallis

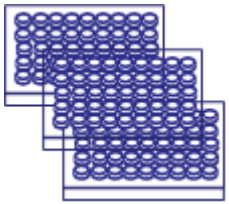
- In 1997 an artist named Howard Hallis started drawing a 'Picture of Everything', it took 13 years to complete, stands at 15 x 14 feet.
- The ideal toxicity testing approach provides comprehensive coverage of relevant toxicological responses
- It should identify the mechanism/mode-of-action (with dose-dependence)
- It should identify responses relevant to the species of interest and include consideration of metabolism (detoxification/bioactivation)
- Responses should ideally be translated into tissue-, organ-, and organism-level effects
- It must be economical and scalable

Application of High-Throughput Assays to Test Thousands of Chemicals



Thousands of Chemicals

Concentration Response Screening

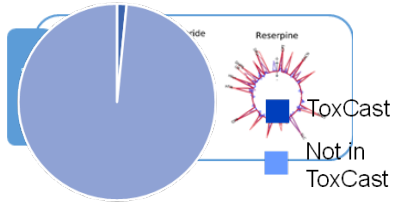


ToxCast Assays

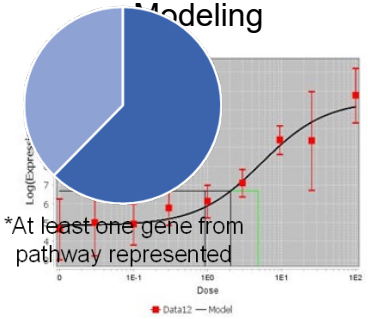
Transcription Factors
Transporter
Cytokines
Kinases
Nuclear Receptors
CYP450 / ADME
Cholinesterase
Phosphatases
Proteases
XME metabolism
GPCRs
Ion channels

~700 Assay Endpoints

Gene Coverage Mode-of-Action Identification



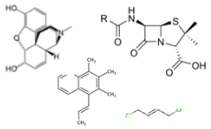
Pathway Coverage* Concentration Response Modeling



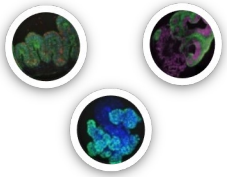
*At least one gene from pathway represented

- 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

Incorporating High-Content Technologies to Increase Biological Coverage

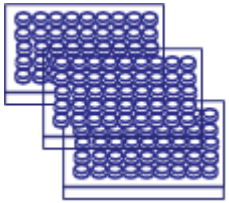


Thousands of Chemicals

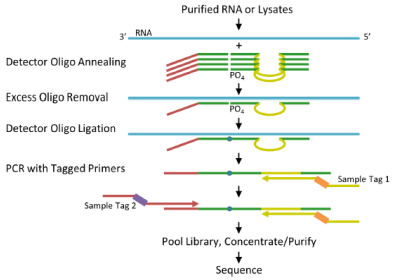


Multiple Cell Types

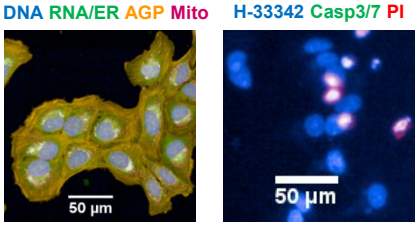
Concentration Response Screening



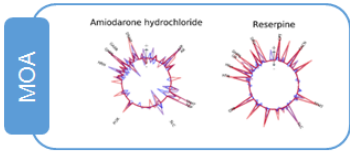
Whole Genome Transcriptomics



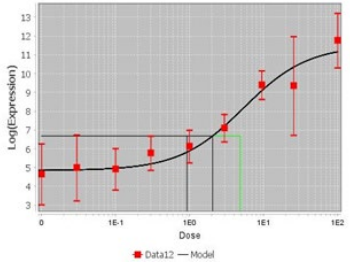
Multi-Parameter Cellular Phenotypic Profiling



Mode-of-Action Identification



Concentration Response Modeling



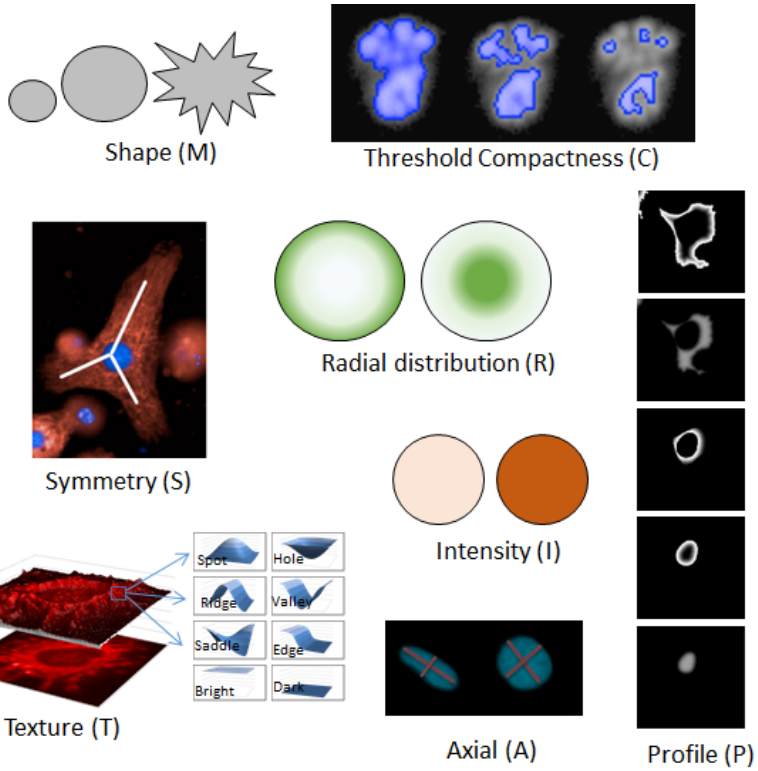
- 384-well, laboratory automation compatible
- Relatively inexpensive ($2.50 - $1,500 per chemical)
- Broad complementary coverage of molecular and phenotypic responses
- Integration of reference materials and controls for performance standards
- Increased portability

High-Throughput Phenotypic Profiling as a Measure of 'Cellular Pathology'

United States Environmental Protection Agency

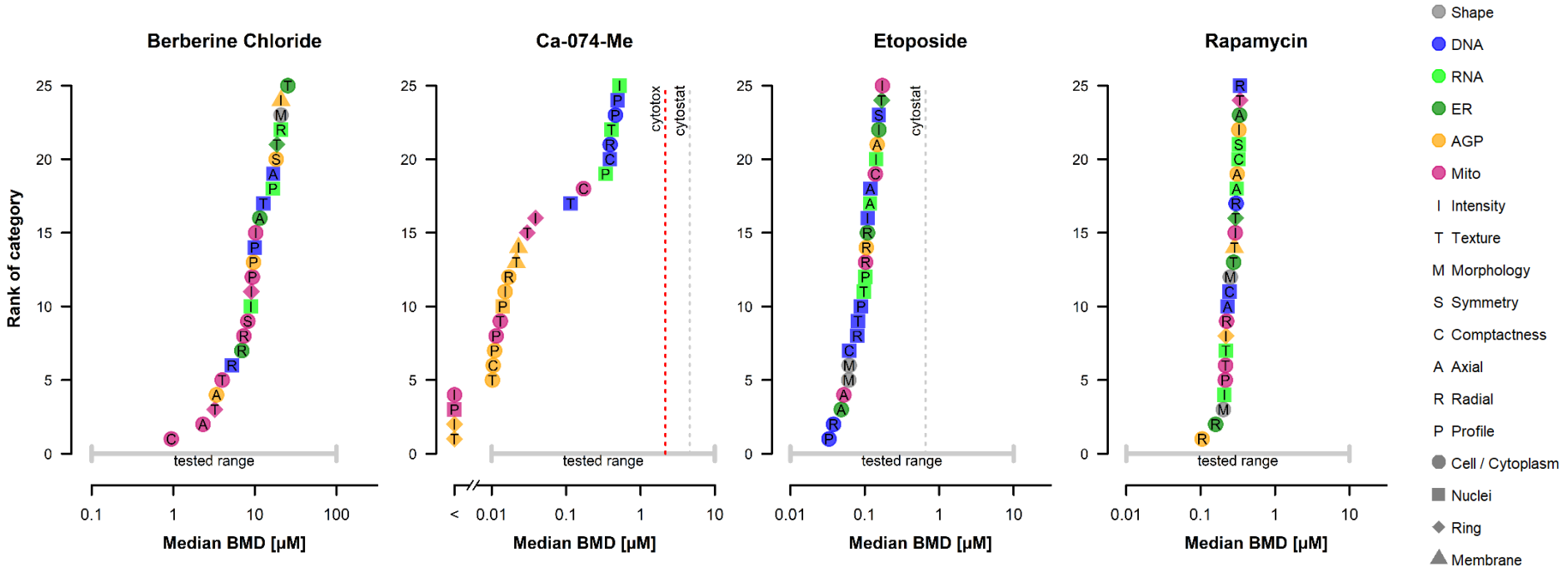
Cell Compartments

Non-Ab Dyes	NUCLEUS	RING	CYTOPLASM	MEMBRANE	CELL
DNA	S,C,A,R, P,I,T,M	--	--	--	S,C,A,R, P,M
RNA	S,C,A,R, P,I,T	--	--	--	S,C,A,R, P
ER	S,C,A,R, P,I,T	I,T	I,T	I	S,C,A,R, P
AGP	S,C,A,R, P,I,T	I,T	I,T	I,T	S,C,A,R, P
MITO	S,C,A,R, P,I,T	I,T	I,T	I	S,C,A,R, P



~1,300 total phenotypic endpoints

Unique Phenotypic Responses Associated with Different MOAs

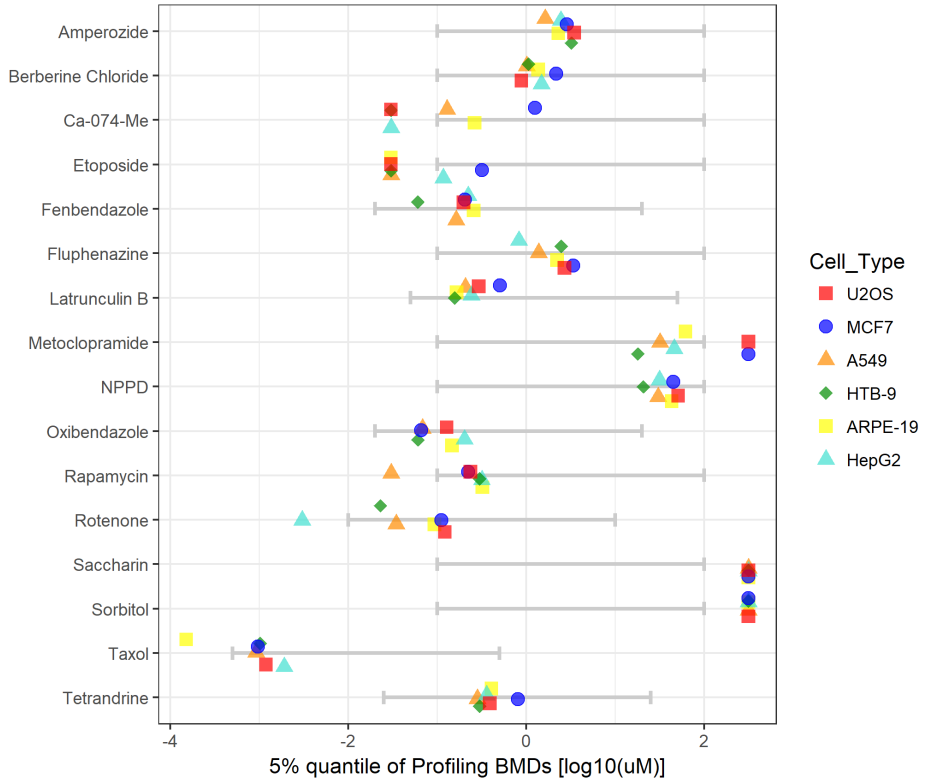


J. Nyffeler, J. Harrill, Unpublished

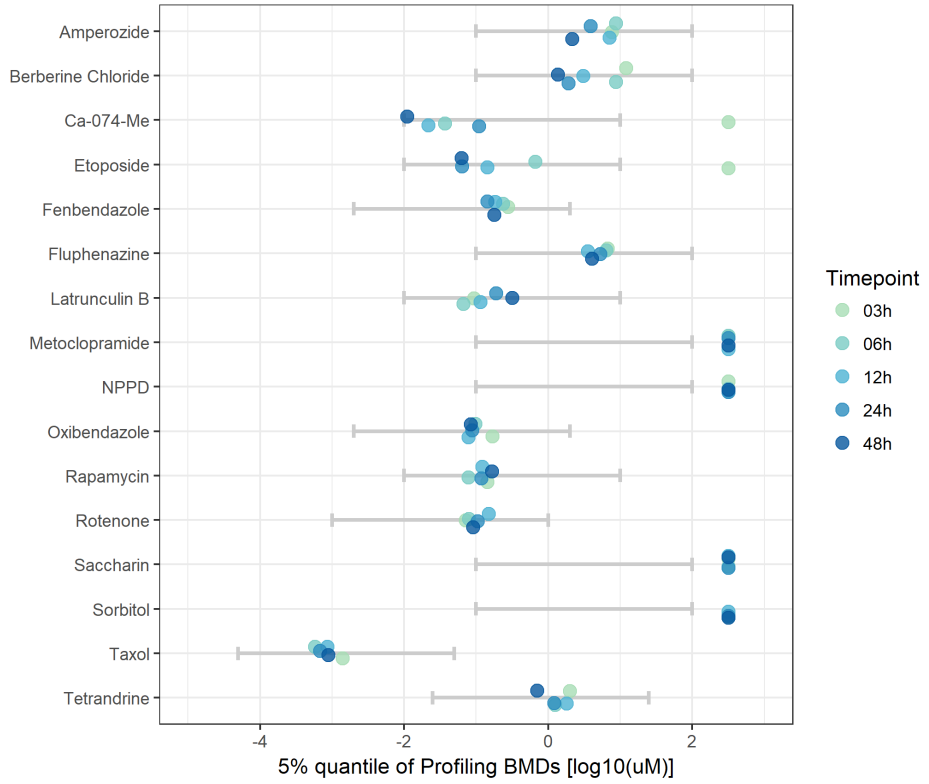
Variation in Phenotypic Potencies Across Cell Type and Time

United States Environmental Protection Agency

Cell Type Differences (48 hr)



Time Point Differences (U2OS cells)

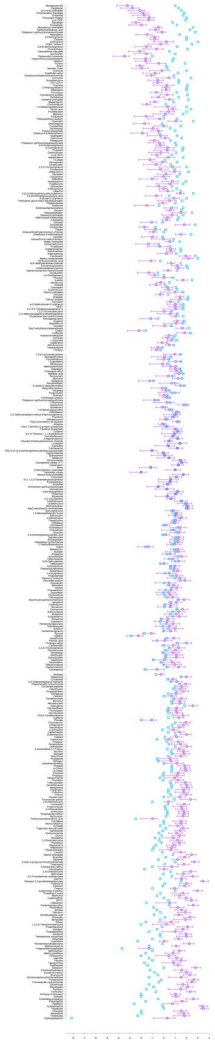


*Data points represent 5th percentile of phenotypic BMDs

Tested range

J. Nyffeler, J. Harrill, Unpublished

Comparing 'Cellular Pathology' with *In Vivo* Effects



Chemicals

Log10 Dose (mg/kg bw)

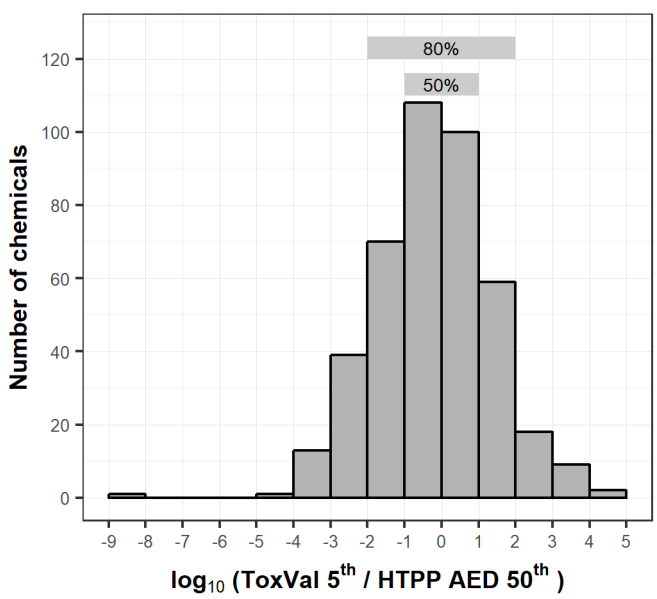
In Vivo POD

Profiling POD

Chemicals Where Cellular Effects are Not Protective

Chem.Name	MoA / Target
Diethylstilbestrol	estrogenic
Profenofos	inhibition of cholinesterase
Mevinphos	inhibition of cholinesterase
	holinesterase
	holinesterase
	cetylcholinesterase
	ıibition of acetylcholine
	or
	cetylcholinesterase
	cetylcholinesterase
	cetylcholinesterase
	cetylcholinesterase
	cetylcholinesterase
	cetylcholinesterase
	ıibition of acetylcholine
Methamidophos	potentially inhibition of acetylcholine
Clodinafop-propargyl	

Using a single cell type (U2OS), ~50% are within 10-fold



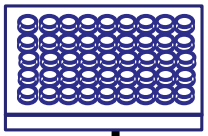
*Results from a single cell type

J. Nyffeler, J. Harrill, Unpublished

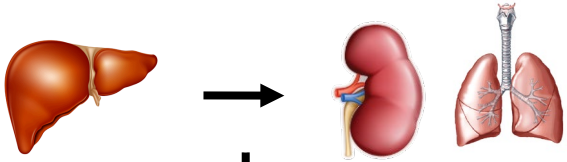
Incorporating Xenobiotic Metabolism in *In Vitro* Test Systems

"Extracellular" Approach

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

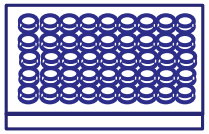


More closely models effects of hepatic metabolism and generation of circulating metabolites

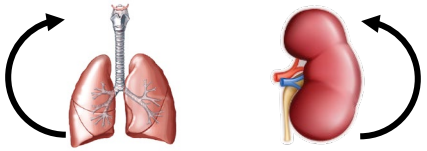


"Intracellular" Approach

Chemical metabolism inside the cell in cell-based assays



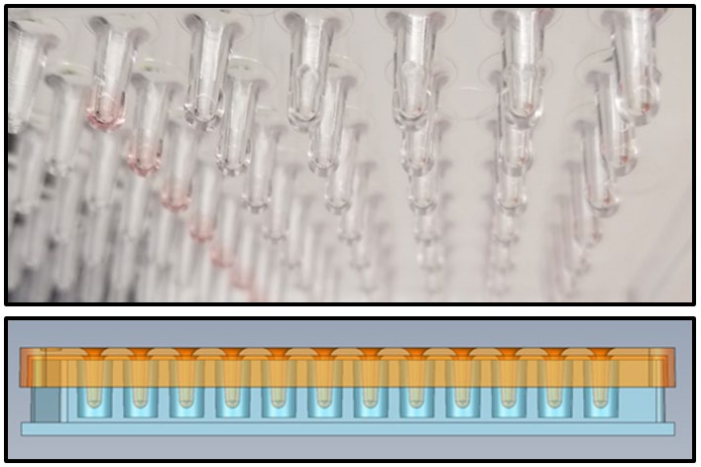
More closely models effects of target tissue metabolism



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

Application of Extracellular Strategy to Identify Estrogenic Metabolites

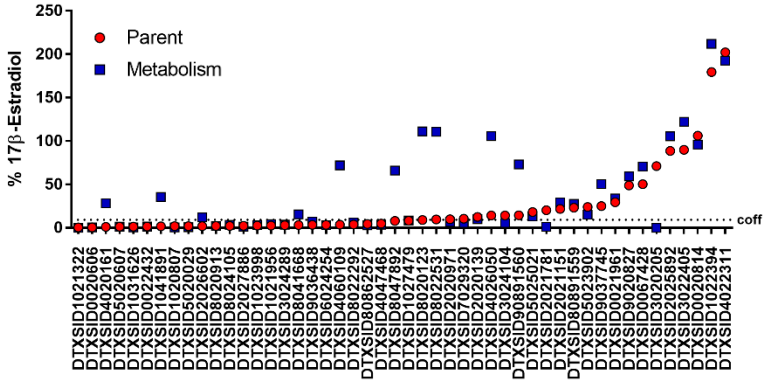
AIME Method: S9 Fraction Immobilization in Alginate Microspheres on 96- or 384-well peg



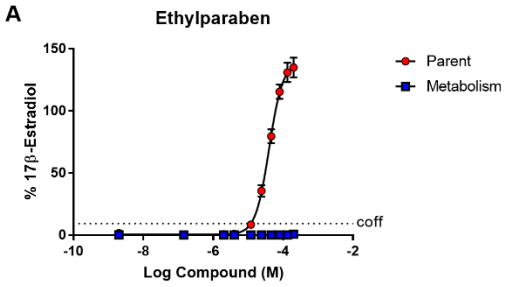
Screening Window of VM7 (formerly BG1) ER Transactivation Assay

		Metabolism	
		Neg	Pos
NRS	Neg	0.91	0.89
	Pos	0.91	0.71
		Z'	

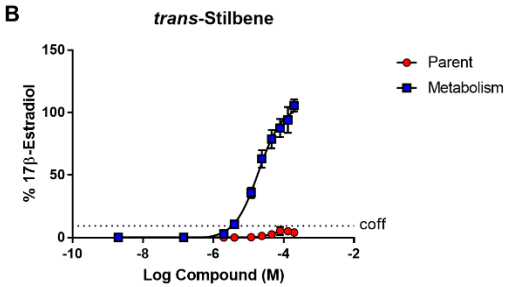
Pilot Screening Results of Pinto et al., 2016 Library



Example Detoxification



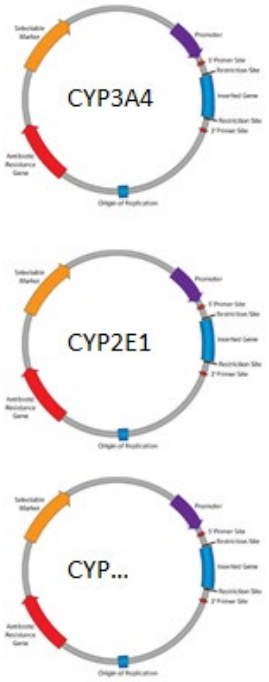
Example Bioactivation



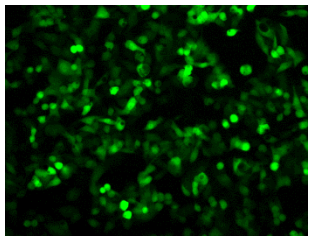
D. DeGroot, C. Deisenroth, Unpublished

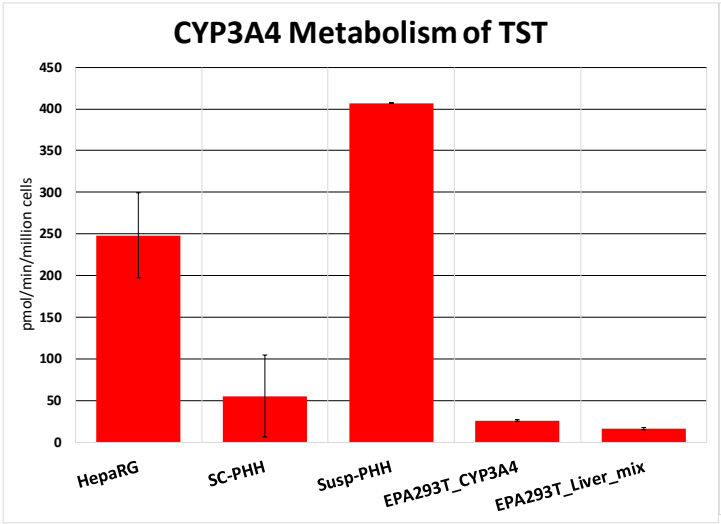
Application of Intracellular Strategy to Identify Cytotoxic Metabolites

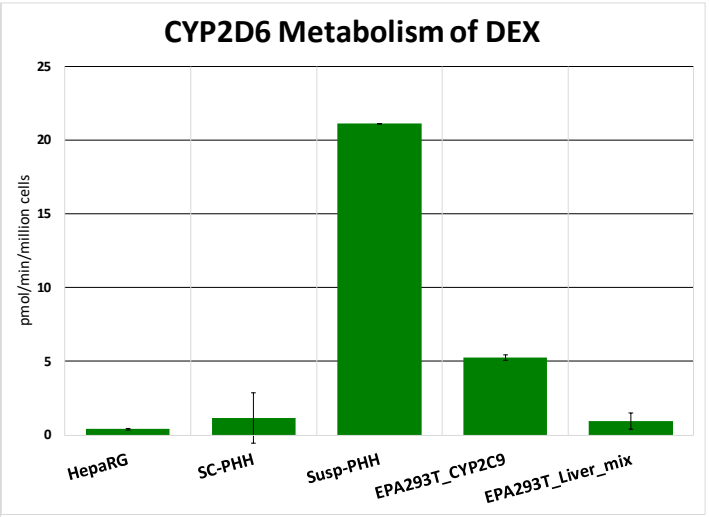
United States Environmental Protection Agency

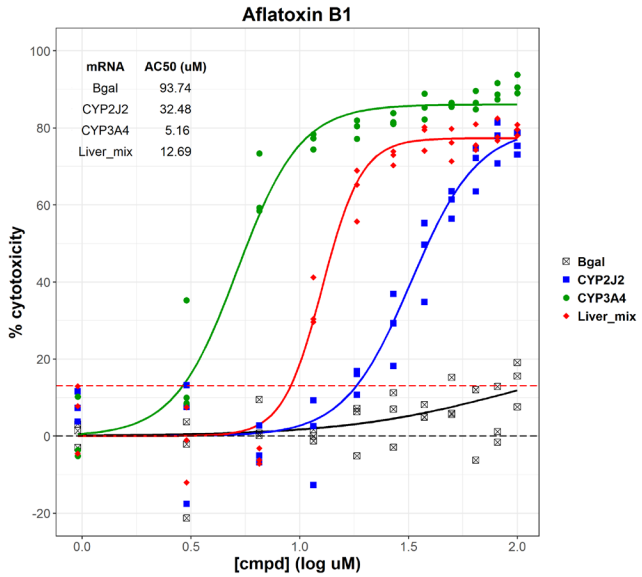


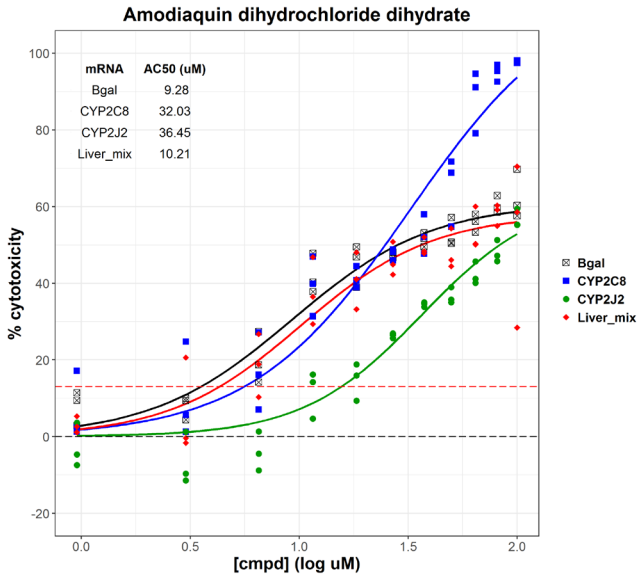
mRNA







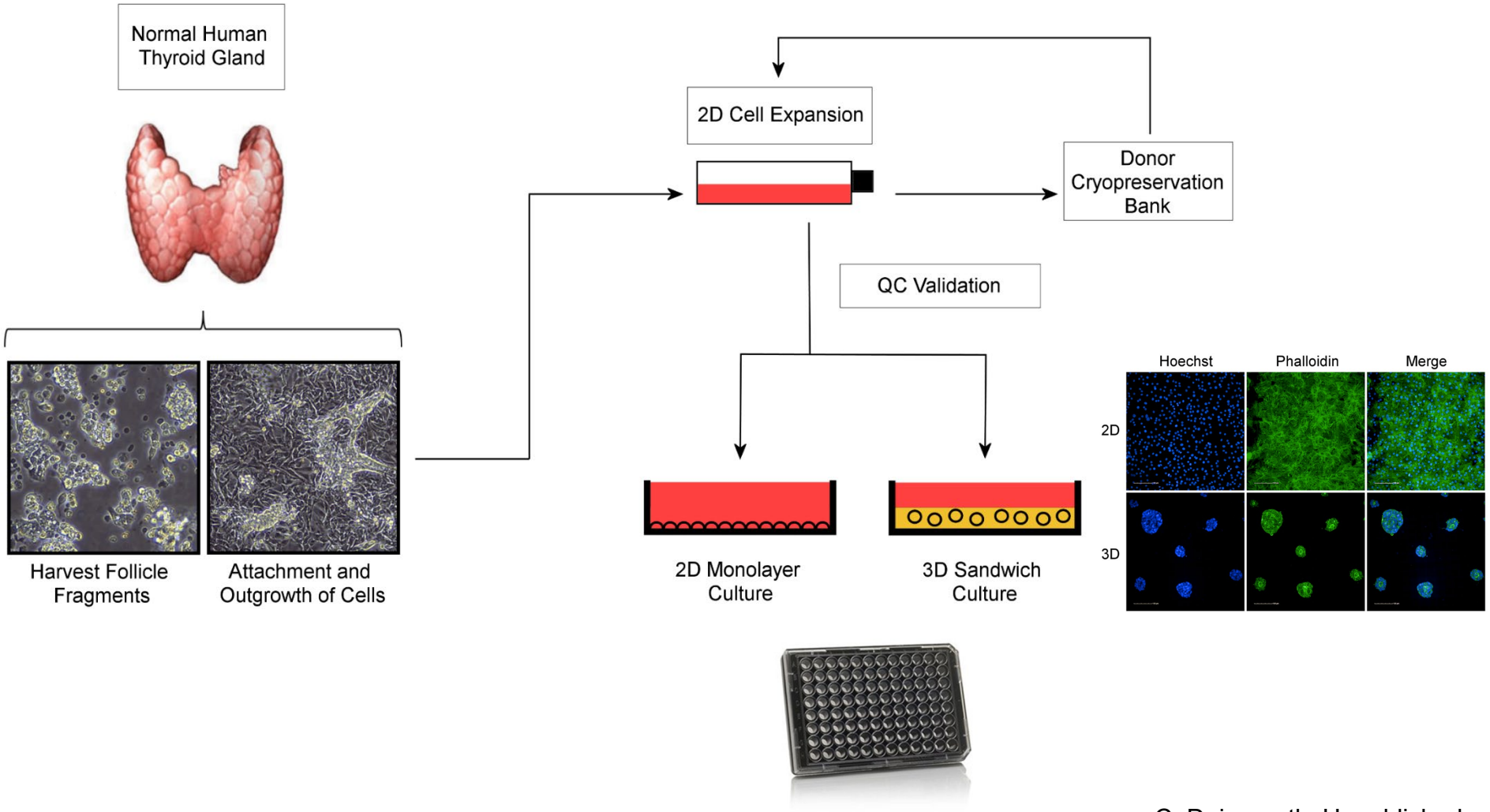




Simmons et al., 2018

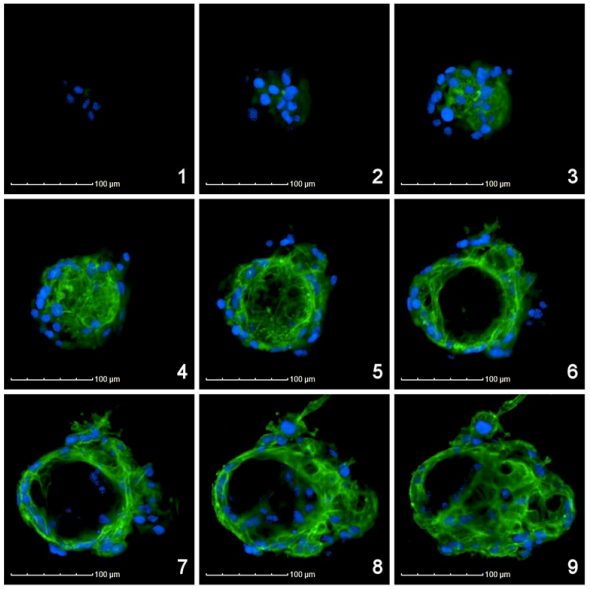
National Center for Computational Toxicology

Developing Organotypic Culture Models to Identify Tissue/Organ Effects



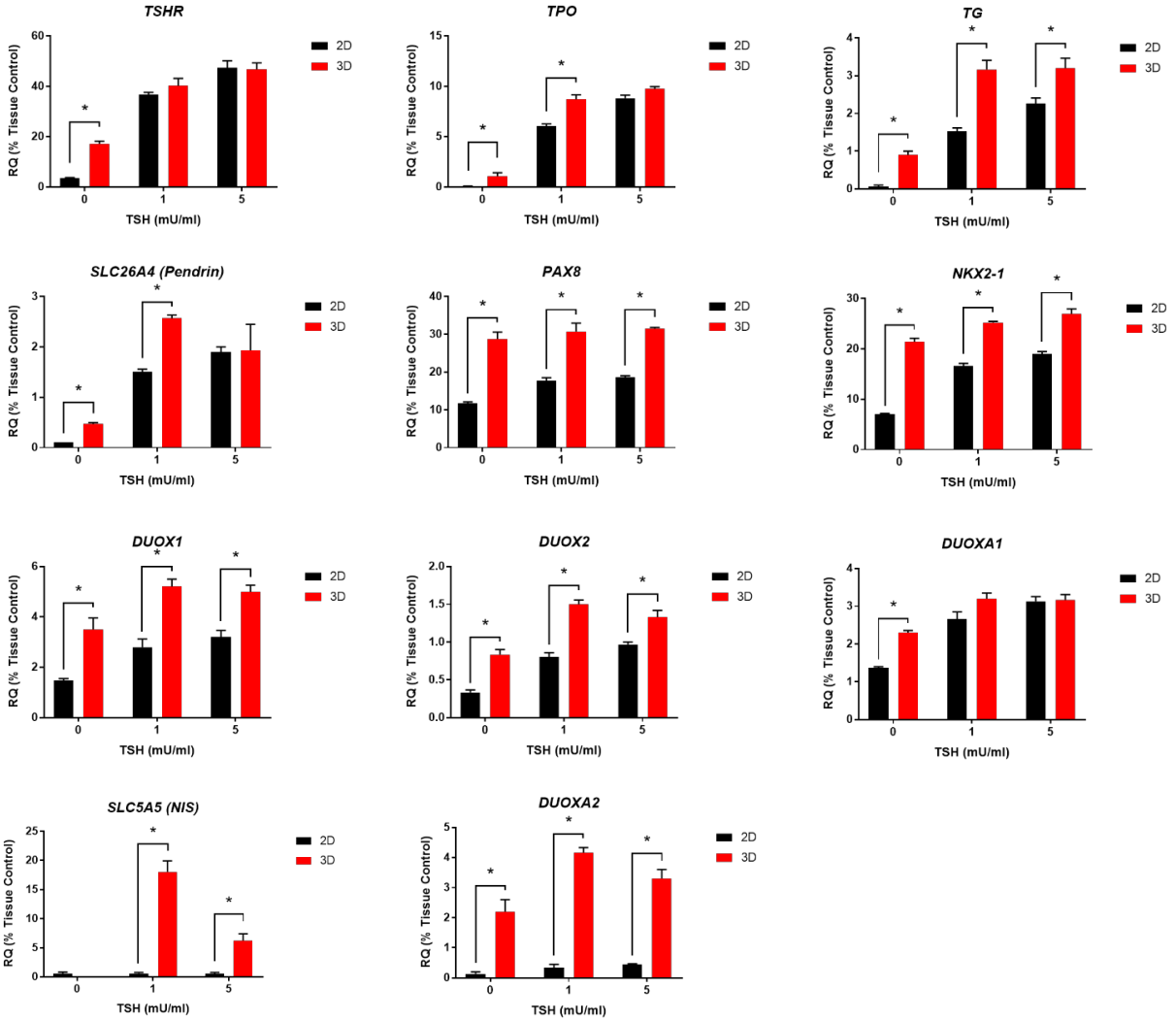
C. Deisenroth, Unpublished

3D Thyroid Model Shows More Relevant Structure and Gene Expression

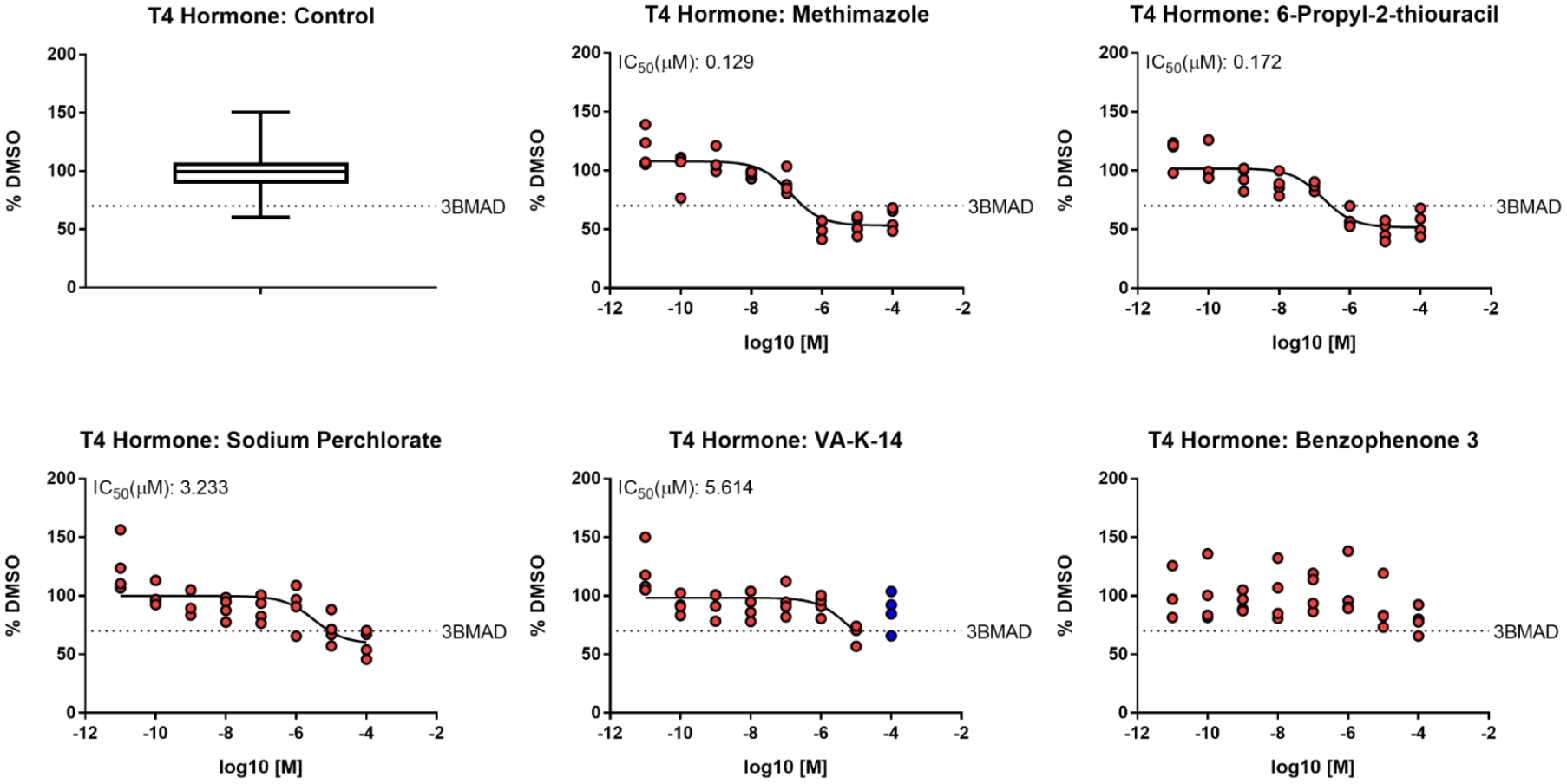


Blue, Hoechst 33342 /DNA
Green, Phalloidin/Actin

C. Deisenroth, Unpublished



Inhibition of Thyroid Hormone Synthesis by Reference Chemicals



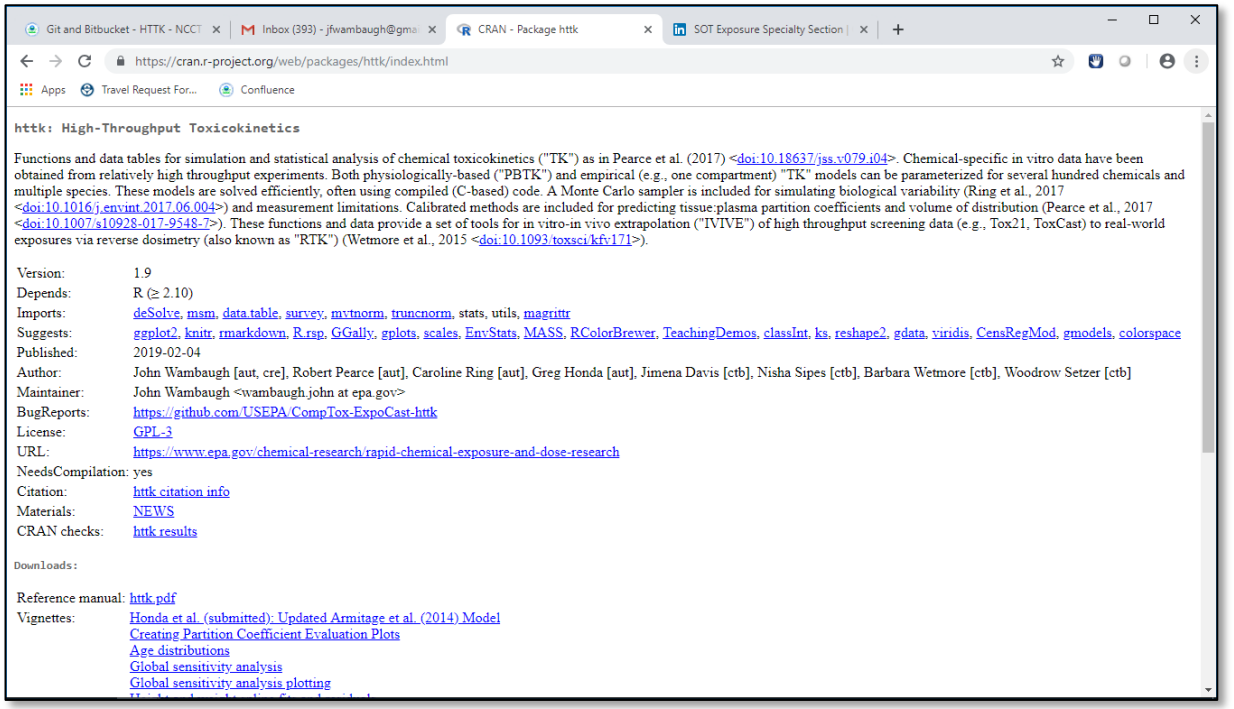
C. Deisenroth, Unpublished

Putting Alternative Test Results in a Dose and Exposure Context

Liver Metabolism | Tissue Partitioning | Plasma Protein Binding

Population-Based IVIVE Model

Oral Dose Required to Achieve Concentrations Equivalent to *In Vitro* Bioactivity



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

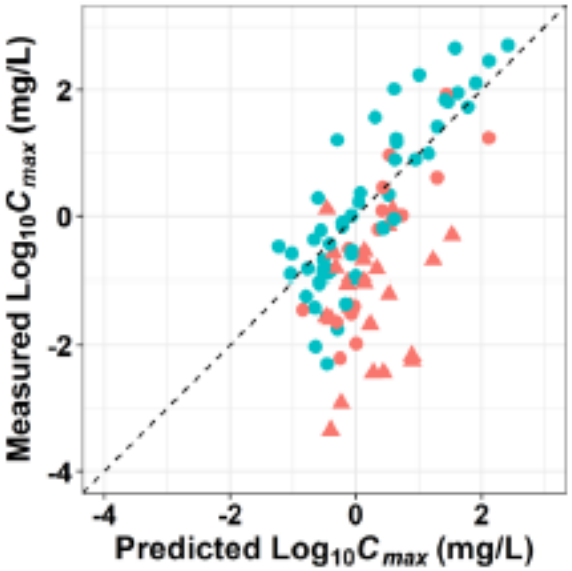
R package "httk"

- 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

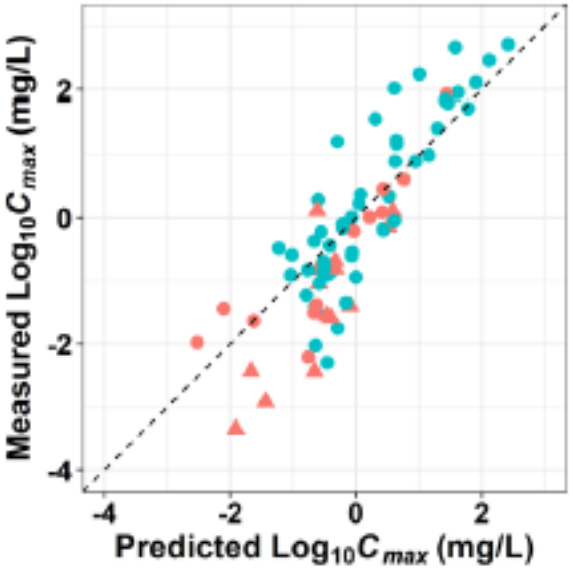
Rotroff *et al., Tox Sci.*, 2010
Wetmore *et al., Tox Sci.*, 2012
Wetmore *et al., Tox Sci.*, 2015

Incorporating Measurements and Predictions of Bioavailability

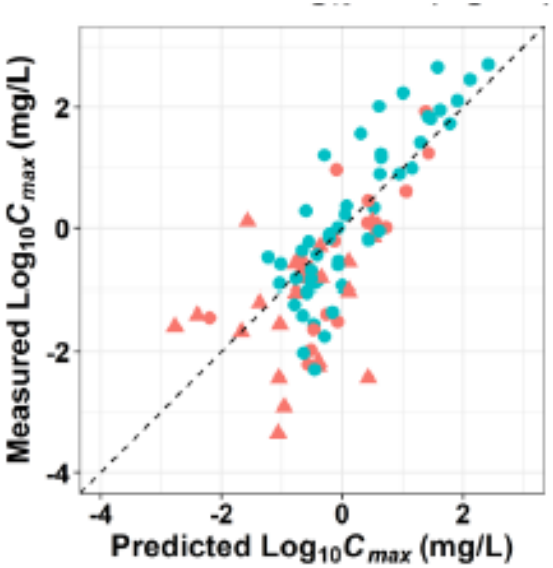
Assume 100% Bioavailability



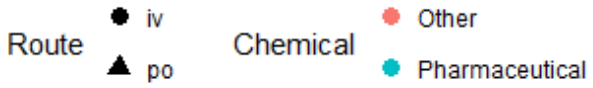
Using CaCo2 Bioavailability



Using New QSAR Model

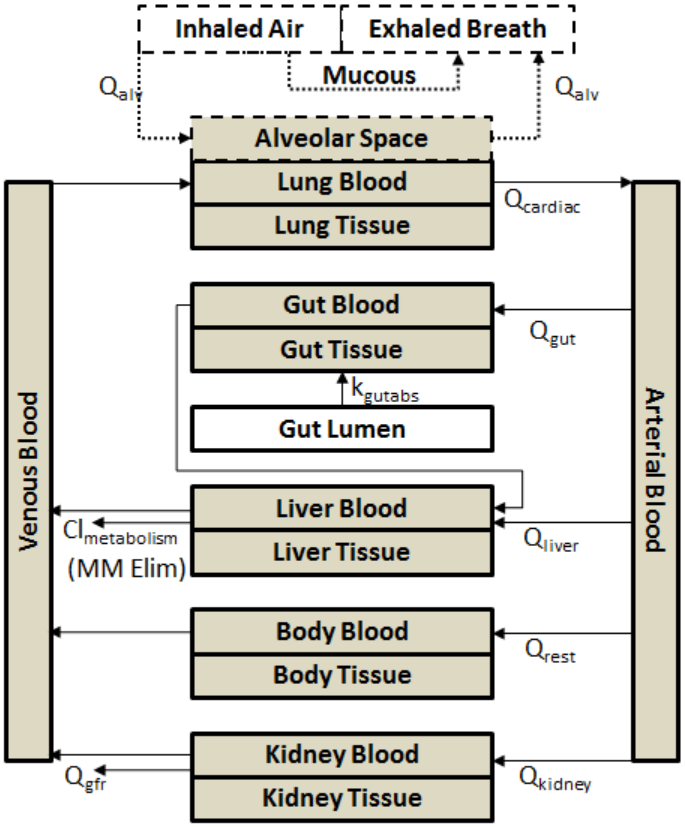


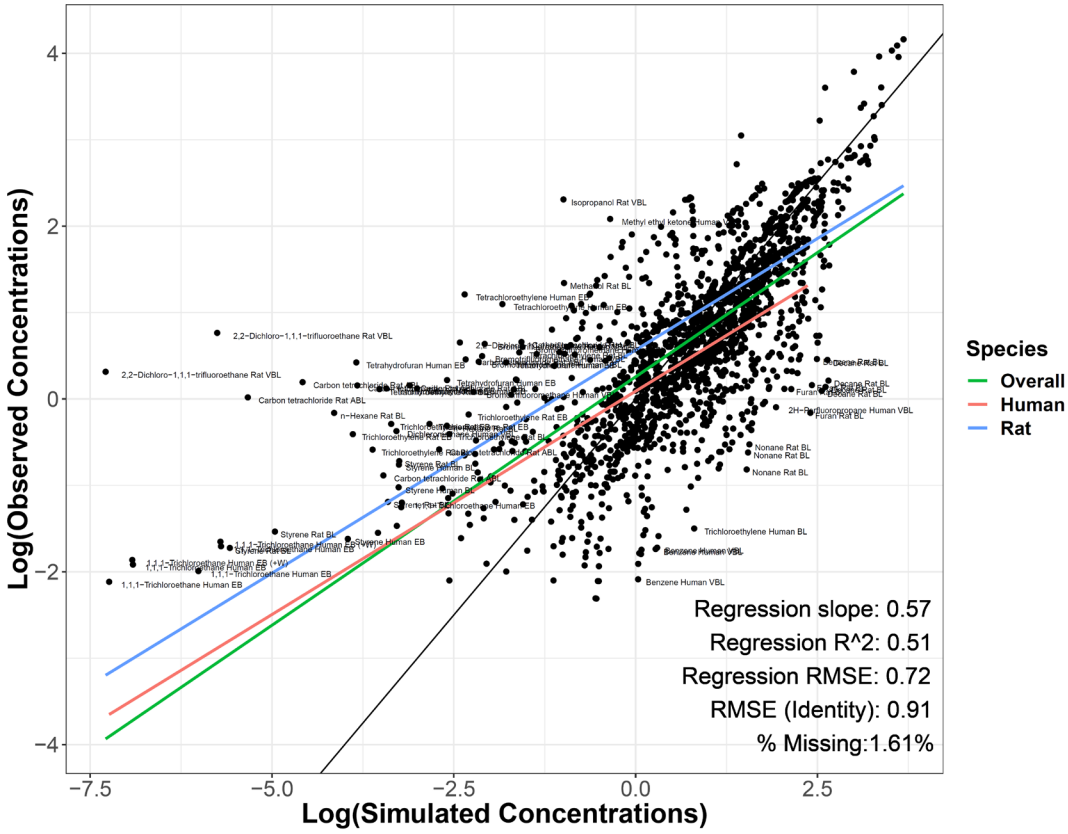
Value	Route	Stat.	F_{bio} = 1	Meas. F_{bio}	Meas. P_{AB}	QSAR P_{AB}
AUC	All	RMSE	0.96	0.98	0.99	1.05
		COR	0.75	0.86	0.86	0.79
C_{max}	All	RMSE	1.14	0.76	0.76	0.90
		COR	0.66	0.86	0.83	0.76



Wambaugh et al., 2018; Honda, unpublished

Adding Inhalation Route of Exposure





Wambaugh et al., 2018; Honda, unpublished

Drive to Characterize Variability and Relevance of Current Toxicity Models

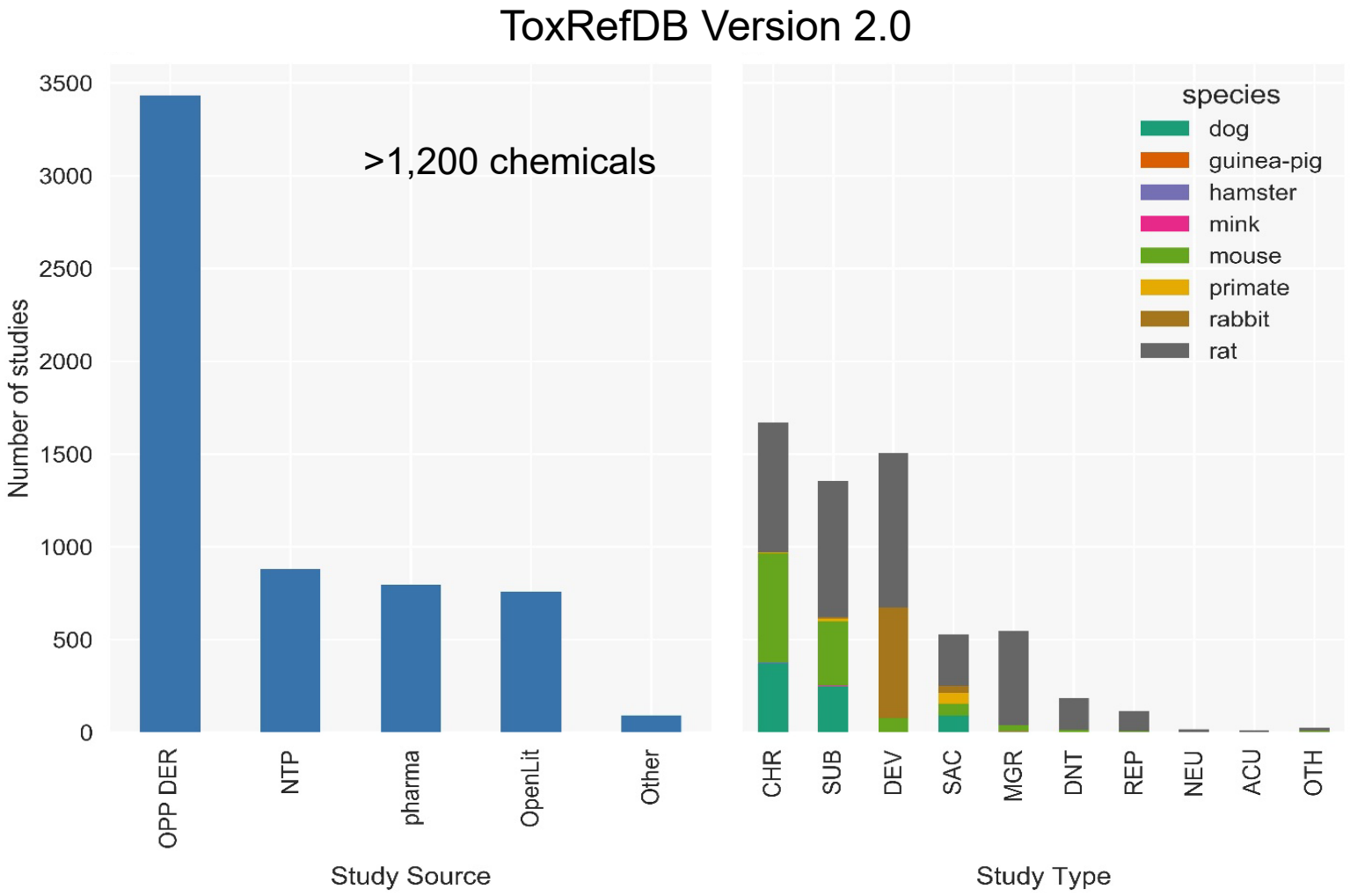
In US, Section 4(h) in amended TSCA says –

- New approach methods (NAMs) need to provide "information of equivalent or better scientific quality and relevance…" than the traditional animal models

In Europe, REACH says –

- Annex XI: "Results obtained from suitable *in vitro* methods may indicate the presence of a certain dangerous property or may be important in relation to a mechanistic understanding, which may be important for the assessment…" BUT confirmation using standard *in vivo* tests are still required unless:
    - Results are derived from an in *vitro* method whose scientific validity has been established by a validation study, according to internationally agreed validation principles; AND
    - Results are adequate for the purpose of classification and labelling and/or risk assessment; AND
    - Adequate and reliable documentation of the applied method is provided.

Building a Database of Legacy *In Vivo* Toxicity Studies



Katie Paul-Friedman, In Press

Qualitative Reproducibility of Traditional Toxicity Studies

Reproducibility in Target Organ Effects in Repeat Dose Toxicity Studies

Organ	Species	Repeated negative	Mixed effects	Repeated positive	% Concordance
Liver	dog	20			71.7
	mouse	30			71.2
	rat	42			71.0
Kidney	dog	49			64.1
	mouse	61			63.3
	rat	60			57.1
Spleen	dog	64	21	7	77.2
	mouse	93	31	15	77.7
	rat	132	84	29	65.7
Testes	dog	65	20	7	78.3
	mouse	110	20	9	85.6
	rat	135	87	23	64.5
Adrenal gland	dog	76	12	4	87.0
	mouse	109	23	7	83.5
	rat	142	83	20	66.1

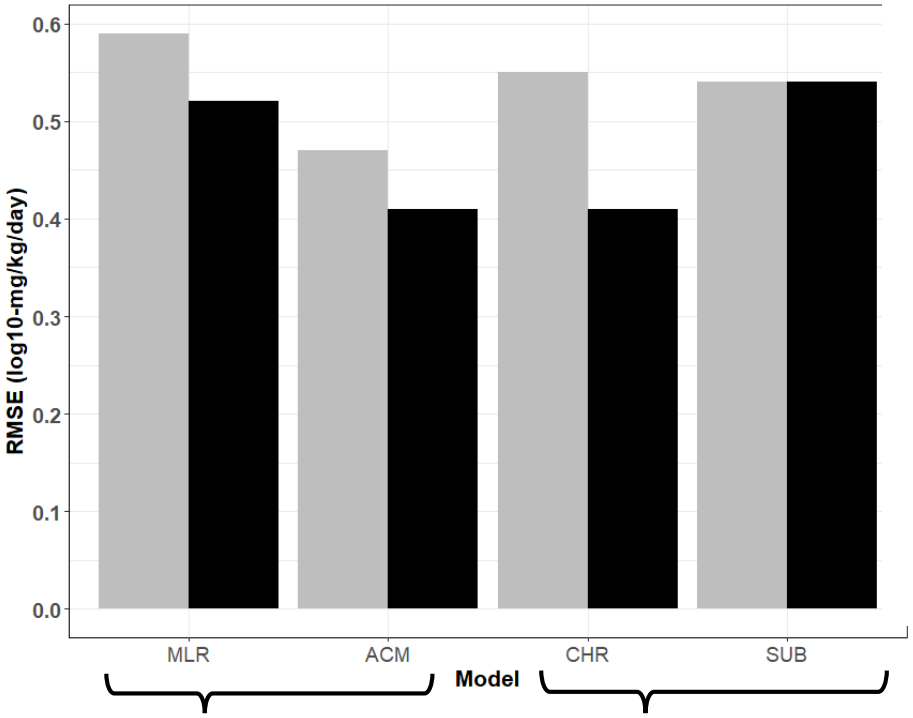
56% concordance across species

39% concordance across species

LyLy Pham and Katie Paul-Friedman, Unpublished

Quantitative Reproducibility in Traditional Toxicity Studies

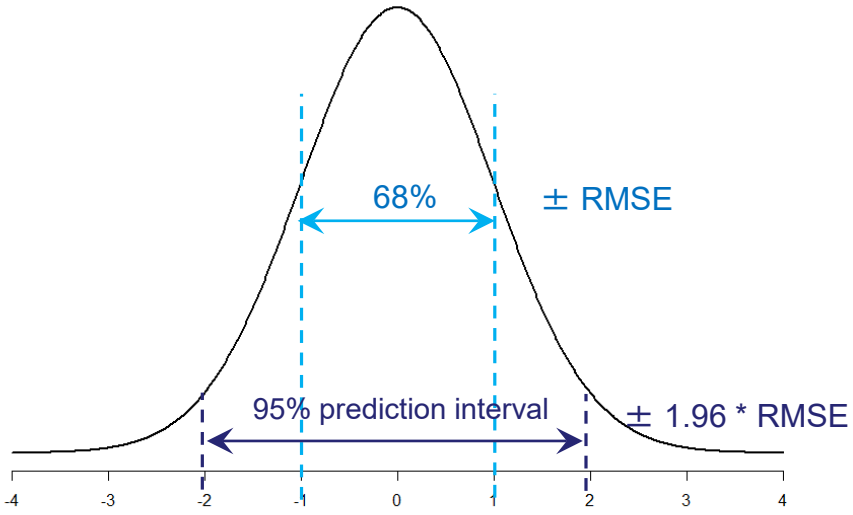
Variability in Quantitative Effect Levels from *In Vivo* Repeat Dose Toxicity Studies



Two ways to statistically model the data across multiple study types

Variability within a specific study type

RMSE ranged from 0.41 to 0.59 log10-mg/kg/day, depending on model and dataset



Using an RMSE=0.59, the 95% CI of an LEL/LOAEL is:

1 mg/kg/day ➔ 0.07 – 14 mg/kg/day.

10 mg/kg/day ➔ 0.7 – 143 mg/kg/day.

This confidence interval spans the difference between GHS STOT Category 1 (<10 mg/kg/d) and Category 2 (<100 mg/kg/d)

LyLy Pham and Katie Paul-Friedman, Unpublished

Human Relevance of Current *In Vivo* Toxicological Models

…data compiled from 150 compounds with 221 human toxicity events reported. The results showed the true positive human toxicity concordance rate of 71% for rodent and non-rodent species, with non-rodents alone being predictive for 63% of human toxicity and **rodents alone for 43%.**

Regulatory Toxicology and Pharmacology 32, 56–67 (2000)
doi:10.1006/rtph.2000.1399, available online at http://www.idealibrary.com on IDEAL®

Concordance of the Toxicity of Pharmaceuticals in Humans and in Animals

Harry Olson,[1] Graham Betton,[2] Denise Robinson,[3] Karluss Thomas,[3] Alastair Monro,[1] Gerald Kolaja,[4] Patrick Lilly,[5] James Sanders,[6] Glenn Sipes,[7] William Bracken,[8] Michael Dorato,[9] Koen Van Deun,[10] Peter Smith,[11] Bruce Berger,[12] and Allen Heller[13]

[1]*Pfizer Inc., Groton, Connecticut;* [2]*AstraZeneca Pharmaceuticals, Macclesfield, England;* [3]*ILSI-HESI, Washington, DC, 20036;* [4]*Pharmacia & Up.John, Kalamazoo, Michigan;* [5]*Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut;* [6]*Rhone-Poulenc Rorer, Collegeville, Pennsylvania;* [7]*University of Arizona, Tucson, Arizona;* [8]*Abbott Laboratories, Abbott Park, Illinois;* [9]*Eli Lilly and Co., Greenfield, Indiana;* [10]*Janssen Research Foundation, Beerse, Belgium;* [11]*Monsanto-Searle Laboratories, Skokie, Illinois;* [12]*Sanofi-Synthelabo, Inc., Malvern, Pennsylvania; and* [13]*Bayer Corporation, West Haven, Connecticut*

Received January 22, 2000

This report summarizes the results of a multinational pharmaceutical company survey and the outcome of an International Life Sciences Institute (ILSI) Workshop (April 1999), which served to better understand concordance of the toxicity of pharmaceuticals observed in humans with that observed in experimental animals. The Workshop included representatives from academia, the multinational pharmaceutical industry, and international regulatory scientists. The main aim of this project was to examine the strengths and weaknesses of animal studies to predict human toxicity (HT). The database was developed from a survey which covered only those compounds where HTs were identified during clinical development of new pharmaceuticals, determining whether animal toxicity studies identified concordant target organ toxicities in humans. Data collected included codified compounds, therapeutic category, the HT organ system affected, and the species and duration of studies in which the corresponding HT was either first identified or not observed. This survey includes input from 12 pharmaceutical companies with data compiled from 150 compounds with 221 HT events reported. Multiple HTs were reported in 47 cases. The results showed the true positive HT concordance rate of 71% for rodent and nonrodent species, with nonrodents alone being predictive for 63% of HTs and rodents alone for 43%. The highest incidence of overall concordance was seen in hematological, gastrointestinal, and cardiovascular HTs, and the least was seen in cutaneous HT. Where animal models, in one or more species, identified concordant HT, 94% were first observed in studies of 1 month or less in duration. These survey results support the value of *in vivo* toxicology studies to predict for many significant HTs associated with pharmaceuticals and have helped to identify HT categories that may benefit from improved methods. © 2000 Academic Press

INTRODUCTION

A vitally important theme in toxicology is the search for and the assessment of *in vitro* and *in vivo* models that are predictive for adverse effects in humans exposed to chemicals. The conduct of toxicology studies in laboratory animals is driven by experience, historical precedence, and governmental requirements, and the results of these studies usually, and reasonably, lead to restrictions on the use, or method of use, of the chemicals concerned. Such a process must be based on the assumption that the current choice of animal models and the design of the studies are truly predictive of human hazard. The reliability of this assumption has far-reaching repercussions in terms of the potential for inappropriate use of animals and the unnecessary deprivation of, or restrictions in the use of, valuable chemicals including pharmaceuticals. Identification of any weaknesses in the assumption could lead to revisions of existing regulations and stimulate the search for better methods for the safety evaluation of chemicals in the future.

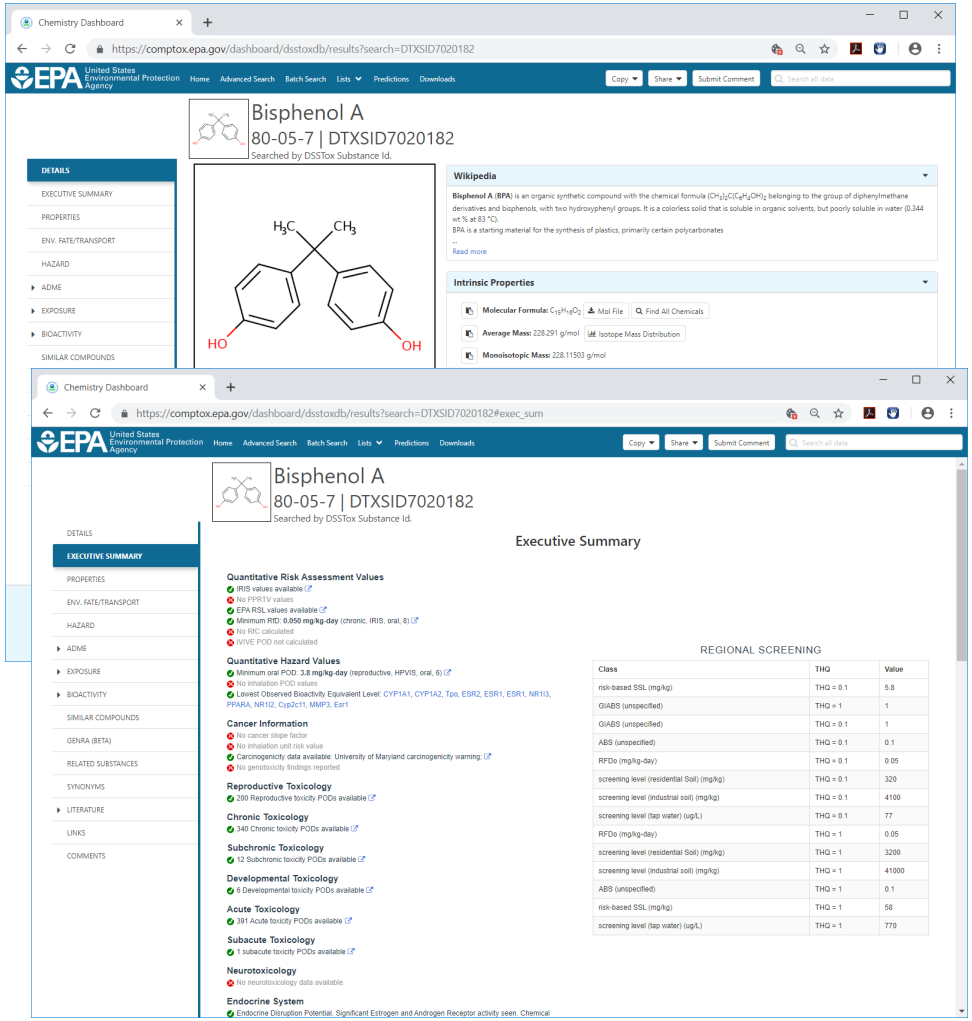
There have been relatively few attempts to methodically assess the correlation between the toxicity caused by chemicals in animals and in humans. This is not surprising, given that the toxicity of many chemicals observed in humans is after accidental exposure, the quantitative details of which in terms of duration and intensity are often not known. Chemicals, which are components of the diet, either macro- or micro-, are more susceptible to evaluation of their toxicity in animals and in humans, provided that the means to carry out epidemiological studies are available. However, a rich source of relevant information is pharmaceutical chemicals. For these, the human exposure is controlled and measured accurately. In addition, clinical studies of drugs employ systematic clinical examinations and

0273-2300/00 $35.00

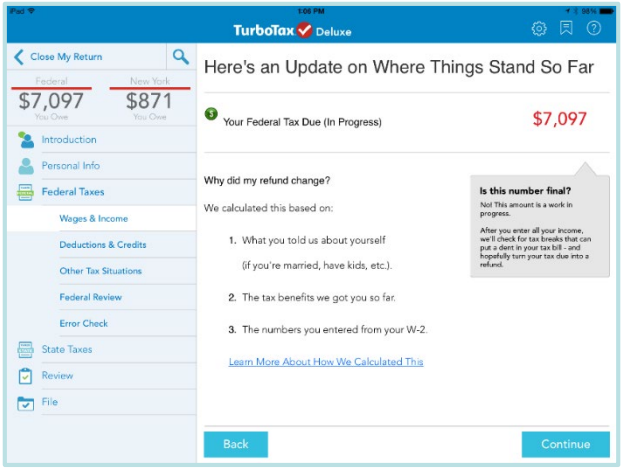
Enabling Translation Through Data Consolidation and Visualization

Data

- Now with 875,000 chemicals (up from ~760,000).
- High throughput *in vitro* assay information including new assays and more detailed descriptions
- In vivo toxicity values for human health and eco
- QSAR predictions for chemical properties
- Important lists (e.g., PFAS)
- ADME and exposure
- Functional use
- Literature search interface
- Read across workflow



Integrating Data for Regulatory Application with Decision Support Tools



- RapidTox is a suite of workflows that facilitate the application of data surfaced in the CompTox dashboard in diverse assessment decision contexts
- Flexible integration of information related to chemical properties, fate and transport, hazard, exposure, and risk assessment
- Enable expert users to review the assumptions made, refine results, and record the decisions
- Presents data from new approach methods together with traditional toxicology data
- Three workflows currently under development
  - Chemical binning for TSCA (OCSPP)
  - Emergency response (OLEM)
  - Site-specific screening assessments (OLEM)

Translation of Results Through Regulatory Focused Case Studies

Bloomberg BNA

Daily Environment Report™

Reproduced with permission from Daily Environment Report, 223 DEN B-1, 11/18/16. Copyright © 2016 by The Bureau of National Affairs, Inc. (800-372-1033) http://www.bna.com

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 workshop the agency convened that lays the groundwork for tests that can reduce reliance on animals, costs and in many cases provide better information.

DR. ROBERT KAVLOCK

Chemical Research in Toxicology

Perspective

pubs.acs.org/crt

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*,∥

†Office of Research and Development, U.S. Environmental Protection Agency, Washington, D.C. 20460, United States
‡Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, ON K1A 0K9, Canada
§Computational Assessment & Dissemination Unit, European Chemicals Agency, 00120 Helsinki, Finland
∥Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711, United States

ABSTRACT: Changes in chemical regulations worldwide have increased the demand for new data on chemical safety. New approach methodologies (NAMs) are defined broadly here as including *in silico* approaches and *in chemico* and *in vitro* assays, as well as the inclusion of information from the exposure of chemicals in the context of hazard [European Chemicals Agency, "New Approach Methodologies in Regulatory Science", 2016]. NAMs for toxicity testing, including alternatives to animal testing approaches, have shown promise to provide a large amount of data to fill information gaps in both hazard and exposure. In order to increase experience with the new data and to advance the applications of NAM data to evaluate the safety of data-poor chemicals, demonstration case studies have to be developed to build confidence in their usability. Case studies can be used to explore the domains of applicability of the NAM data and identify areas that would benefit from further research, development, and application. To ensure that this science evolves with direct input from and engagement by risk managers and regulatory decision makers, a workshop was convened among senior leaders from international regulatory agencies to identify common barriers for using NAMs and to propose next steps to address them. Central to the workshop were a series of collaborative case studies designed to explore areas where the benefits of NAM data could be demonstrated. These included use of *in vitro* bioassays data in combination with exposure estimates to derive a quantitative assessment of risk, use of NAMs for updating chemical categorizations, and use of NAMs to increase understanding of exposure and human health toxicity of various chemicals. The case study approach proved effective in building collaborations and engagement with regulatory decision makers and to promote the importance of data and knowledge sharing among international regulatory agencies. The case studies will be continued to explore new ways of describing hazard (i.e., pathway perturbations as a measure of adversity) and new ways of describing risk (i.e., using NAMs to identify protective levels without necessarily being predictive of a specific hazard). Importantly, the case studies also highlighted the need for increased training and communication across the various communities including the risk assessors, regulators, stakeholders (e.g., industry, non-governmental organizations), and the general public. The development and application of NAMs will play an increasing role in filling important data gaps on the safety of chemicals, but confidence in NAMs will only come with learning by doing and sharing in the experience.

Accelerating the Pace of Chemical Risk Assessment APCRA

CONTENTS

1. OVERVIEW

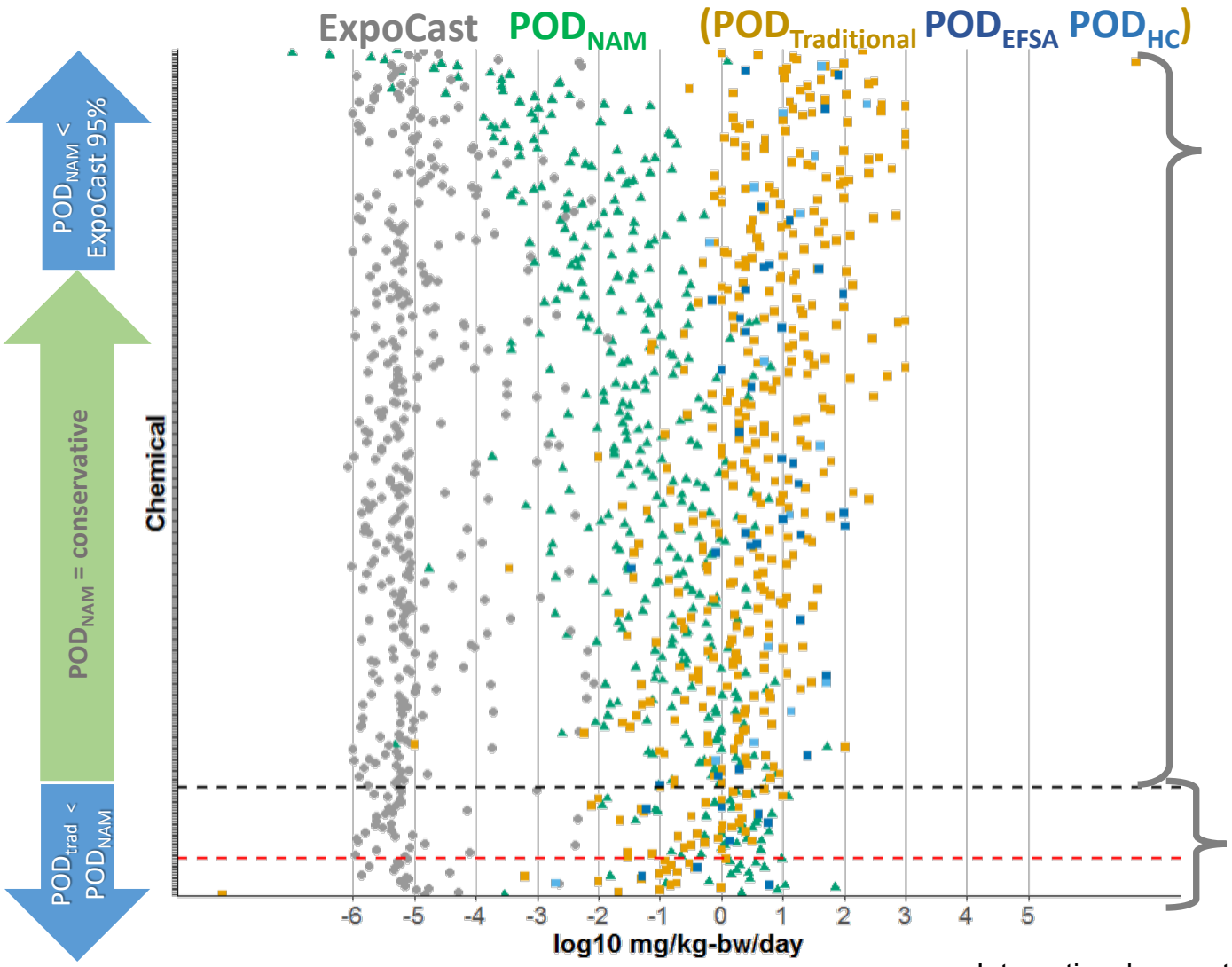
The modernization of the U.S. Toxic Substances Control Act (TSCA), the implementation of European Union's Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), the next phase of the Canadian Chemicals Management Plan (CMP), and many international chemical management policies and laws have escalated the demand for data on the safety of chemicals. To meet this demand, a variety of new data streams—in hazard, exposure, and dose evaluation—are being considered to augment traditional toxicology data which has mostly relied on animal models. The new data are diverse and include data from high-throughput toxicity and toxicokinetic testing, molecular epidemiology, toxicogenomics, exposure science, computational chemistry, and new animal models, among others.

Received: December 19, 2017
Published: March 30, 2018

ACS Publications ©XXXX American Chemical Society A

- 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 Evaluating Bioactivity as a Protective Point-of-Departure



For ~92% of the chemicals, POD$_{NAM}$ was conservative.

(~100-fold on average)

Chemicals where POD$_{NAM}$ was not conservative enriched in OPs/carbamates

International case study with EPA, ASTAR, ECHA, Health Canada, and EFSA

EPA United States Environmental Protection Agency

Take Home Messages…

- Charting a new path in toxicology will require a continued commitment to a different future
- 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
- New methods should be evaluated in the context of the variability and relevance of existing models
- Enabling application of new technologies to regulatory 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

EPA's National Center for Computational Toxicology