EPA
United States
Environmental Protection
Agency

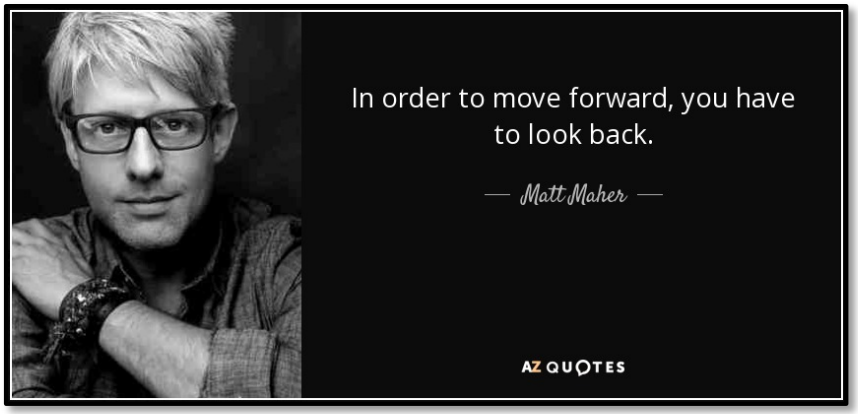
Looking Back to Go Forward in Toxicology and Chemical Risk Assessment

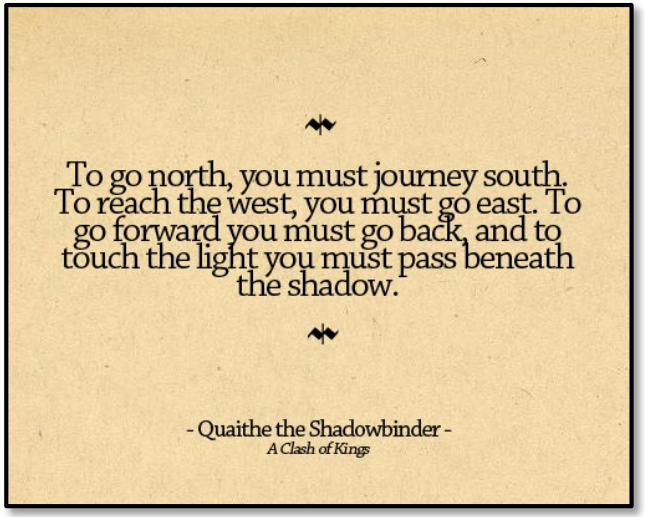
ICCR Meeting

July 11, 2019

Rusty Thomas
Director
National Center for Computational Toxicology

Many Philosophers Lay Claim to These or Similar Words…





But, Let's Explore the Approach in the Context of Tox Testing and NAMs…

Do Traditional Animal Models Predict Human Toxicity?

…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

What is the 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

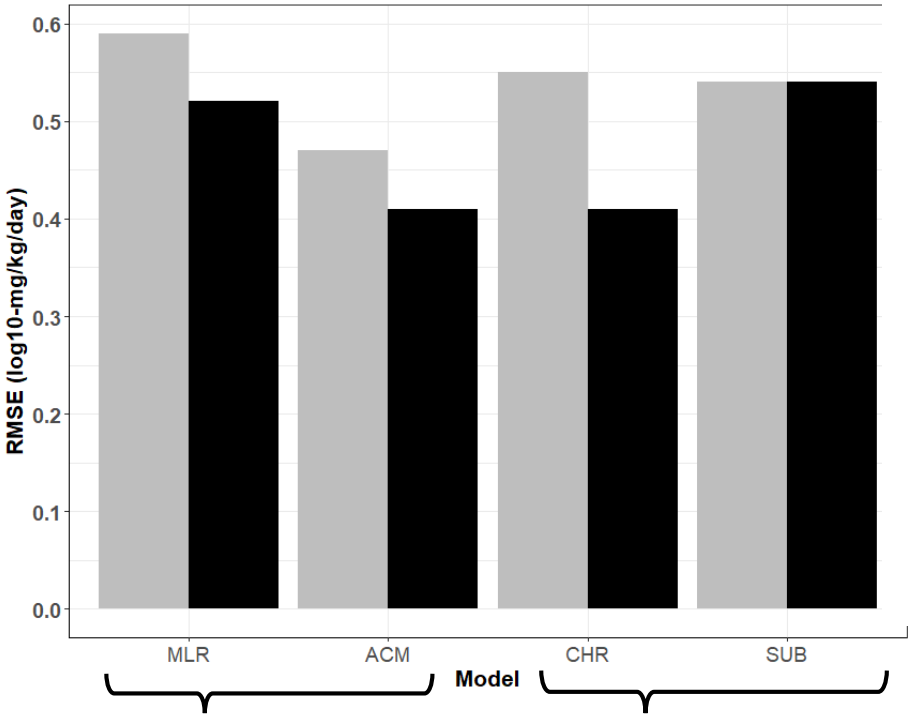
56% concordance across species

39% concordance across species

LyLy Pham and Katie Paul-Friedman, Unpublished

What is the Quantitative Reproducibility in Traditional Toxicity Studies?

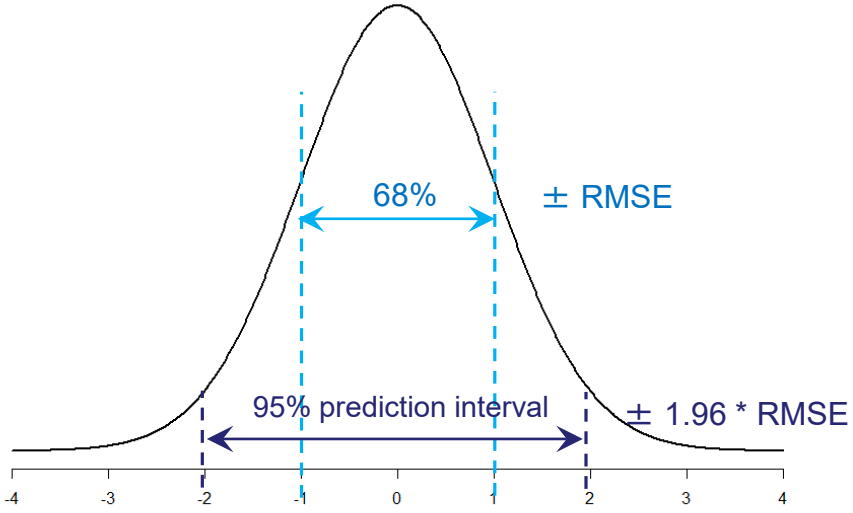
Variability in Quantitative Effect Levels from *In Vivo* Repeat Dose Toxicity Studies



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:

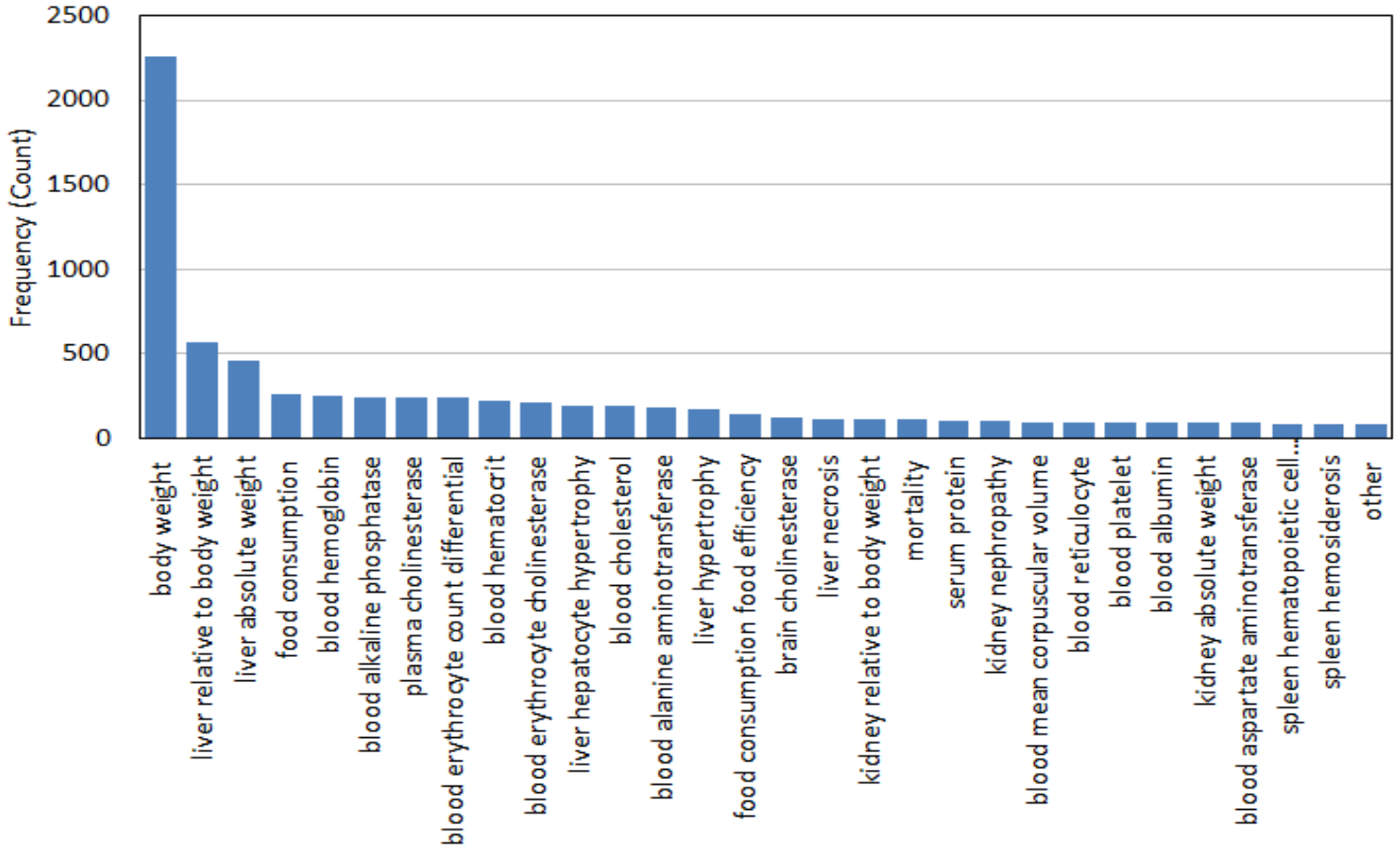
1 mg/kg/day ➔ 0.07 – 14 mg/kg/day.

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

What are the Most Common Critical Effects Used in Regulatory Decisions?



Critical Effect Endpoints in Repeat Dose Tox Studies

Katie Paul-Friedman, Unpublished

We've Largely Overcome the Challenges By Being Protective…When We Can't Be Predictive

Chemicals with Unknown MOA

EPA/630/P-02/002F
December 2002
Final Report

A REVIEW OF THE REFERENCE DOSE AND REFERENCE CONCENTRATION PROCESSES

Prepared for the
Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC

Bob
Gary
Lee
Carc
Gary
Susa
Dein

Table 2-2. Uncertainty/safety factors for various reference values

Reference value	UF[a]				FQPA[b]
	U_A	U_H	U_L	U_D	
ARE	1, 3, 10	1, 3, 10	1, 3, 10	ND	NA
AEGL	1, 3, 10	1, 3, 10	3[c]	ND[d]	NA
OPP acute and intermediate RfDs	10	10	3, 10	ND[e]	10±
OW HAs	1, 3, 10	1, 3, 10	1, 3, 10	case-specific	NA
ATSDR MRLs	1, 3, 10	1, 3, 10	1, 3, 10	ND[d]	NA

[a] Uncertainty factors: U_A = animal-to-human; U_H = within-human variability; U_L = LOAEL-to-NOAEL; U_D = database deficiency.
[b] Additional safety factor required under FQPA.
[c] Endpoint = lethality, not really a LOAEL-to-NOAEL adjustment in this case.
[d] Database deficiencies considered, and a factor may be included for intermediate RfDs if, for example, there is no reproduction and fertility study.
[e] Overlaps with the FQPA safety factor (see U.S. EPA, 2002b)

ND = not done
NA = not applicable

Chemicals with MOA

Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity

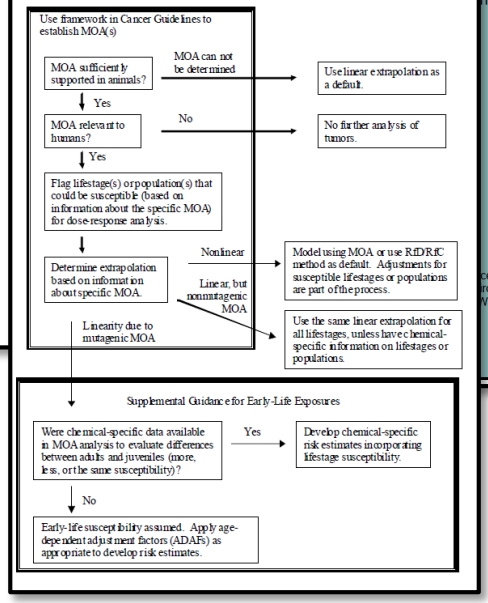
Office of Pesticide Programs
Science Policy on

The Use of Data on Cholinesterase Inhibition Risk Assessments
hosphorous and Carbamate Pesticides

August 18, 2000

ce of Pesticide Programs
ironmental Protection Agency
Washington DC 20460

Figure 1-1. Flow chart for early-life risk assessment using mode of action framework.



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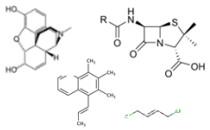
Can We Apply NAMs Under a Similar Framework?

Key Mile Markers in the Future of Toxicity Testing

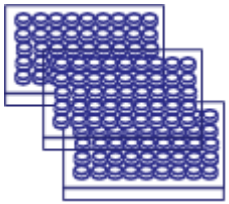
- Define predictive vs protective domains based on chemical promiscuity
- Incorporate technological advances to evaluate large numbers of chemicals across toxicological space
- Put results into a dose and exposure context
- Systematically address limitations of *in vitro* test systems
- Evaluate bioactivity across a diverse battery of *in vitro* assays as a quantitative estimate of potential adverse *in vivo* effect levels
- Case studies on uncertainty and variability in NAM-based toxicity values

Application of High-Throughput Assays to Test Thousands of Chemicals



Thousands of Chemicals

Concentration Response Screening

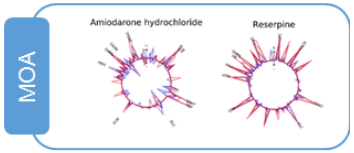


ToxCast Assays

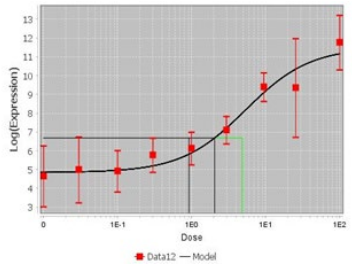
Transcription Factors
Transporter
Cytokines
Kinases
Nuclear Receptors
CYP450 / ADME
Cholinesterase
Phosphatases
Proteases
XME metabolism
GPCRs
Ion channels

~700 Assay Endpoints

Mode-of-Action Identification

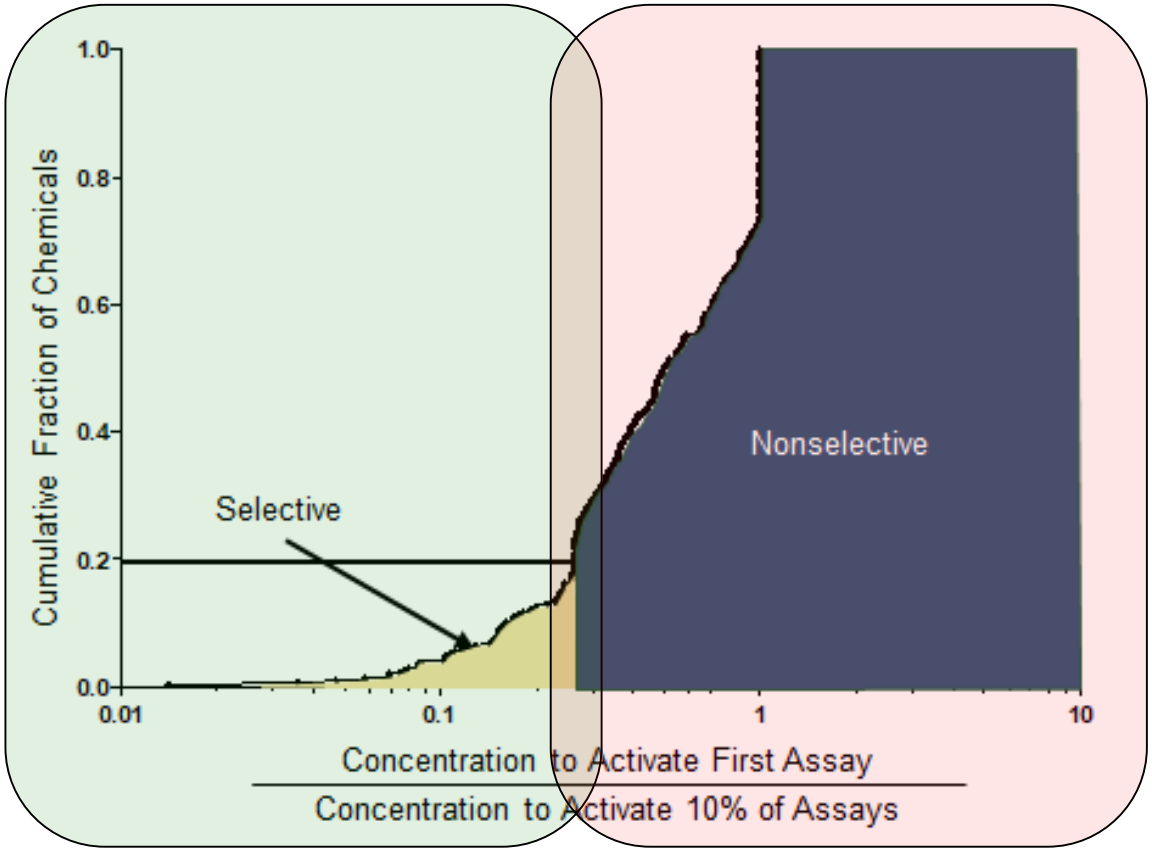


Concentration Response Modeling



- 96, 384, and 1536-well format
- Coverage of molecular and phenotypic responses
- Multiple assay vendors/labs

Defining Predictive vs Protective Domains Using Mechanistic Promiscuity

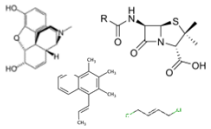


Predictive

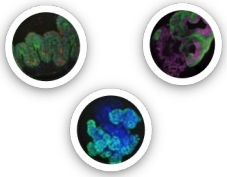
Protective

Thomas et al., *Tox Sci*, 2013

Incorporating High-Content Technologies to Increase Biological Coverage

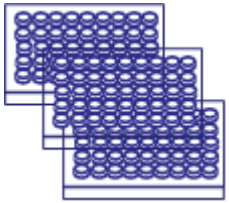


Thousands of Chemicals

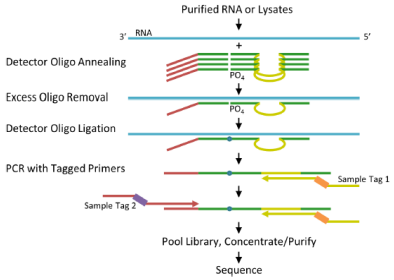


Multiple Cell Types

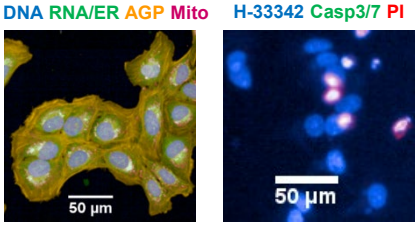
Concentration Response Screening



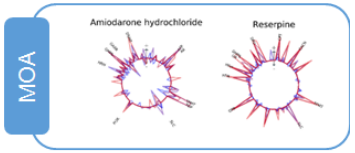
Whole Genome Transcriptomics



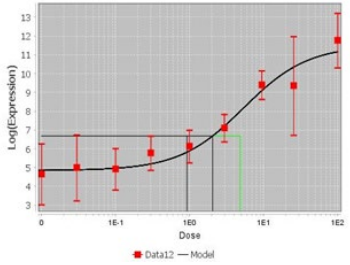
Multi-Parameter Cellular Phenotypic Profiling



Mode-of-Action Identification



Concentration Response Modeling



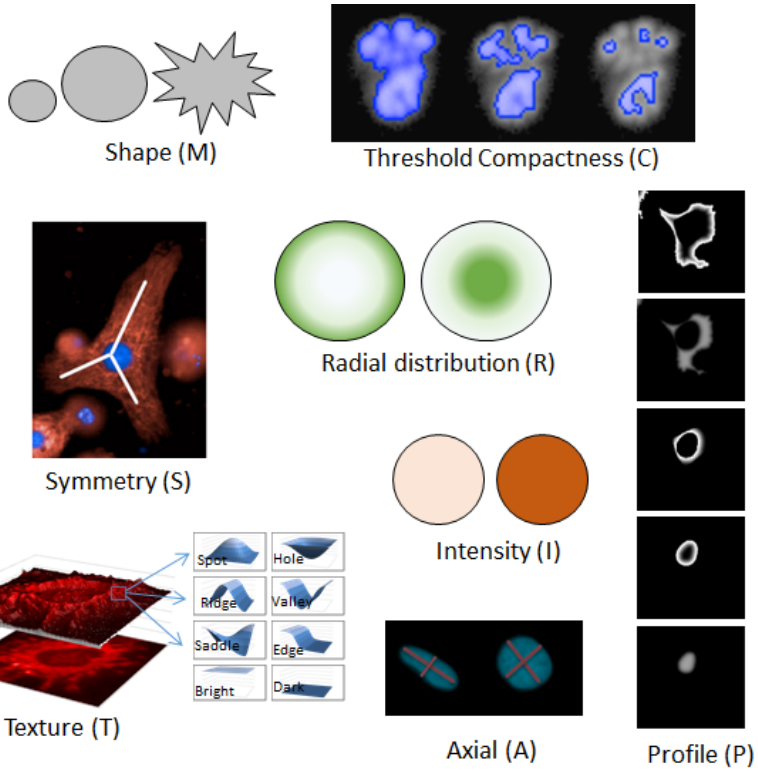
- 384-well, laboratory automation compatible
- Relatively inexpensive ($2.50 - $1,500 per chemical)
- Broad complementary coverage of molecular and phenotypic responses
- Integration of reference materials and controls for performance standards
- Increased portability

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

United States Environmental Protection Agency

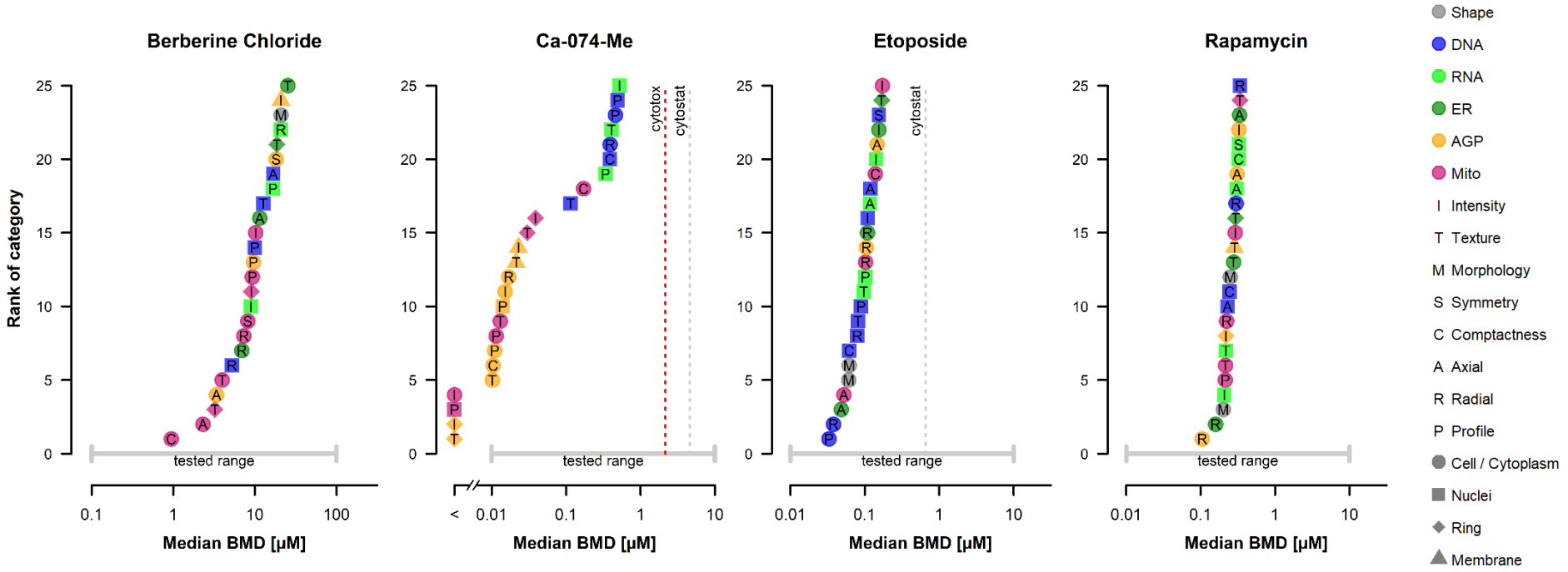
Cell Compartments

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

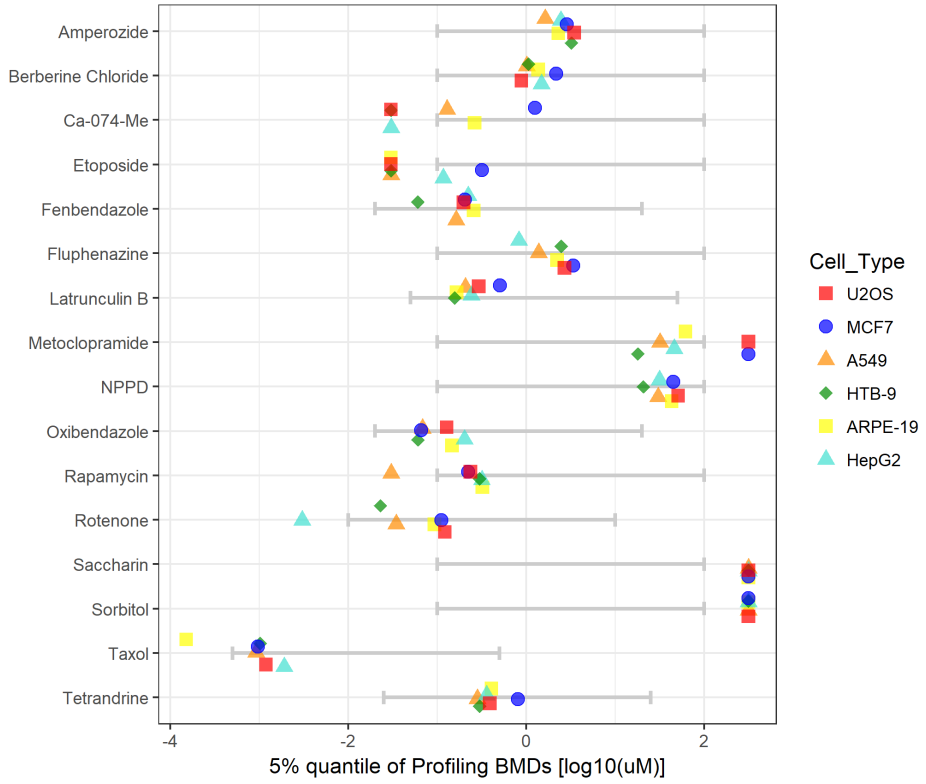


J. Nyffeler, J. Harrill, Unpublished

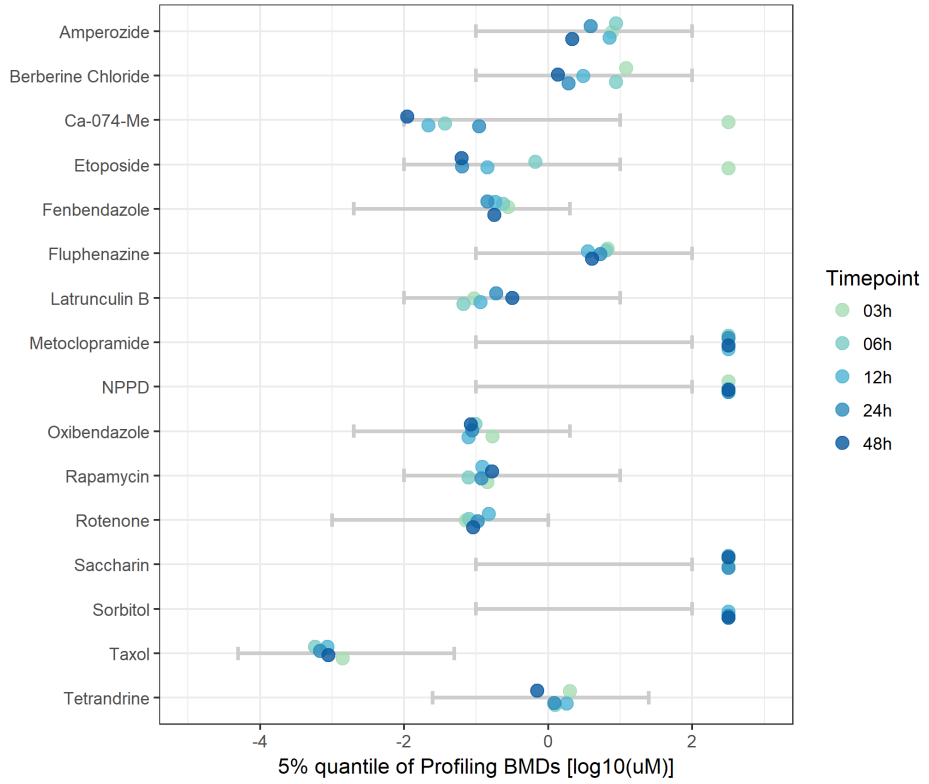
Variation in Phenotypic Potencies Across Cell Type and Time

United States Environmental Protection Agency

Cell Type Differences (48 hr)



Time Point Differences (U2OS cells)

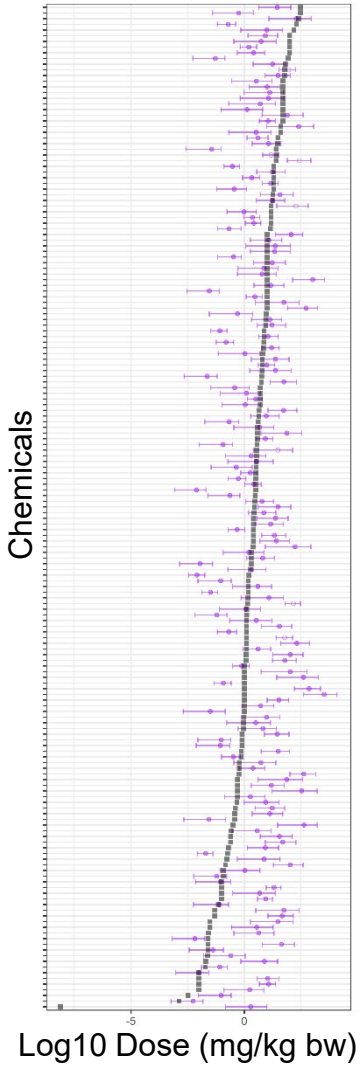


*Data points represent 5th percentile of phenotypic BMDs

Tested range

J. Nyffeler, J. Harrill, Unpublished

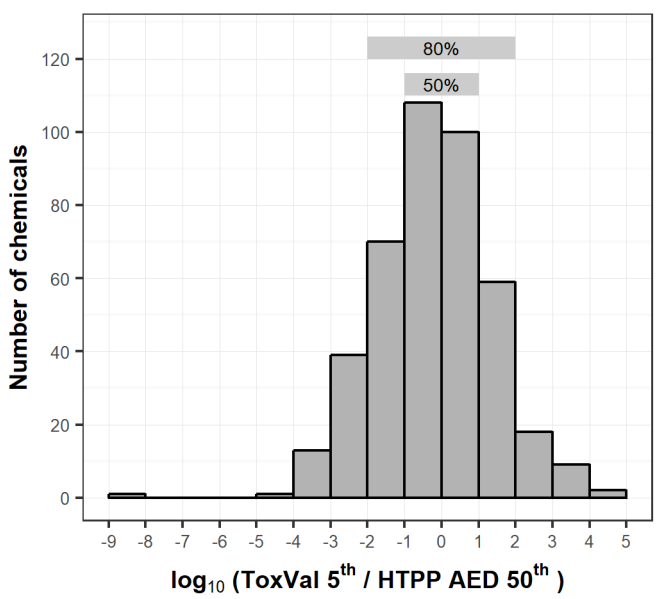
Comparing 'Cellular Pathology' with *In Vivo* Effects



Chemicals 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

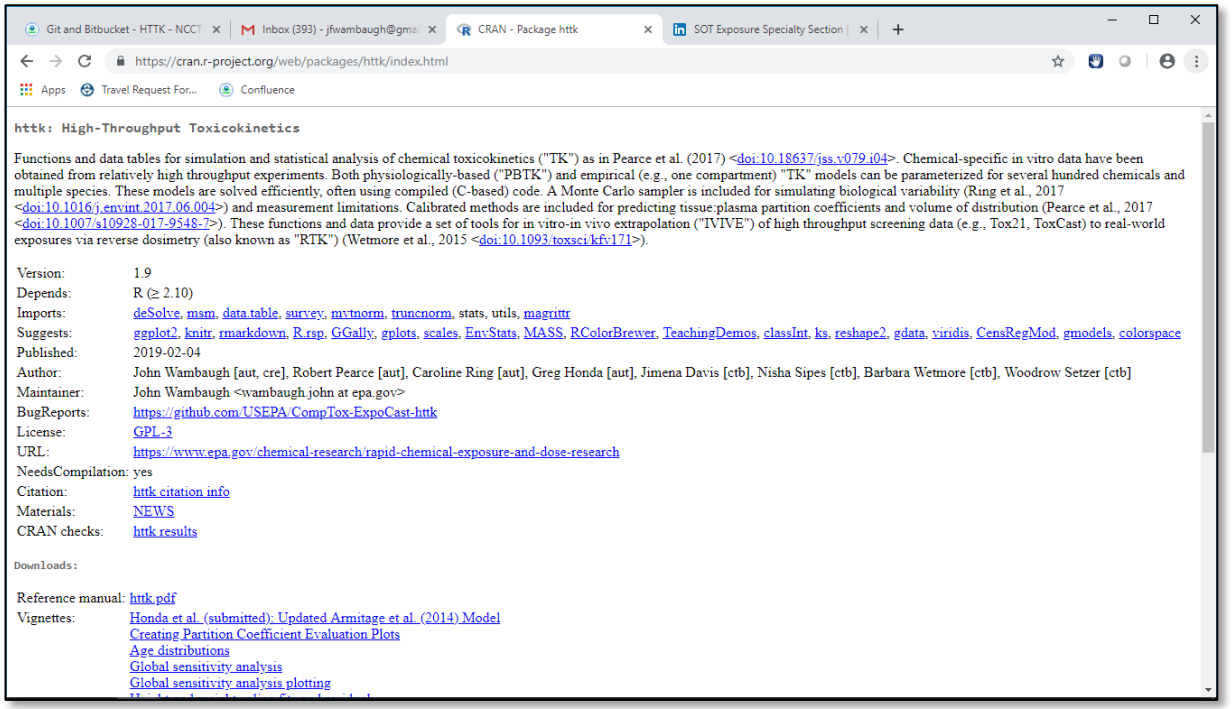
J. Nyffeler, J. Harrill, Unpublished

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

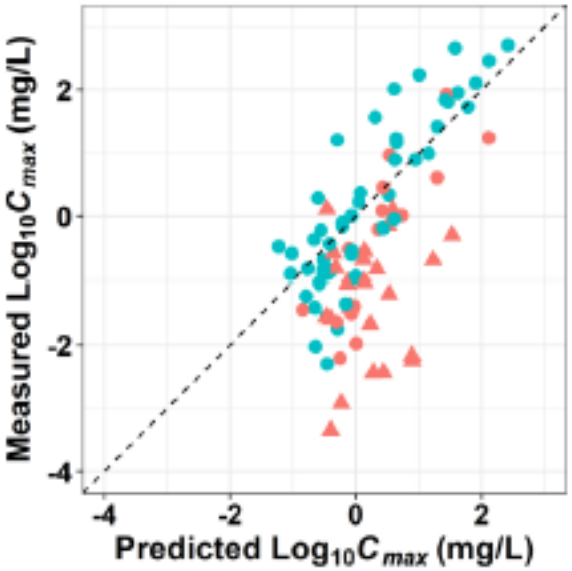
R package "httk"

- 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

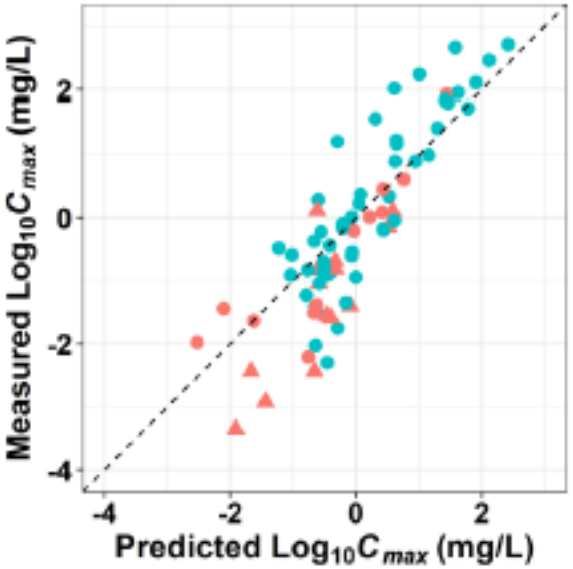
Rotroff *et al., Tox Sci.*, 2010
Wetmore *et al., Tox Sci.*, 2012
Wetmore *et al., Tox Sci.*, 2015

Incorporating Measurements and Predictions of Bioavailability

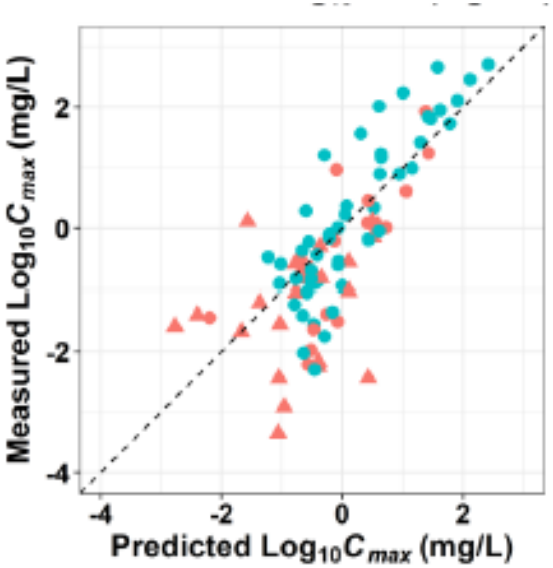
Assume 100% Bioavailability



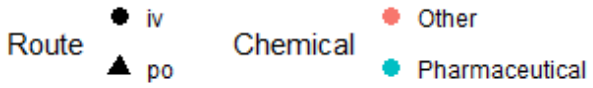
Using CaCo2 Bioavailability



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

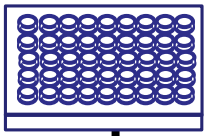


Wambaugh et al., 2018; Honda, unpublished

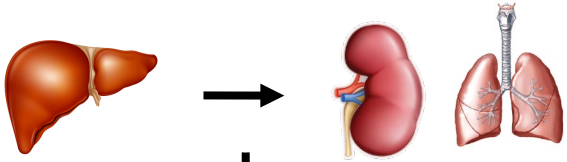
Incorporating Xenobiotic Metabolism in *In Vitro* Test Systems

"Extracellular" Approach

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

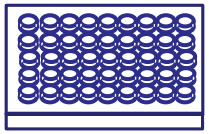


More closely models effects of hepatic metabolism and generation of circulating metabolites

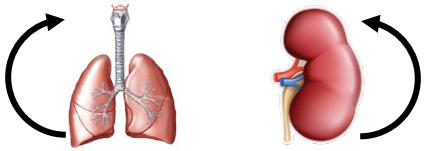


"Intracellular" Approach

Chemical metabolism inside the cell in cell-based assays



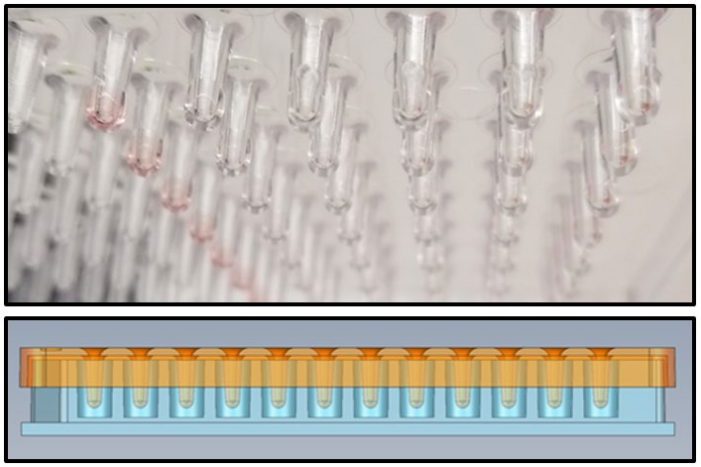
More closely models effects of target tissue metabolism



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

Application of Extracellular Strategy to Identify Estrogenic Metabolites

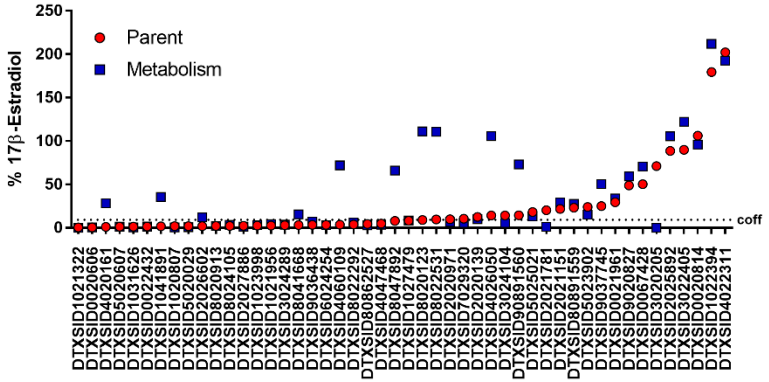
AIME Method: S9 Fraction Immobilization in Alginate Microspheres on 96- or 384-well peg



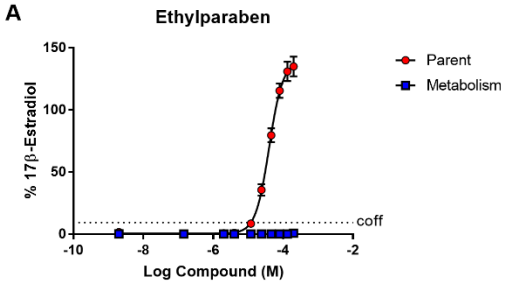
Screening Window of VM7 (formerly BG1) ER Transactivation Assay

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

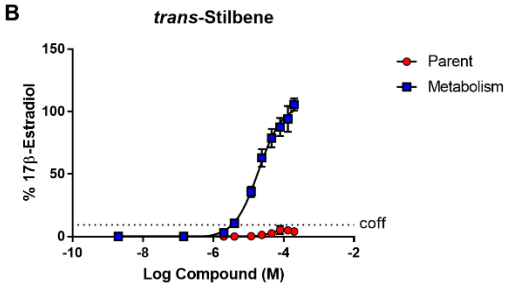
Pilot Screening Results of Pinto et al., 2016 Library



Example Detoxification



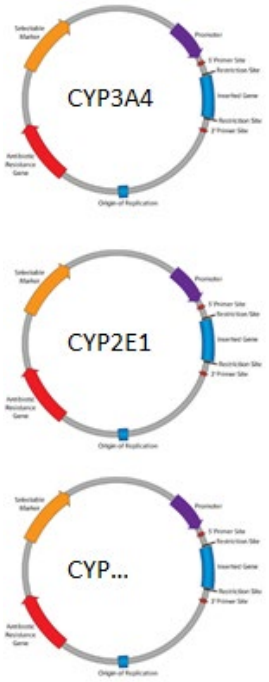
Example Bioactivation



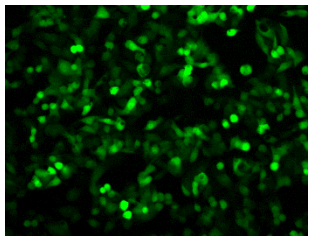
Collaboration with Unilever
D. DeGroot, C. Deisenroth, Unpublished

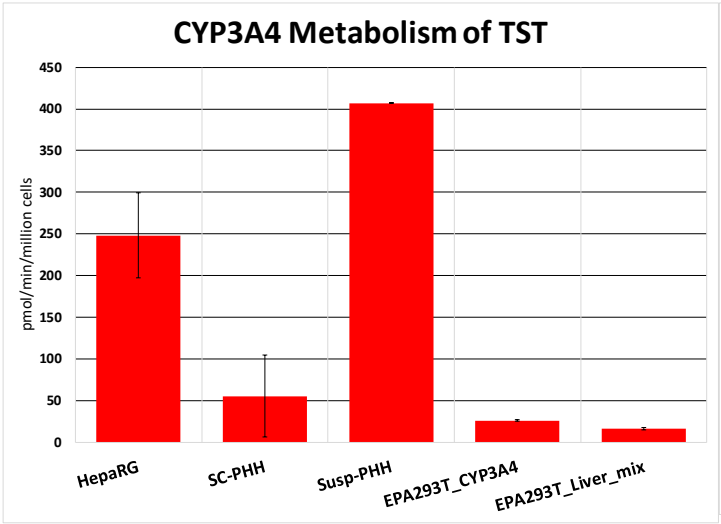
Application of Intracellular Strategy to Identify Cytotoxic Metabolites

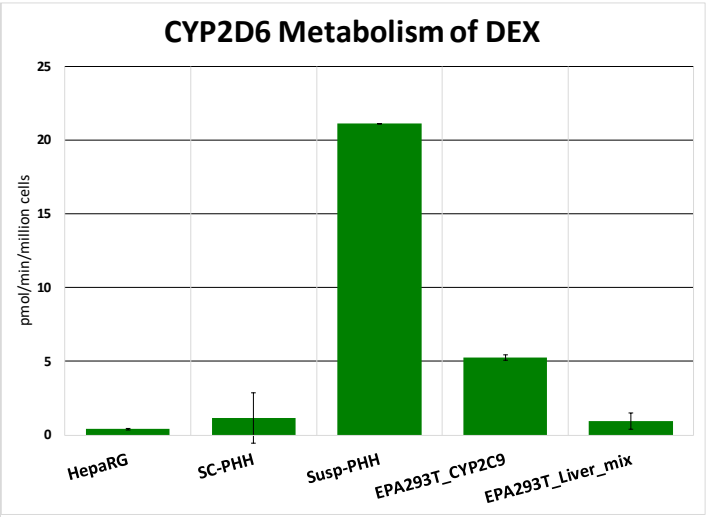
United States Environmental Protection Agency

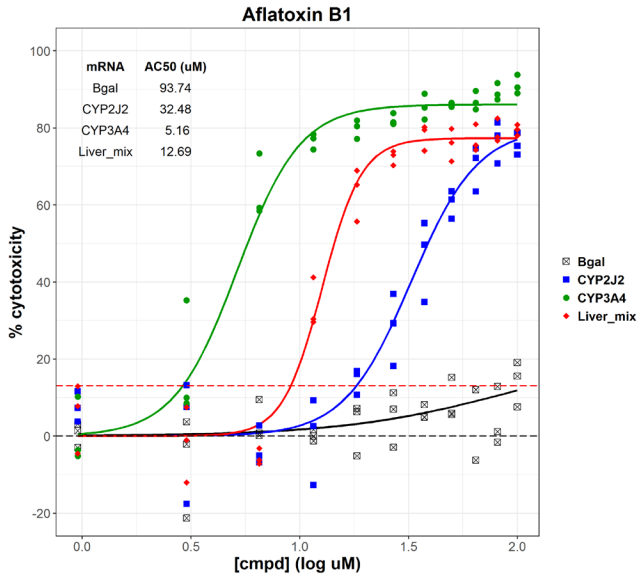


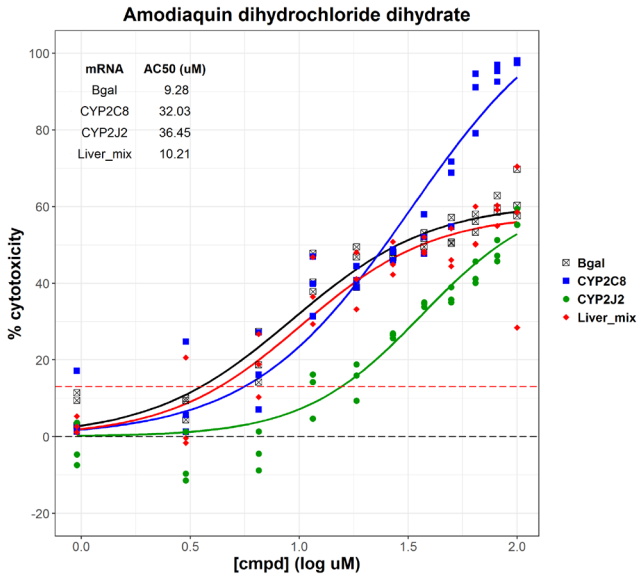
mRNA







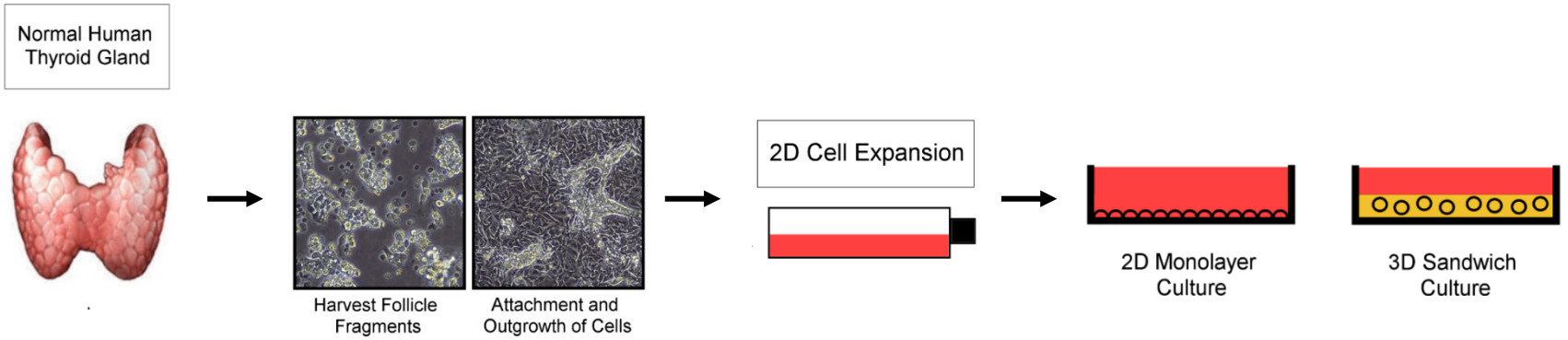


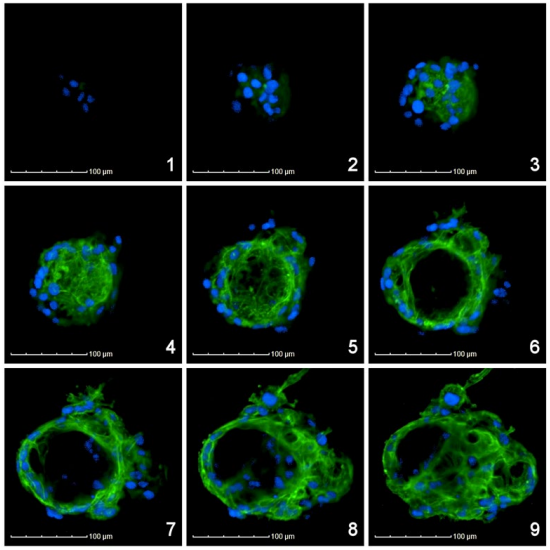


Simmons et al., 2018

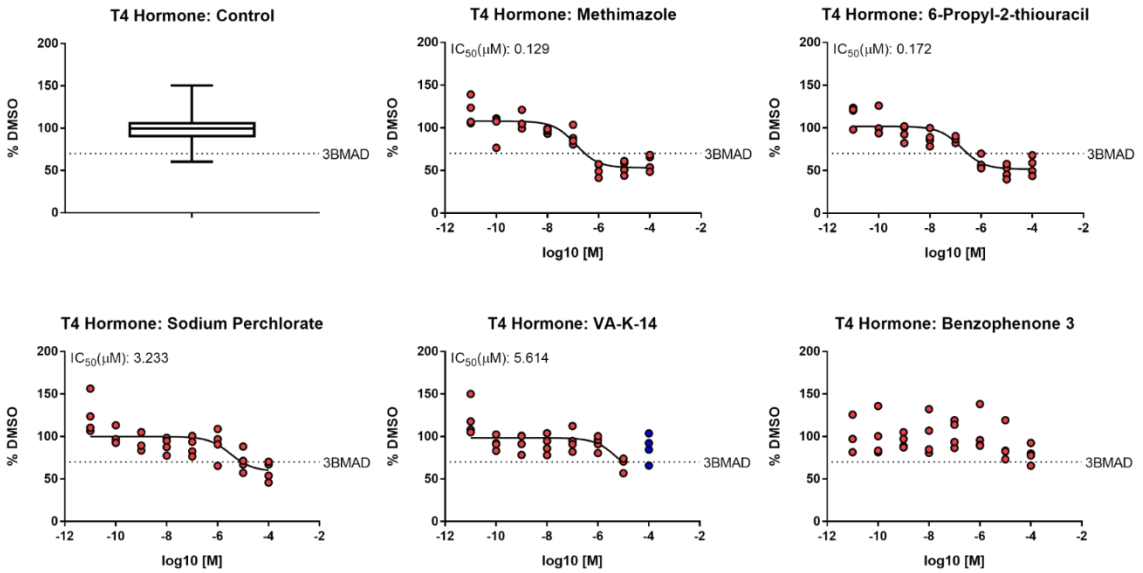
National Center for Computational Toxicology

Developing Organotypic Culture Models to Identify Tissue/Organ Effects





Blue, Hoechst 33342 /DNA
Green, Phalloidin/Actin

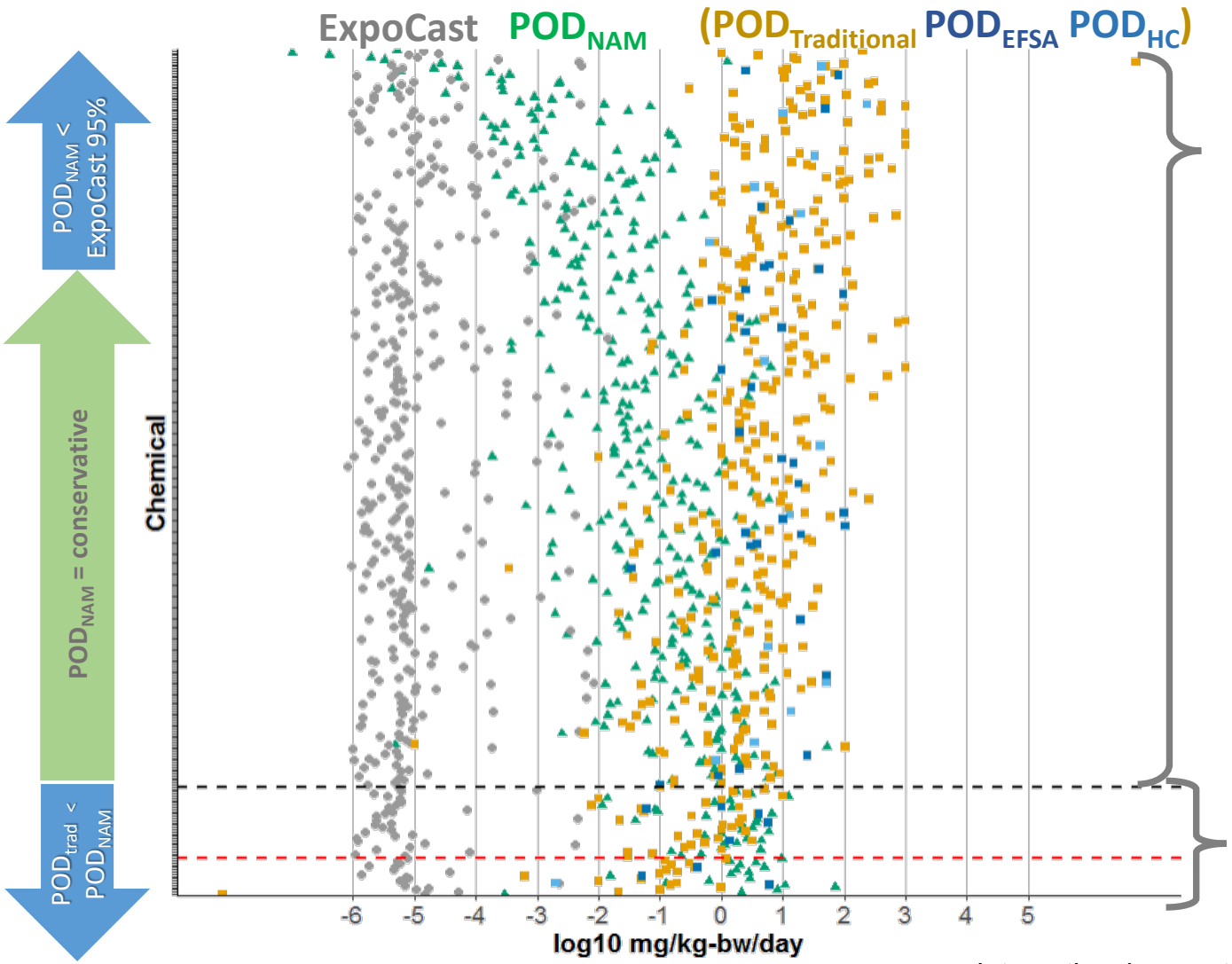


C. Deisenroth, Unpublished

Regulatory Focused Case Study on Bioactivity as a Point-of-Departure

- 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.

Results form the Bioactivity as a Point-of-Departure Case Study



For ~92% 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

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

On-Going Case Study Comparing Traditional and NAM-Based Toxicity Values

UF_A
(0, 3, 10)

UF_H
(0, 3, 10)

$$RfD_{NAM}\ (mg/kg/d) = \frac{\text{Bioactivity } 5^{th} \text{ Percentile} + \text{HTTK (variability)}}{UF_H\ (3) + UF_D\ (?)^*}$$

UF_L
(0, 3, 10)

UF_D
(0, 3, 10)

Preliminary Results Comparing Traditional and NAM-Based Toxicity Values

Chemical	CASRN	POD (mg/kg-day)[a]	Composite UF	RfD (mg/kg-day)[b]	AED_{95} (mg/kg-day)	RfD_{NAM} (mg/kg-day)[c]
Bisphenol A	80-05-7	50 (L)	1000	5.00E-02 (I)	0.02897	9.66E-03
Butylate	2008-41-5	5 (N)	100	5.00E-02 (I)	0.028281	9.43E-03
Caprolactam	105-60-2	50 (N)	100	5.00E-01 (I)	0.010422	3.47E-03
4-Chloro-2-methylaniline	95-69-2	3.69 (N)	1000	3.00E-03 (P)	0.000728	2.43E-04
4-Chloroaniline	106-47-8	12.5 (L)	3000	4.00E-03 (I)	0.011983	3.99E-03
o-Cresol	95-48-7	50 (N)	1000	5.00E-02 (I)	0.230287	7.68E-02
p-Cresol	106-44-5	13.94 (B)	100	1.00E-01 (A)	5.082245	1.69E+00
Bis(2-ethylhexyl) Hexanedioate	103-23-1	170 (N)	300	6.00E-01 (I)	0.11635	3.88E-02
1,4-Dichlorobenzene	106-46-7	7 (N)	100	7.00E-02 (A)	0.034121	1.14E-02
Diisopropyl methylphosphonate	1445-75-6	75 (N)	1000	8.00E-02 (I)	0.115161	3.84E-02
2-Methyl-4,6-dinitrophenol	534-52-1	0.8 (L)	10000	8.00E-05 (P, Appendix)	0.000542	1.81E-04
2,4-Dinitrophenol	51-28-5	2 (L)	1000	2.00E-03 (I)	0.006405	2.14E-03
2-Mercapto-benzothiazole	149-30-4	3.56 (B)	1000	4.00E-03 (P)	0.261347	8.71E-02

[a] Point-of-departure (POD): (B)= BMDL; (N)= NOAEL; (L)= LOAEL
[b] RfDs (or MRLs) derived from multiple sources: (A)= ATSDR; (I)= IRIS; (P)= PPRTV; (O)= OPP
[c] $RfD_{NAM} = AED_{95} / UF_{NAM}$ of 3

EPA United States Environmental Protection Agency

Preliminary Results Comparing Traditional and NAM-Based Toxicity Values

Chemical	CASRN	RfD_{IRIS} (mg/kg)	POD (mg/kg)[a]	Composite UF	Basis	AED_{95} (mg/kg)	RfD_{NAM} (mg/kg)
Bis(2-ethylhexyl)hexanedioate	103-23-1	0.6	170 (N)	300	Parental body weight, liver weight; Fetus reduced ossification, dialated ureters, litter size and weight	0.29	0.1
4-Chloroaniline	106-47-8	0.004	12.5 (L)	3000	Lesions of the splenic capsule	0.097	0.03
Phenol	108-95-2	0.3	93 (B)	300	Maternal weight	0.81	0.27
Anthracene	120-12-7	0.3	1000 (N)	3000	No effects observed	0.013	0.004
2,4-Dinitrotoluene	121-14-2	0.002	0.2 (N)	100	Neurotox, Heinz bodies, billiary hyperplasia	0.01	0.004
Pyrene	129-00-0	0.03	75 (N)	3000	Kidney effects	0.07	0.02
Diisopropyl methylphosphonate	1445-75-6	0.08	75 (N)	1000	No effects observed	0.32	0.11
Fluoranthene	206-44-0	0.04	125 (N)	3000	Nephropathy, liver weight, hematological alterations, clinical effects	0.1	0.03

[a]Values in parentheses = N, NOAEL; L, LOAEL; B, BMD

EPA United States Environmental Protection Agency

Take Home Messages

- A deeper look back at toxicology and risk assessment is an important part of moving forward to a new future
- Toxicity testing and risk assessment approaches should be tailored to the relative biological specificity of the chemical
- Biological activity across a diverse battery of *in vitro* assays provides a conservative, quantitative estimate of potential adverse *in vivo* effect levels
- NAM-based risk assessments will require addressing technical limitations in current test systems and utilizing new technologies that comprehensively cover toxicological space

Acknowledgements and Questions

Tox21 Colleagues:
- NTP
- FDA
- NCATS

EPA Colleagues:
- NERL
- NHEERL
- NCEA

Collaborative Partners:
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- A*STAR
- ECHA
- EFSA
- Health Canada

EPA's National Center for Computational Toxicology