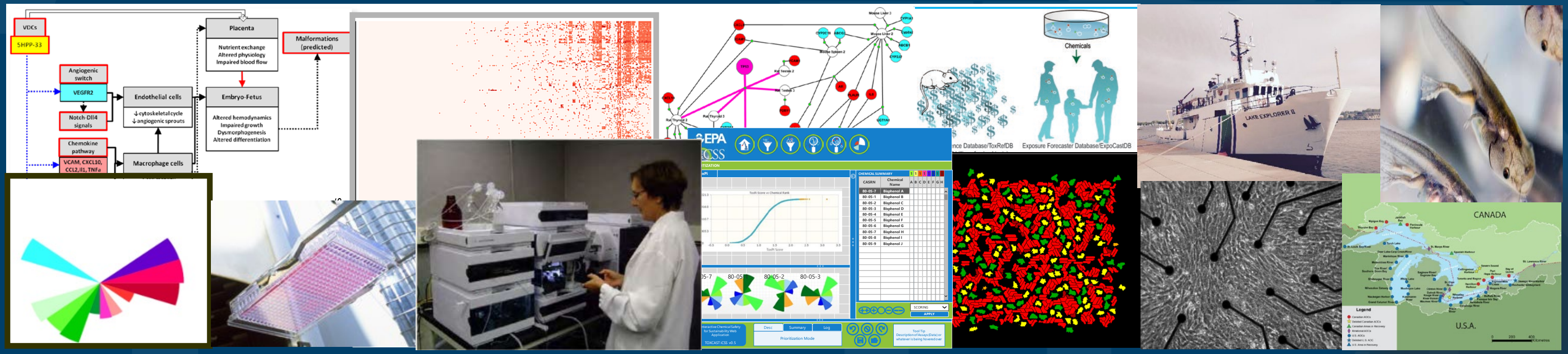
The Development, Evaluation, and Application of New Approach Methods at US EPA

When an Unstoppable Force Meets an Immovable Object



ICCA LRI - NITE workshop

June 20, 2022

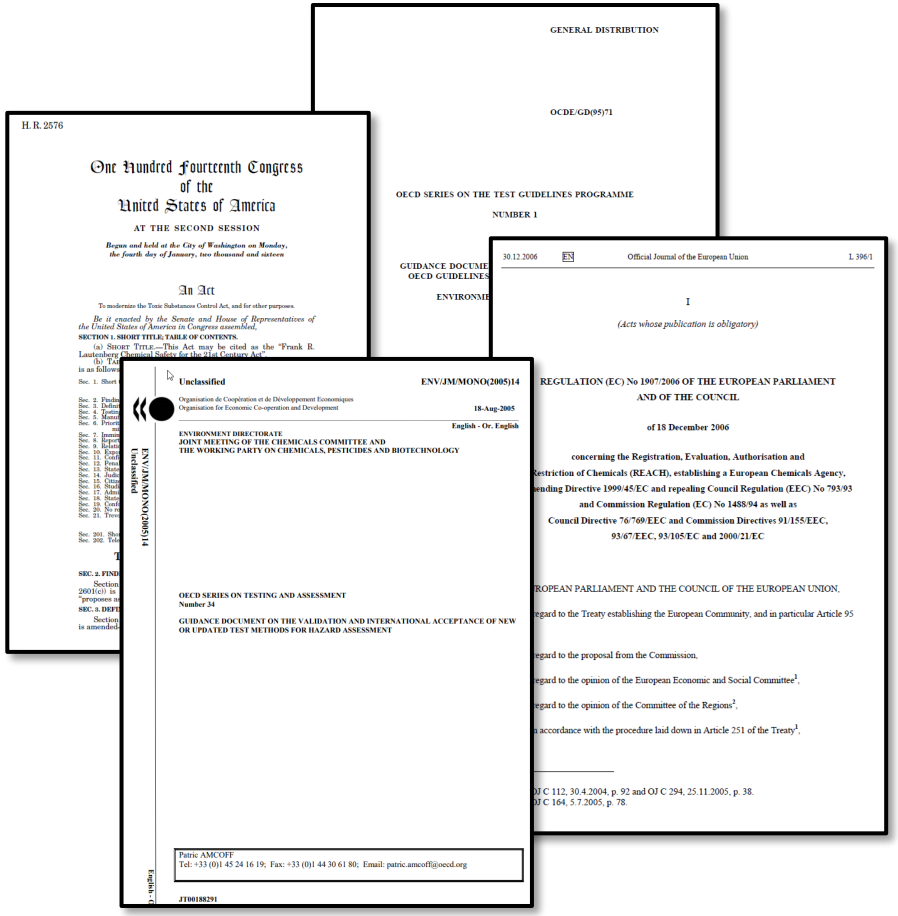
Rusty Thomas
Director
Center for Computational Toxicology and Exposure

United States Environmental Protection Agency

The Original Paradox…

Teumessian fox and the hunting dog Laelaps

The NAM Paradox…



The unstoppable NAM force and the unmovable regulatory systems and processes

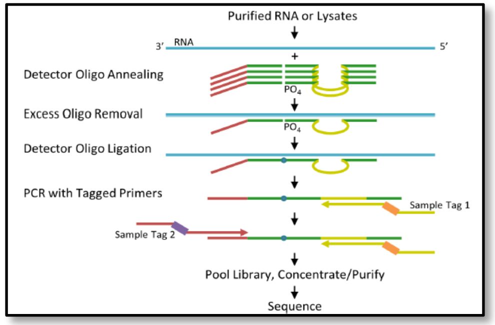
A ‘Zeus-like’ Seven Step Plan to Address This Paradox

1. Continue to innovate with NAMs while systematically address the limitations (a couple examples…)
2. Accept that there is likely not a primary mechanism/mode of action for most environmental/industrial chemicals
3. Work through how to assemble NAMs in a coherent, practical, fit for purpose testing framework
4. Understand how to benchmark new approaches
5. Grapple with the issue of protection vs. prediction in our current and future approaches
6. Evaluate regulatory flexibilities and develop a fit for purpose validation/confidence framework to evaluating new approaches
7. Quantify public health and economic trade-offs of uncertainty, cost, and time in toxicity testing methods

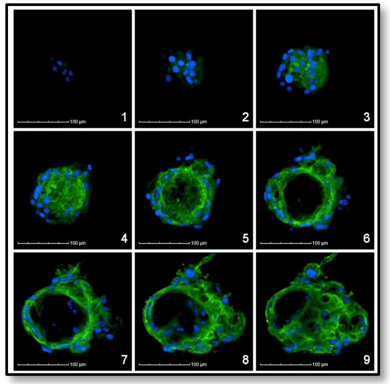
EPA United States Environmental Protection Agency

Step 1: Continue to Innovate and Address Limitations in NAMs

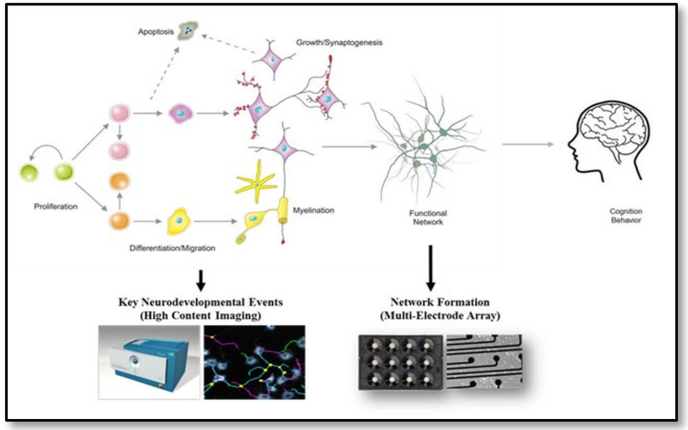
Whole Genome Transcriptomics



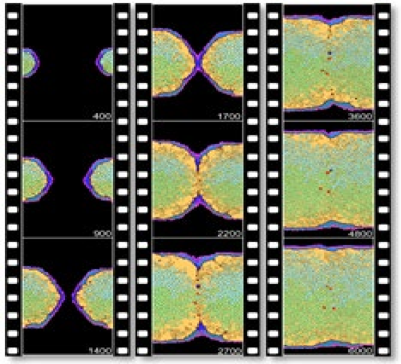
Organotypic Culture Models



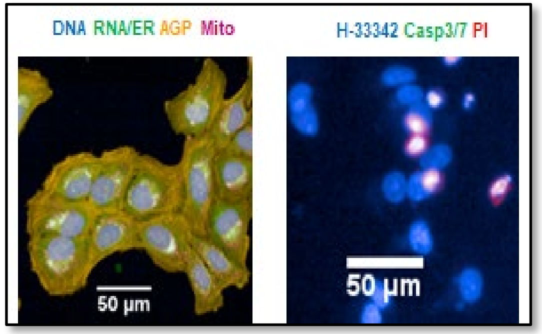
Integrated Approach to Testing and Assessment for DNT



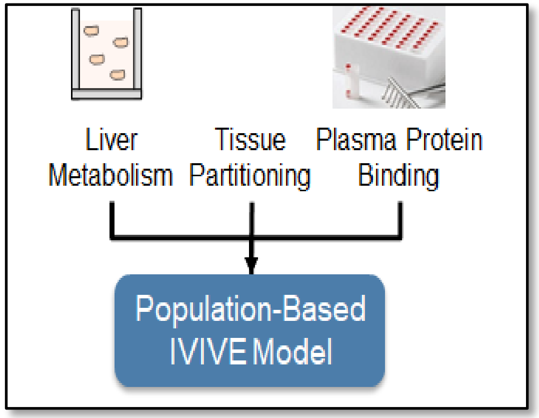
Virtual Tissue Models



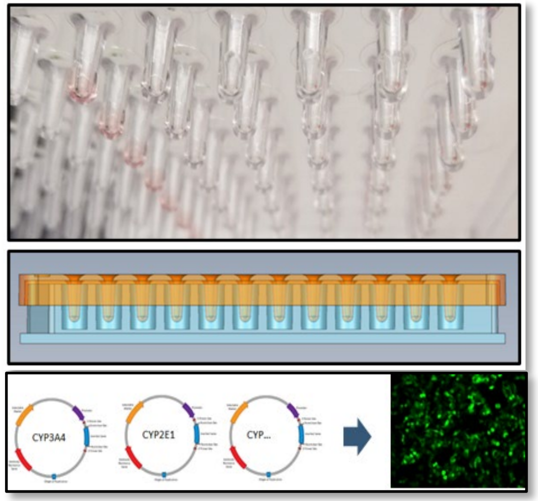
Multi-Parameter Cellular Phenotypic Profiling



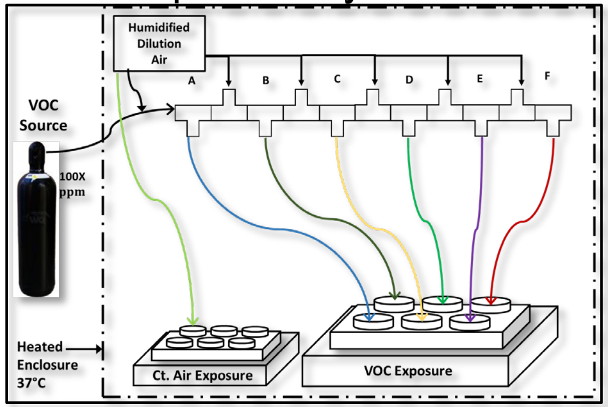
Toxicokinetic Measurements and Modeling



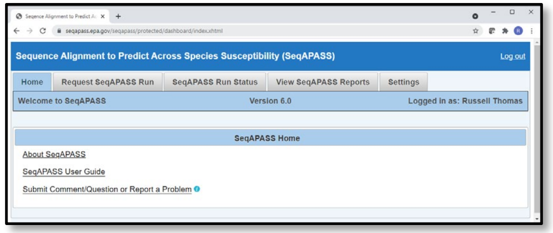
Metabolic Retrofitting



Volatile/Aerosol *In Vitro* Exposure Systems



Sequence Alignment to Predict Across Species Susceptibility



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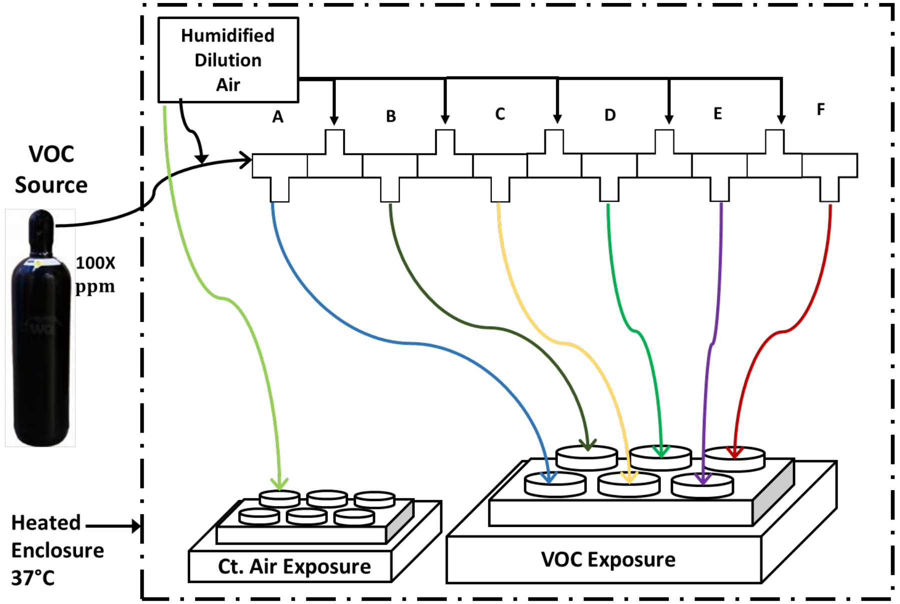
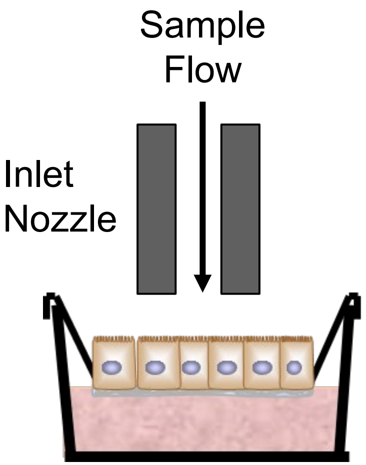
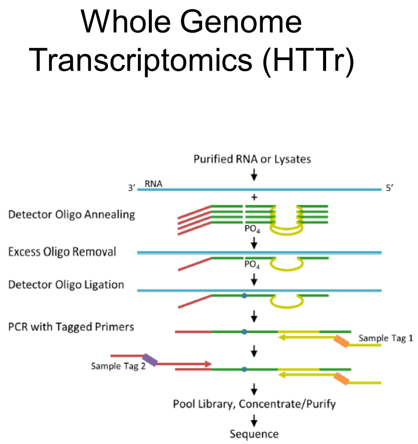
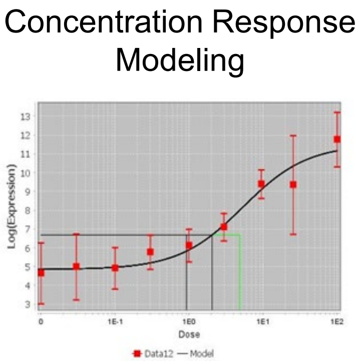
Developing *In Vitro* Exposure Systems for Volatile Chemicals









	BEAS-2B HTTr BMD (ppm)	HBEC HTTr BMD (ppm)	Representative LOAEL (ppm)	Representative NOAEL (ppm)	TLV (ppm)
Acrolein	0.58	--	0.25	NR	0.1
1-Bromopropane	2.25	NA	NR	6040	0.1 *
Formaldehyde	NA	--	6	NR	0.3
1,3-Butadiene	13.98	--	200	NR	10
Carbon Tetrachloride	9.56	NA	20	5	10
Acetaldehyde	NA	--	400	150	25
Trichloroethylene	44.84	28.15	50	25	50
Dichloromethane	142.13	226.73	8400	4200	100

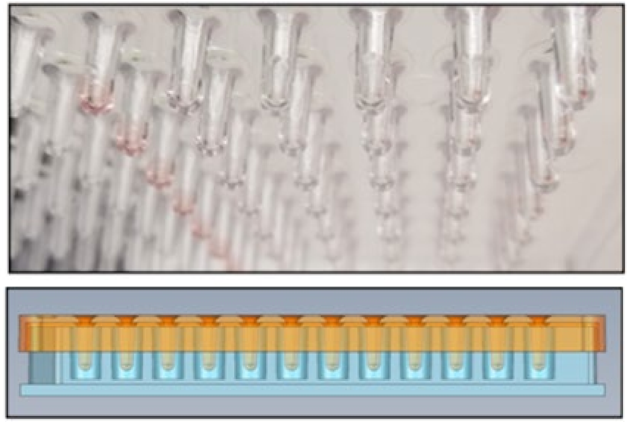
* The ACGIH TLV TWA for 1-bromopropane was updated to 0.1 ppm in 2012. Prior to that the TLV-TWA for 1-bromopropane was 10 ppm.

Speen et al., Toxicol Sci, 2022

EPA United States Environmental Protection Agency

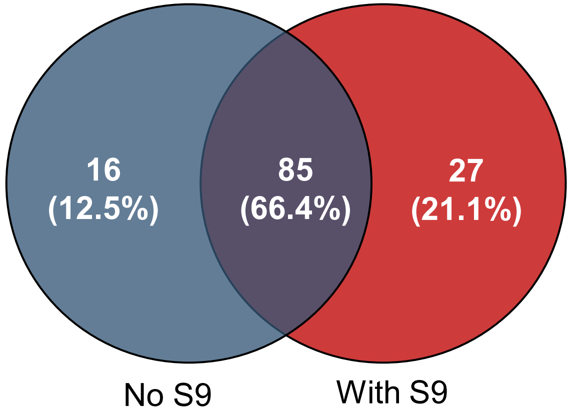
Retrofitting NAMs for Metabolic Competence

Modified Plate Lid Process



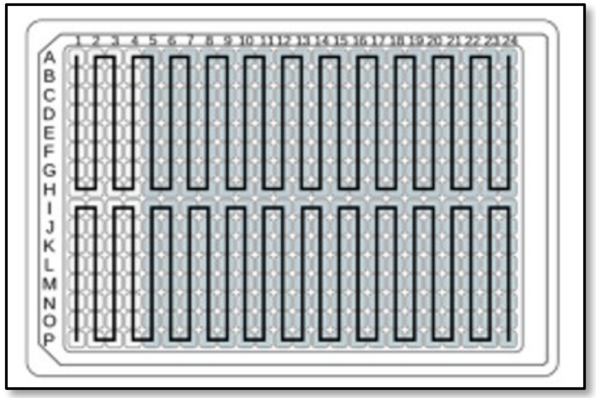
Application to Estrogen Receptor Transactivation Assay

Breakdown of positive responses + metabolism

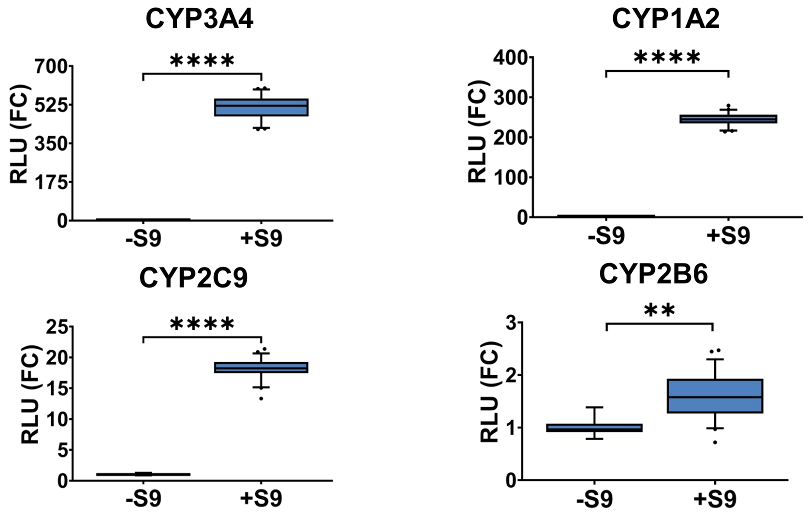


Hopperstad *et al., Toxicol Sci* 2022

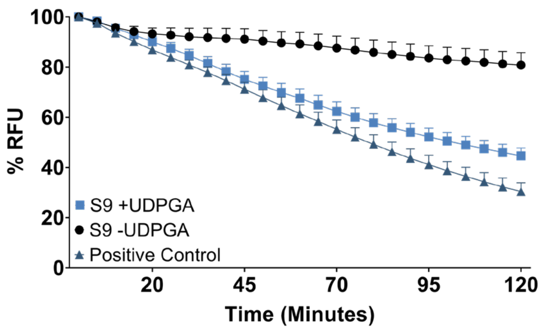
Bioprinting Process



Phase I

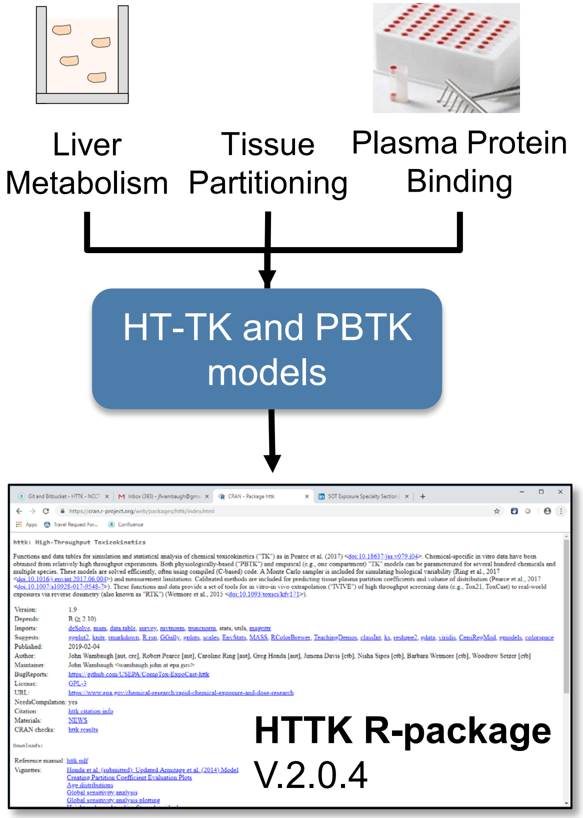


Phase II



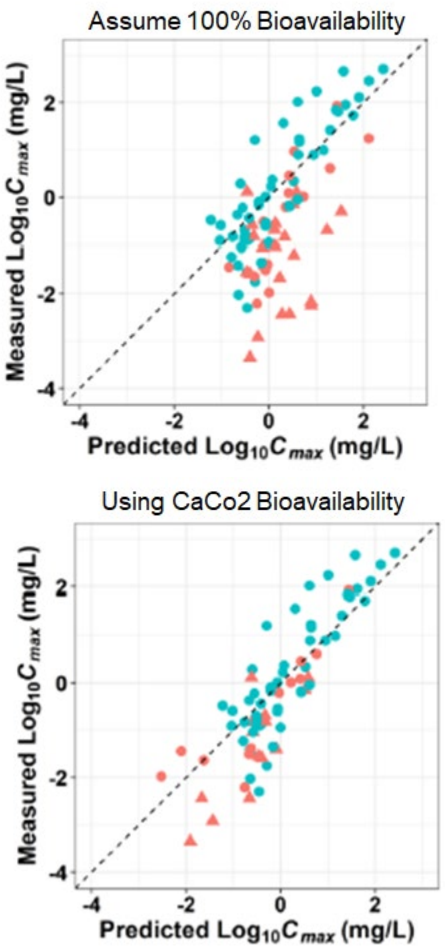
Hopperstad and Deisenroth, Unpublished

Improving Toxicokinetic NAMs for Extrapolating *In Vitro* Concentrations to Administered Doses



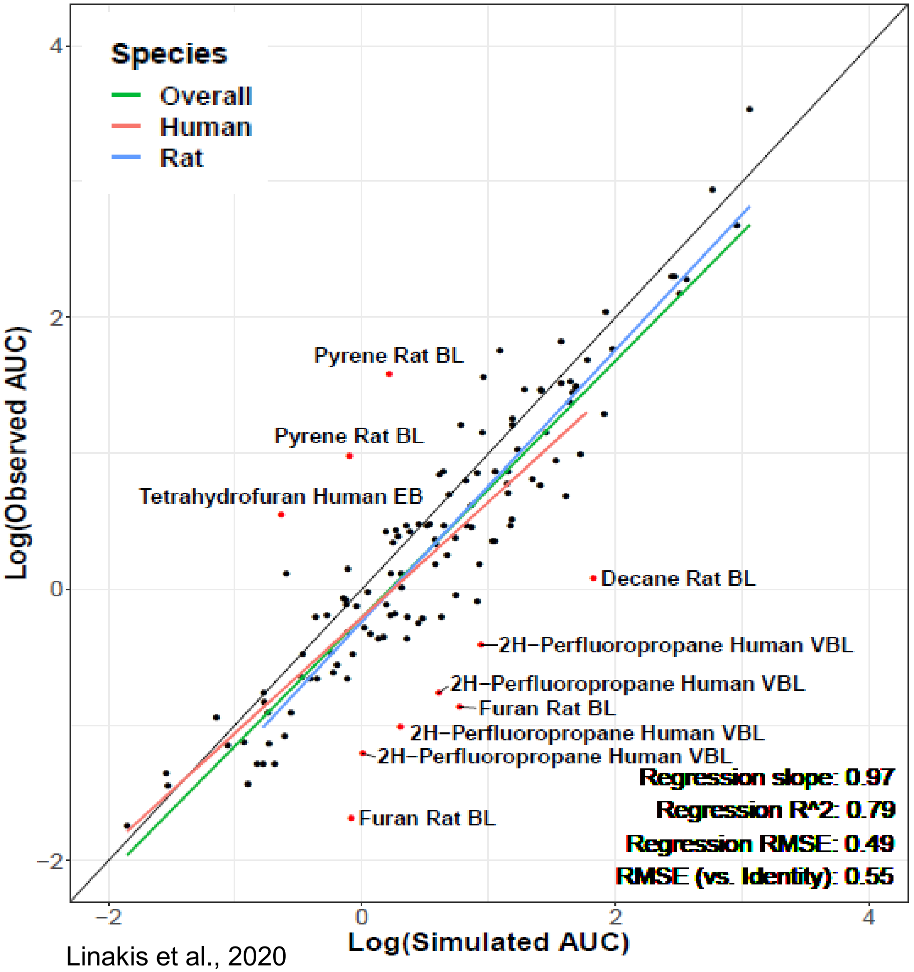
Rotroff *et al.*, *Tox Sci.*, 2010
Wetmore *et al.*, *Tox Sci.*, 2012
Wetmore *et al.*, *Tox Sci.*, 2015
Wambaugh *et al.*, *Tox Sci.*, 2018
Wambaugh *et al.*, *Tox Sci.*, 2019
Linakis *et al.*, *J Expo Sci Environ Epidemiol.* 2020

Experimental Models for Bioavailability



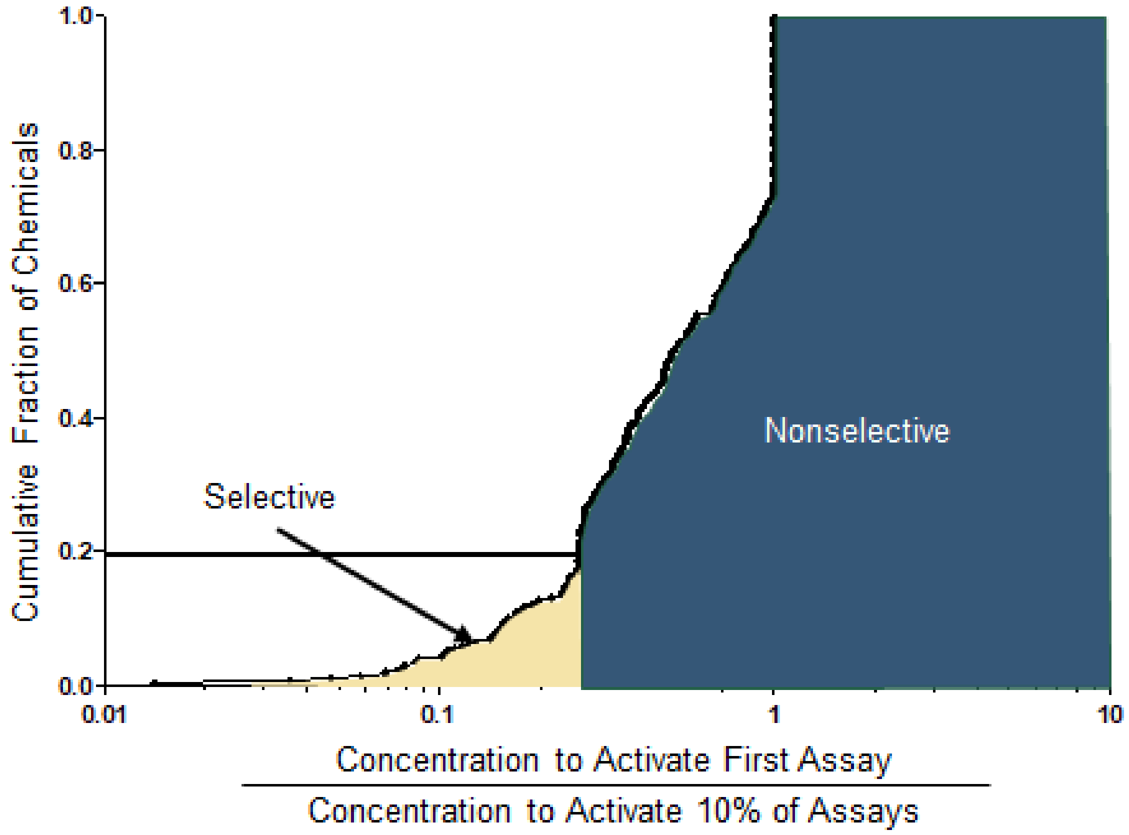
Wambaugh et al., Unpublished

Generic PBTK Model for Inhalation Exposure



Linakis et al., 2020

Step 2: Accept that Most Chemicals Non-Selectively Interact with Biological Systems



Thomas *et al., Tox Sci.*, 2013

Implies that bioactivity (*in vitro* or *in vivo*) can be a good surrogate for potential adverse effects in chemical assessments.

Step 3: Assemble NAMs into a Practical Testing Framework

TOXICOLOGICAL SCIENCES, 169(2), 2019, 317–332
doi: 10.1093/toxsci/kfz058
Advance Access Publication Date: March 5, 2019
Forum

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

FORUM

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

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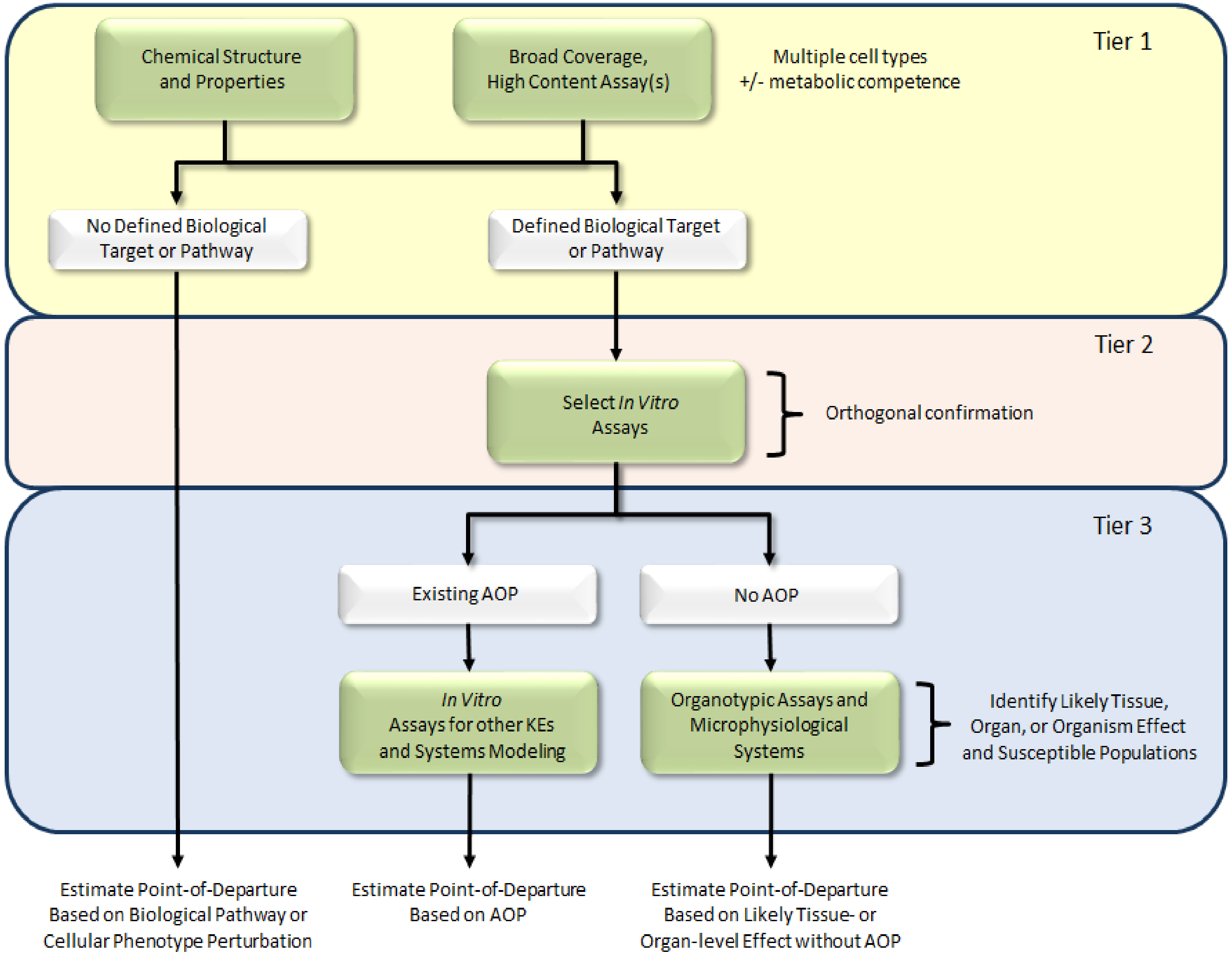
Disclaimer: The U.S. Environmental Protection Agency has provided administrative review and has approved this article for publication. The views expressed in this article are those of the authors and do not necessarily reflect the views of the U.S. Environmental Protection Agency.

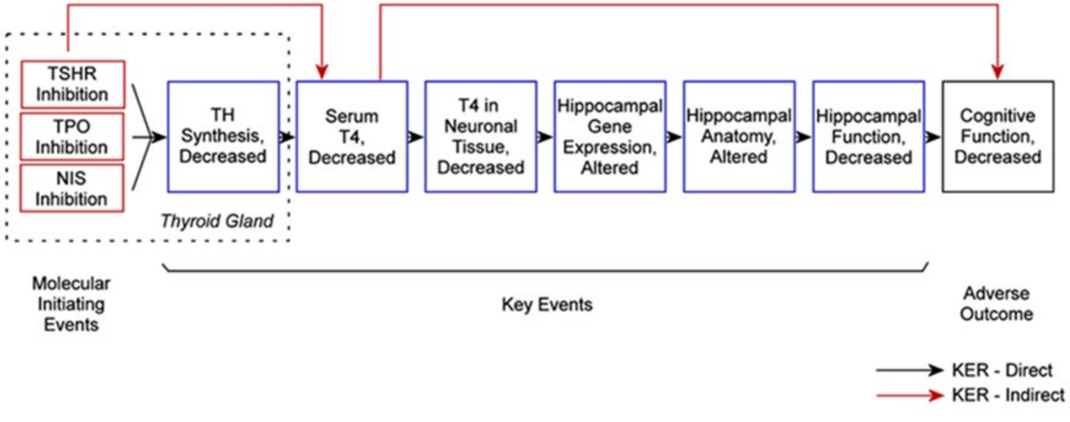
ABSTRACT

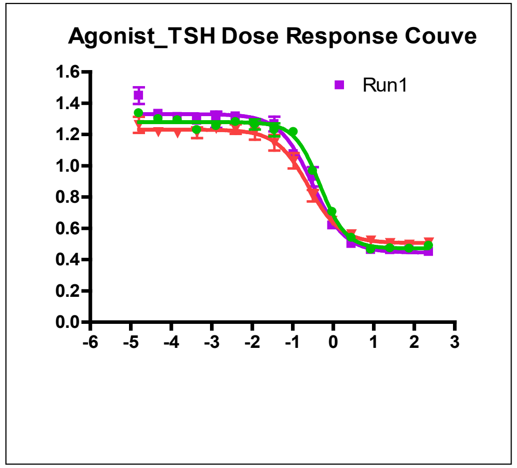
The U.S. Environmental Protection Agency (EPA) is faced with the challenge of efficiently and credibly evaluating chemical safety often with limited or no available toxicity data. The expanding number of chemicals found in commerce and the environment, coupled with time and resource requirements for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



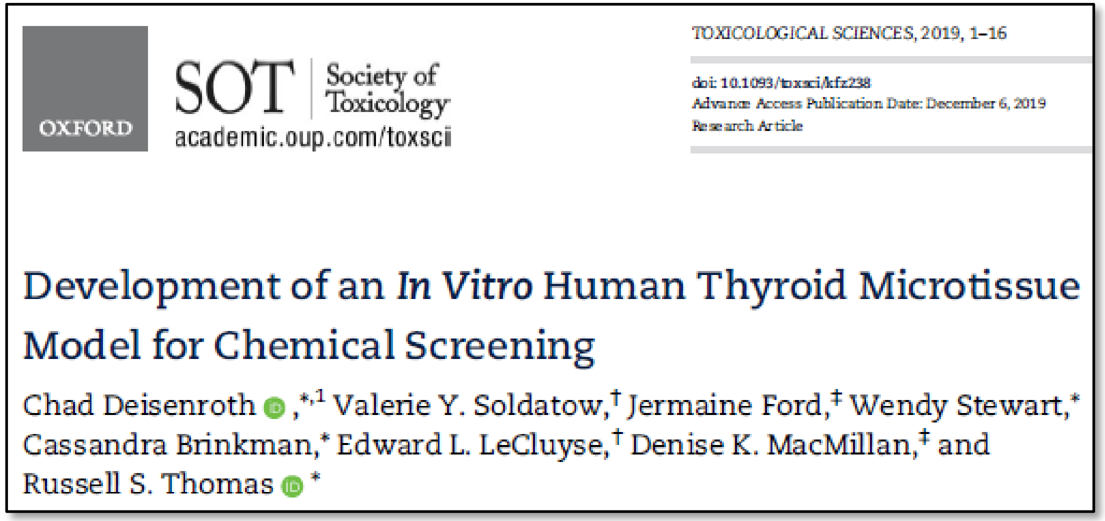
United States Environmental Protection Agency

Developing Organotypic Culture Models to Translate Molecular Events into Tissue Effects





- Original hit rate: 825/7871 = 10%
- Filtered hit rate: 417/4463 = 9%
- Selected prioritized actives: 108/417 = 26%

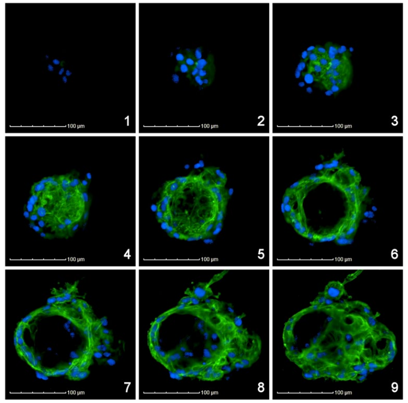

TOXICOLOGICAL SCIENCES, 2019, 1–16

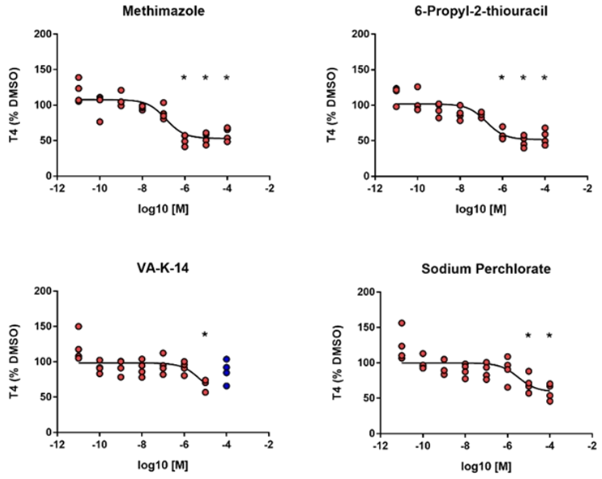
doi: 10.1093/toxsci/kfz238
Advance Access Publication Date: December 6, 2019
Research Article

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

Development of an *In Vitro* Human Thyroid Microtissue Model for Chemical Screening

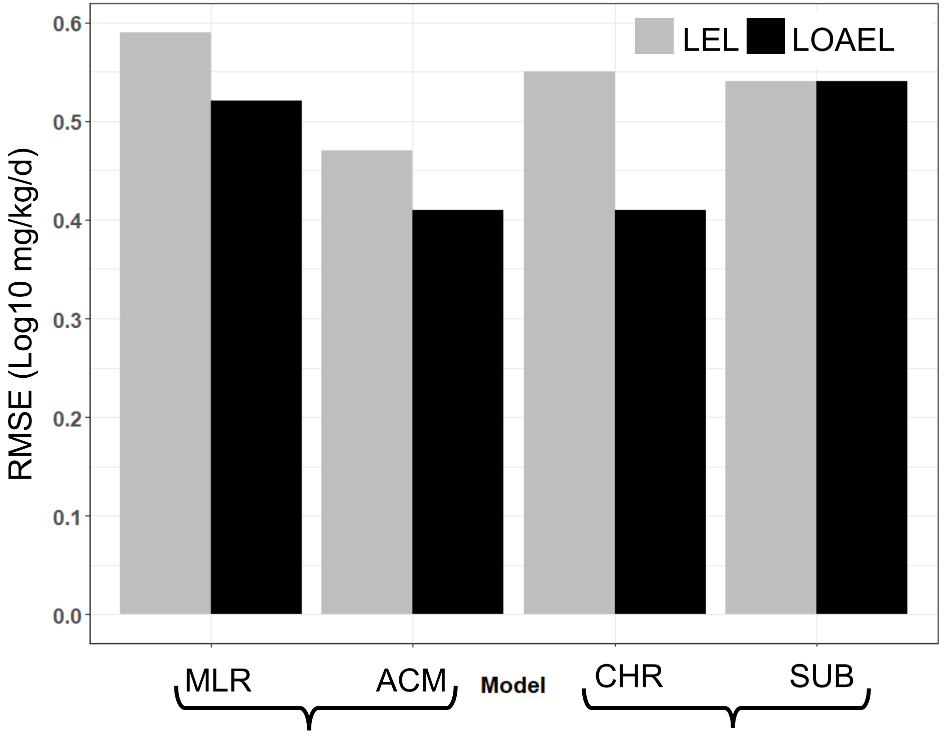
Chad Deisenroth,*[,1] Valerie Y. Soldatow,[†] Jermaine Ford,[‡] Wendy Stewart,* Cassandra Brinkman,* Edward L. LeCluyse,[†] Denise K. MacMillan,[‡] and Russell S. Thomas *





Step 4: Understand How to Benchmark Approaches

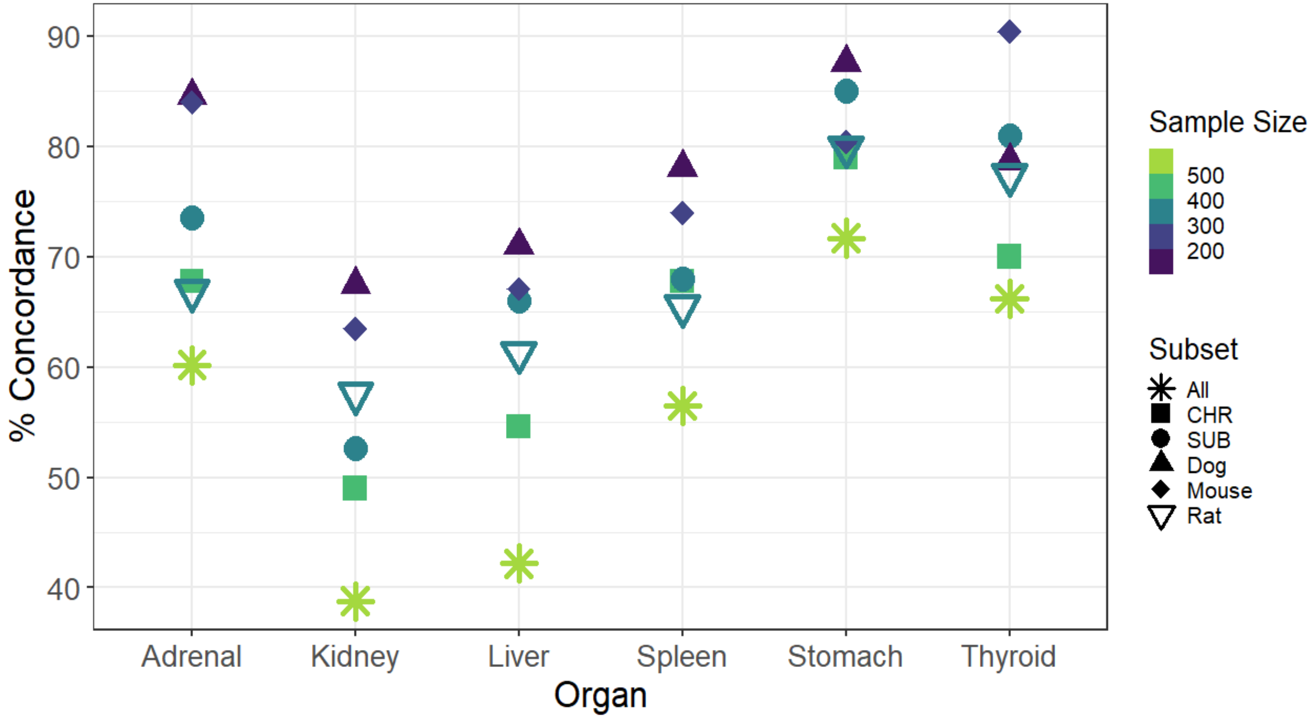
Evaluating LEL/LOAEL Variability in Traditional Toxicity Studies to Set Expectations for NAMs



Using an RMSE=0.59, the 95% Prediction Interval of an LEL/LOAEL is +/- 10-fold (e.g., 1 mg/kg/day, 0.07 – 14)

Pham et al., Comp Toxicol., 2020

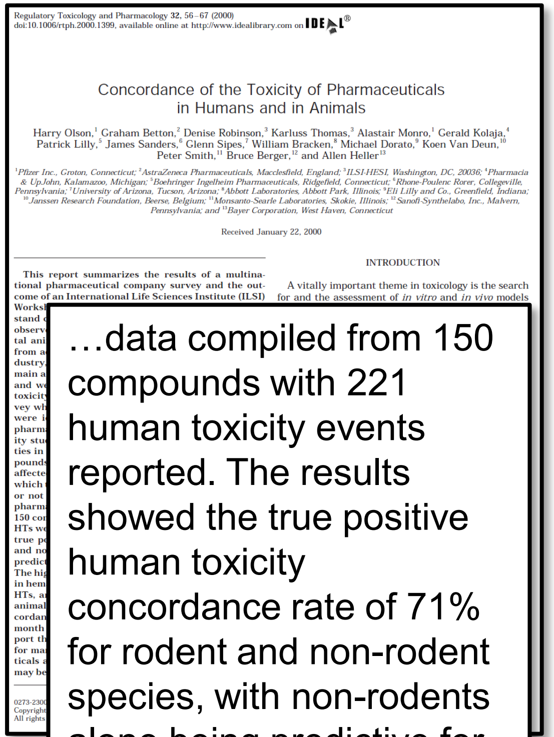
Evaluating Qualitative Concordance of Organ Toxicity



Paul-Friedman, Unpublished

Step 5: Grapple With the Issue of Protection vs Prediction with Current Models and NAMs

Comparisons of Preclinical–to-Clinical Toxicity Responses


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]

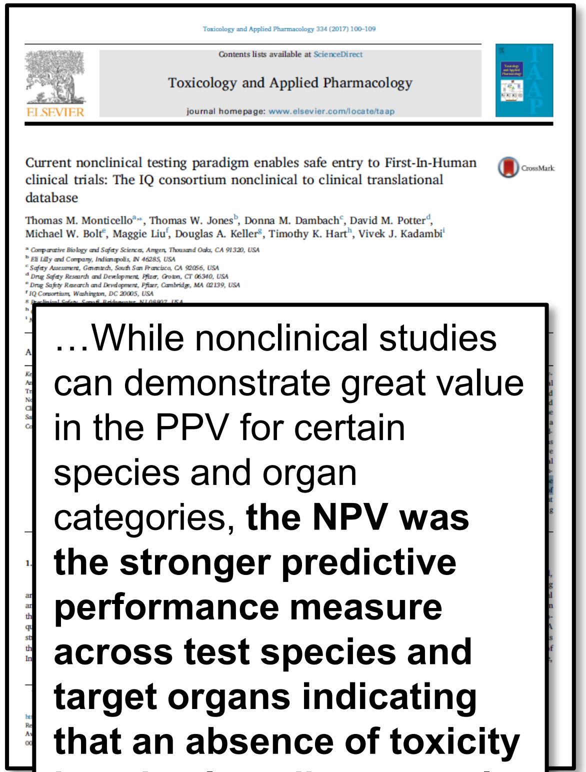
Received January 22, 2000

This report summarizes the results of a multinational pharmaceutical company survey and the outcome of an International Life Sciences Institute (ILSI) Works…

INTRODUCTION

A vitally important theme in toxicology is the search for and the assessment of *in vitro* and *in vivo* 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%.**

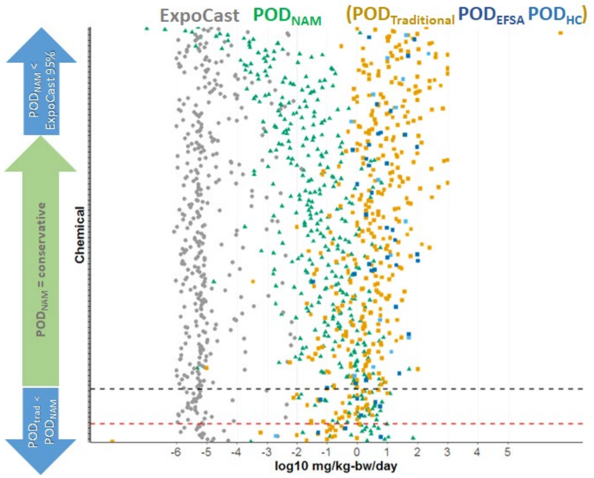

Toxicology and Applied Pharmacology 334 (2017) 100–109
Contents lists available at ScienceDirect
Toxicology and Applied Pharmacology
journal homepage: www.elsevier.com/locate/taap

Current nonclinical testing paradigm enables safe entry to First-In-Human clinical trials: The IQ consortium nonclinical to clinical translational database

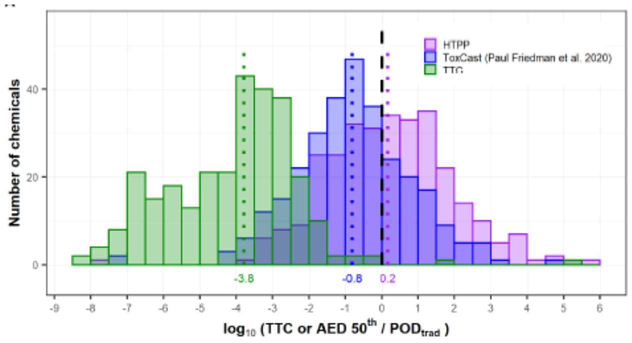
Thomas M. Monticello[a,*], Thomas W. Jones[b], Donna M. Dambach[c], David M. Potter[d], Michael W. Bolt[e], Maggie Liu[f], Douglas A. Keller[g], Timothy K. Hart[h], Vivek J. Kadambi[i]

…While nonclinical studies can demonstrate great value in the PPV for certain species and organ categories, **the NPV was the stronger predictive performance measure across test species and target organs indicating that an absence of toxicity in animal studies strongly predicts a similar outcome in the clinic.**

Case Studies Demonstrating Application of Bioactivity as a Protective POD

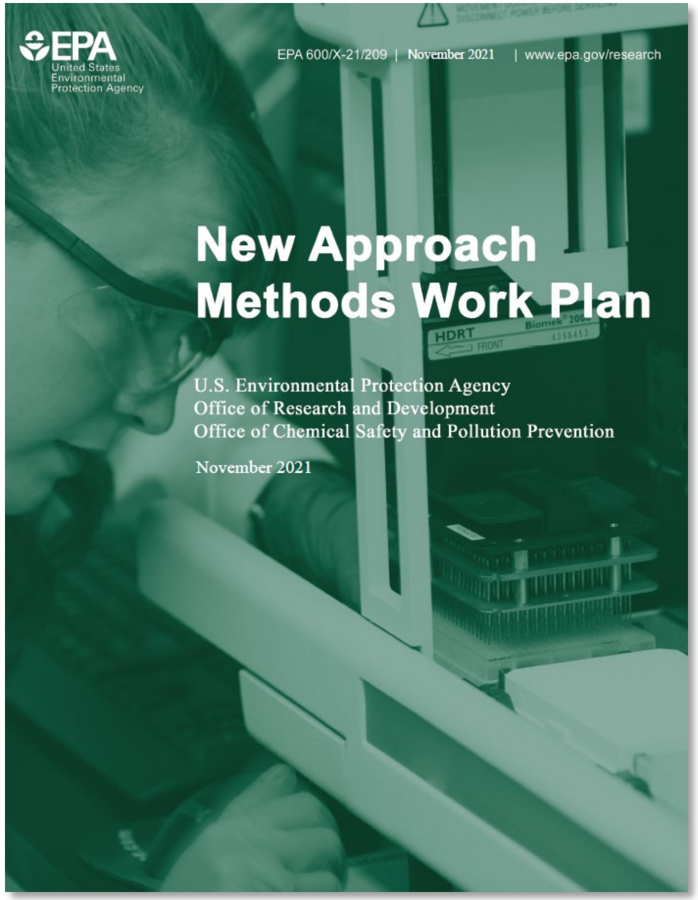


Paul-Friedman et al., 2020



Nyffeler and Harrill, ISMB Poster, 2020

Step 6: Evaluate Regulatory Flexibilities and Develop a Fit-for-Purpose Scientific Confidence Framework



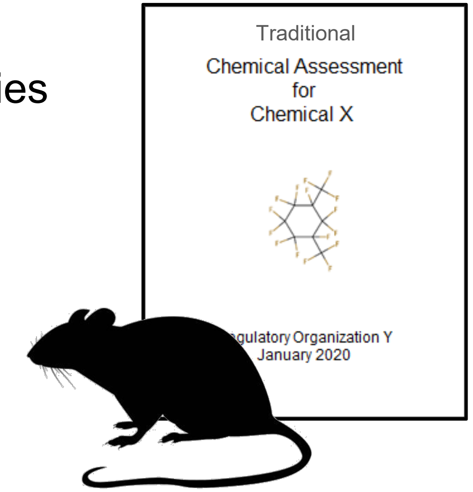
Deliverables:

- EPA review of existing statutes, regulations, policies, and guidance that relate to vertebrate animal testing in 2022
- US National Academies of Sciences report on variability and relevance of existing mammalian toxicity tests in 2023.
- Scientific confidence framework to evaluate the quality, reliability, and relevance of NAMs in 2024.

Step 7: Quantify Trade-Offs of Uncertainty, Cost, and Time in Toxicity Testing Methods

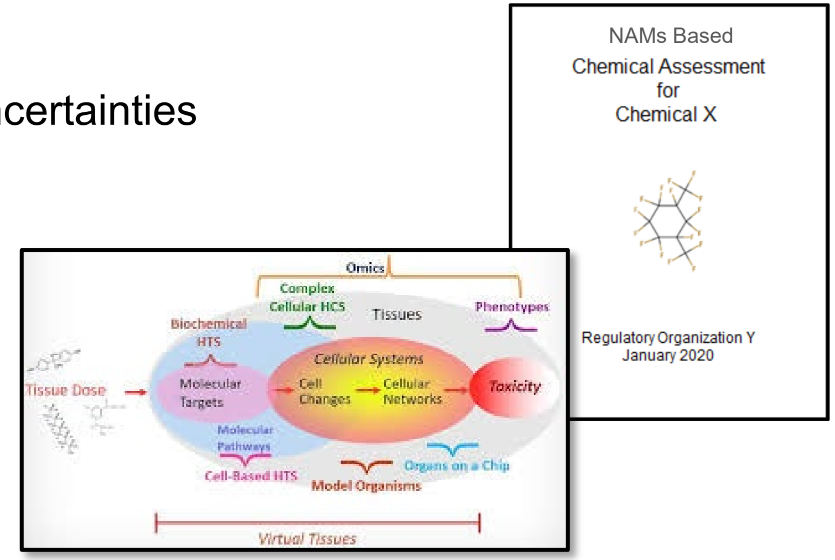
<u>Option 1</u>

- 6 – 20 years
- “Smaller” uncertainties
- $Ks - $Ms



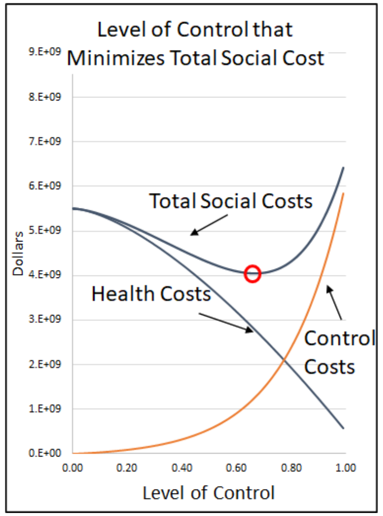
<u>Option 2</u>

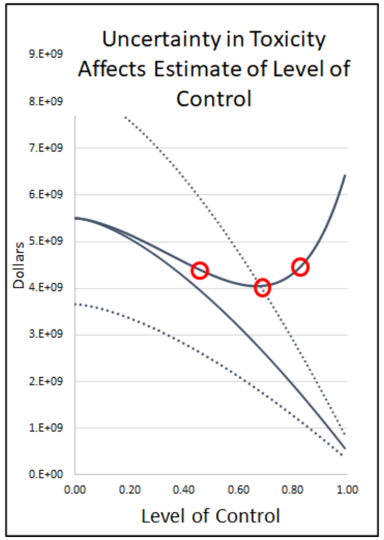
- <1 year
- “Bigger” uncertainties
- $Ks



What choice would you make?

Development of a Value of Information Framework to Evaluate the Trade-Offs in Toxicity Testing





- Value of information (VOI) analysis is a decision analytic method that quantifies the expected value of additional testing/data in reducing decision uncertainty (Tuffaha, 2021).
- VOI requires a method to determine the cost of uncertainty
  - $Total\ Social\ Cost = Total\ Control\ Cost + Total\ Health\ Cost$
- Lots of work in VOI evaluating different tests (e.g., medical tests), but few studies evaluating the impact of time.
- The impact of time can be incorporated by discounting the costs on an annual basis.
- Multiple metrics can be used to compare the value of different toxicity tests adjusted for time and cost of the test
  - **Expected Value of Delayed Sample Information (EVDSI)**
  - Expected Net Benefit of Sampling (ENBS)
  - Return on Investment (ROI)

Hagiwara et al., Risk Anal., 2022

General Conclusions From the Value of Information Studies

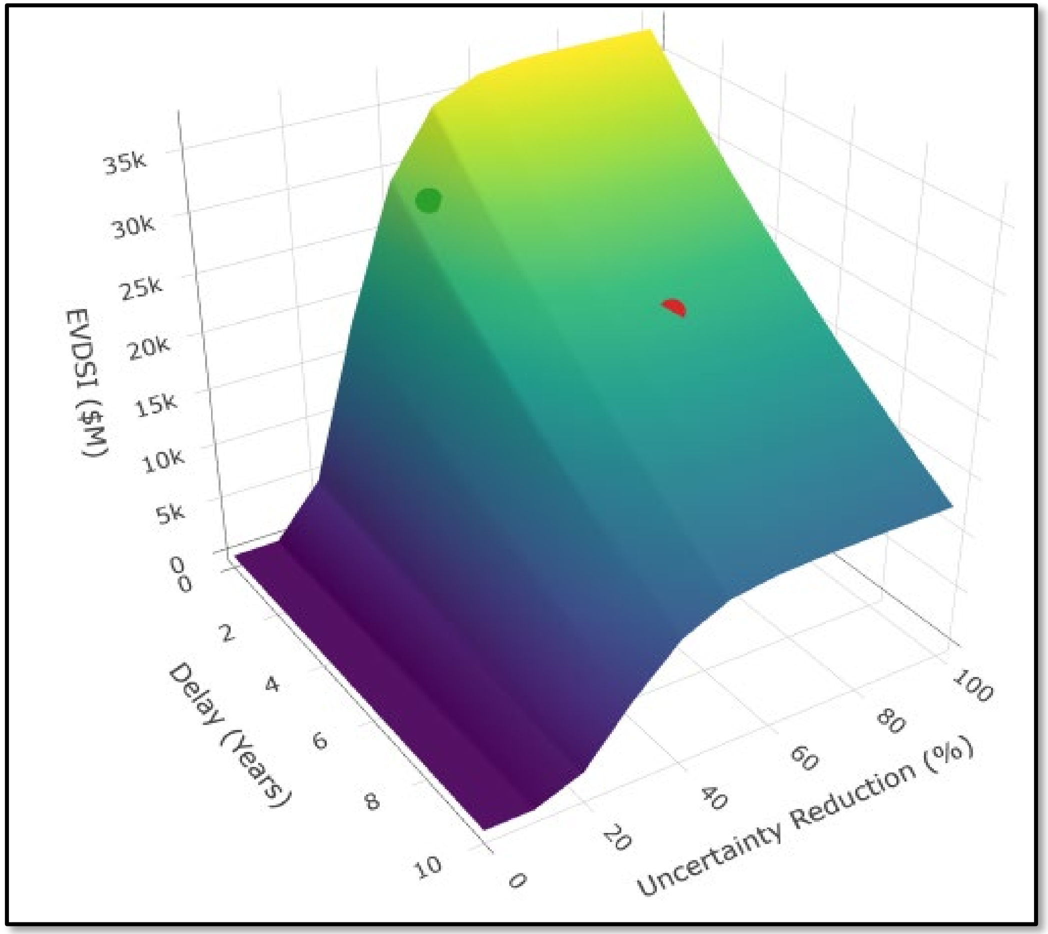
Example Scenarios

- Two hypothetical toxicity tests
  - Test A – lower cost ($5K), shorter duration (1 yr), higher uncertainty (4 orders of magnitude)
  - Test B – higher cost ($5M), longer duration (5 yr), lower uncertainty (2 orders of magnitude)
- Different health endpoints and decision types
  - Chronic and acute effects
  - Chemicals regulated based on benefit-cost analysis and target risk levels

Overall Conclusions

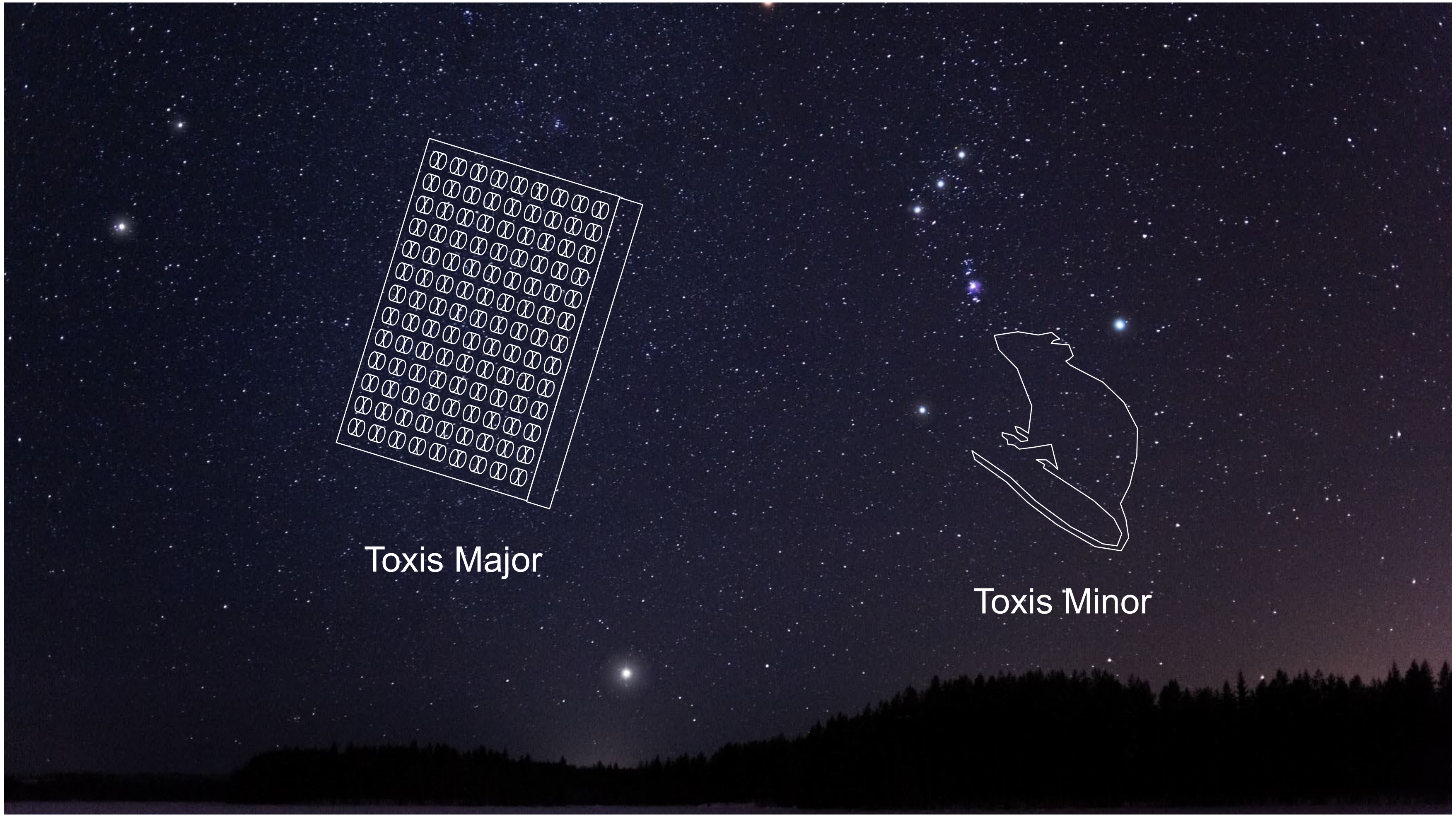
- ***Timeliness has a significant positive impact on the VOI of toxicity tests, even in the presence of smaller reductions in uncertainty.***
- The positive impact of the shorter tests may be multiplicatively amplified by the ability to test more chemicals.

Trade-Offs of Uncertainty and Time of Hypothetical Toxicity Testing Methods
(Chronic Effect, Target Risk Decision Maker)



Hagiwara et al., Risk Anal., 2022

Moving from a Paradox to a Practical Solution



Acknowledgements

Center for Computational Toxicology and Exposure (CCTE) Staff

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- NCATS

EPA Colleagues:
- CEMM
- CPHEA
- CESER
- OCSPP

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

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Gulf Breeze, FL

Cincinnati, OH

Athens, GA