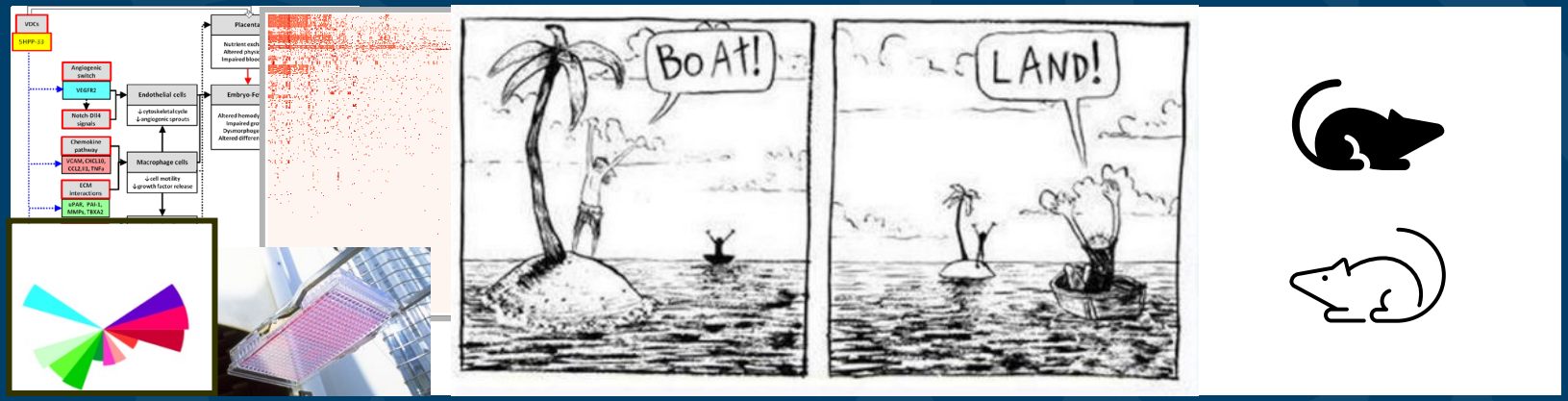
Application of NAMs for Chemical Safety Decisions

Perspectives from the US EPA Office of Research and Development

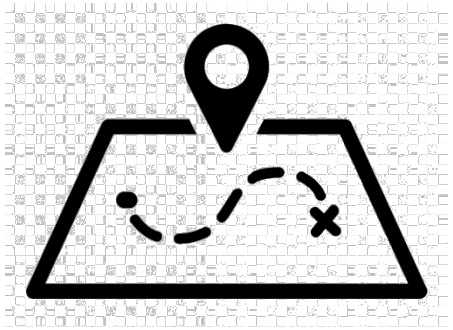


Challenges of Public Health Protection in the 21st Century
BfR Symposium

November 17, 2021

Rusty Thomas
Director
Center for Computational Toxicology and Exposure

Where Are We Currently In Developing and Applying NAMs for Regulatory Decisions?



- Significant ongoing research to systematically addressing the limitations of current NAMs
- Greater acceptance that there is likely not a primary mechanism/mode of action for most environmental/industrial chemicals
- Available frameworks for how to assemble NAMs in a coherent, practical, fit for purpose testing
- Still working on transitioning from apical to molecular endpoints
- Evolving understanding how to benchmark new approaches
- Many organizations grappling with the issue of protection vs. prediction
- Growing need for flexible and fit for purpose validation/confidence frameworks for evaluating new approaches
- Greater understanding the public health and economic trade-offs of testing faster versus uncertainty

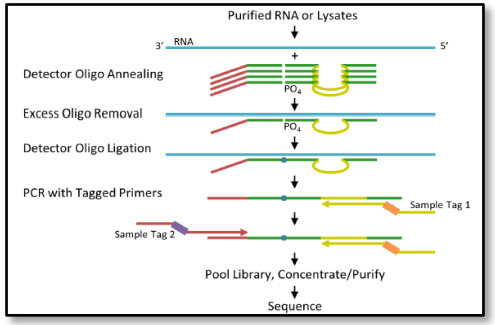
Scientific and Technical Challenges Associated with NAMs

- Limited coverage of important cellular and intracellular processes
- Relatively short duration exposures and extrapolation to chronic effects
- Extrapolating context-dependent molecular/pathway changes to adverse responses in organs and tissues
- Limited metabolic capacity
- “Black box” predictions
- Limited chemical domain of applicability
- Complex data interpretation
- Cross-species extrapolation
- …

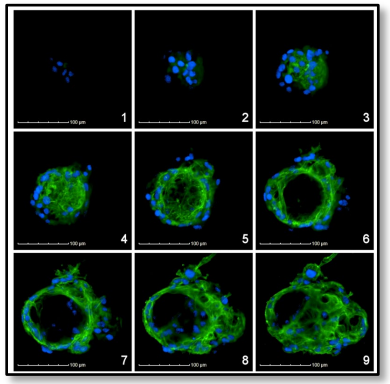
Research Activities and Innovations to Overcome Those Challenges…

United States Environmental Protection Agency

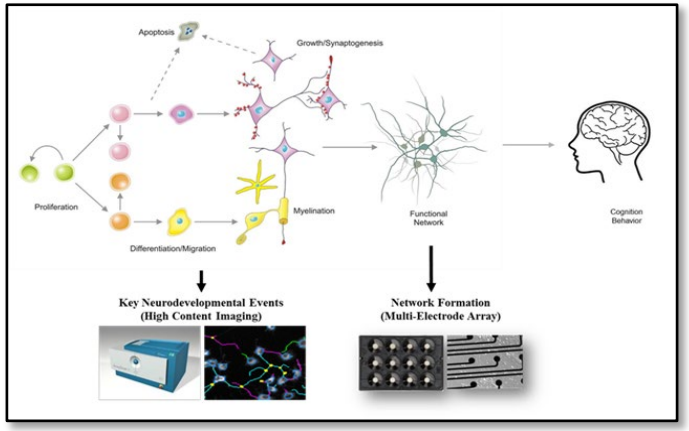
Whole Genome Transcriptomics



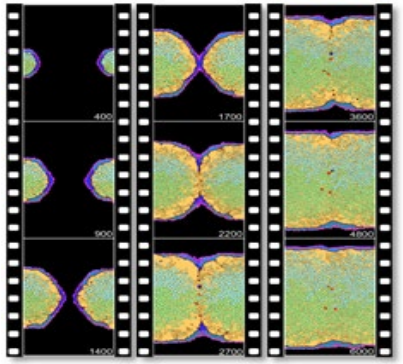
Organotypic Culture Models



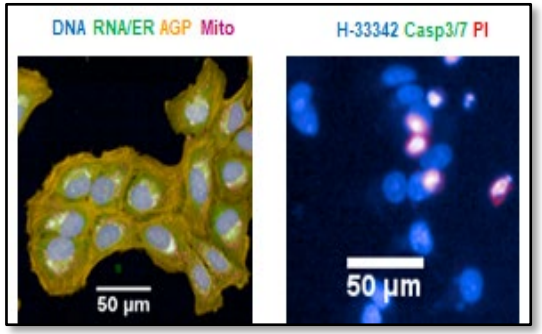
Integrated Approach to Testing and Assessment for DNT



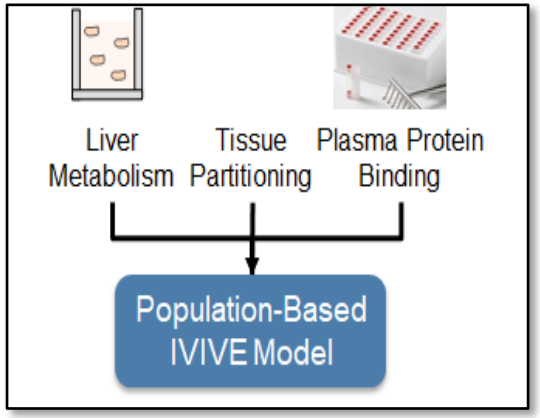
Virtual Tissue Models



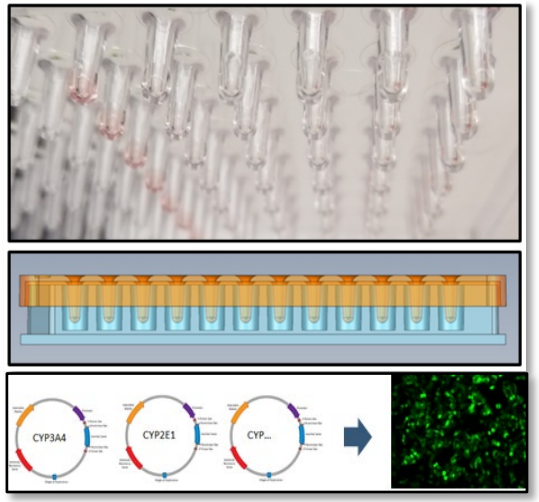
Multi-Parameter Cellular Phenotypic Profiling



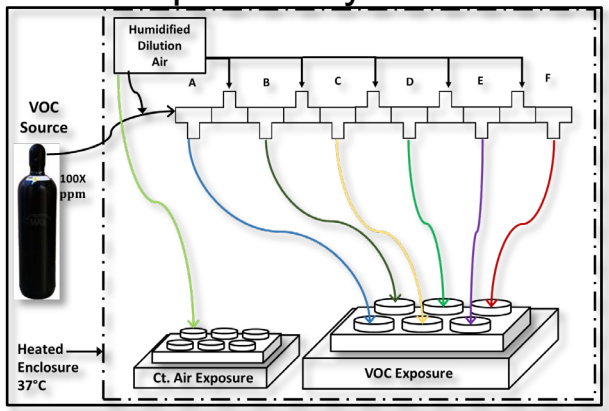
Toxicokinetic Measurements and Modeling



Metabolic Retrofitting

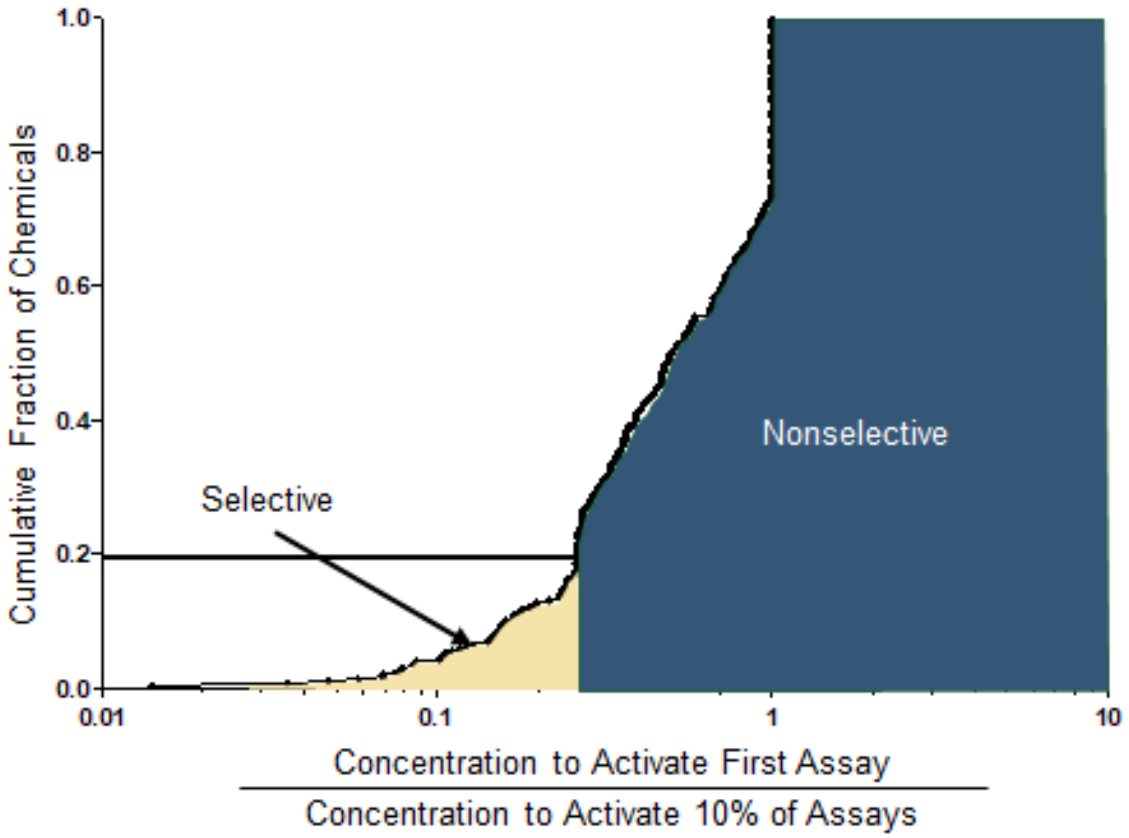


Volatile/Aerosol *In Vitro* Exposure Systems

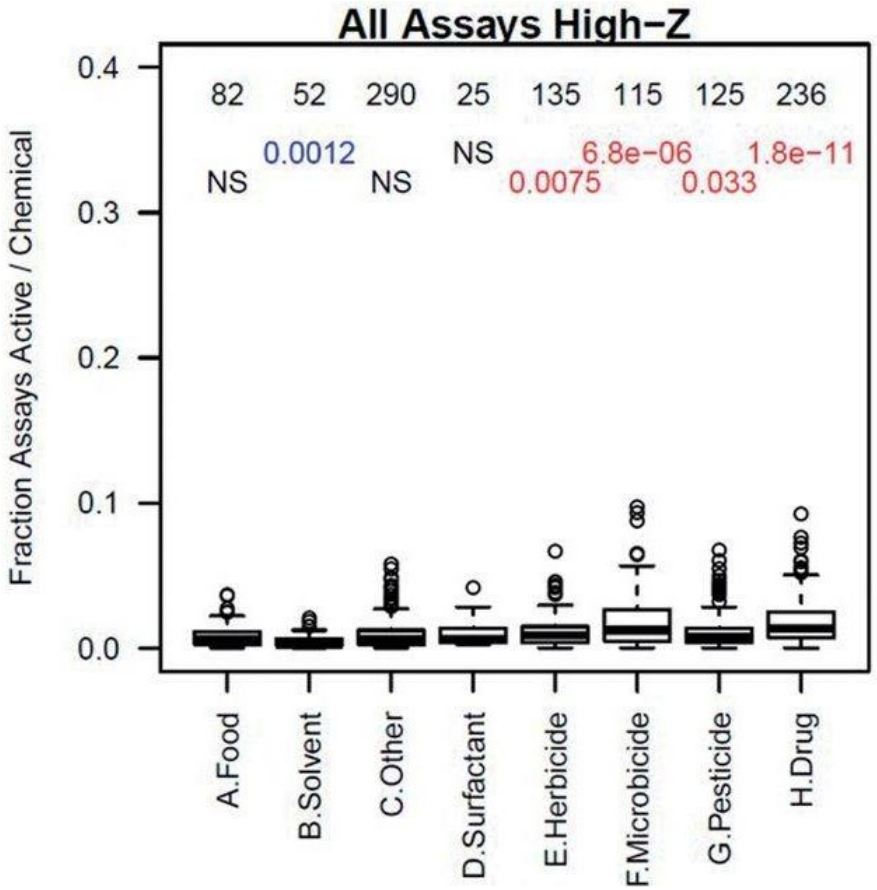


Sequence Alignment to Predict Across Species Susceptibility

Greater Acceptance that Most Chemicals Non-Selectively Interact with Biological Systems



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



Judson *et al., Tox Sci.,* 2016

Assembling 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

FORUM

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

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

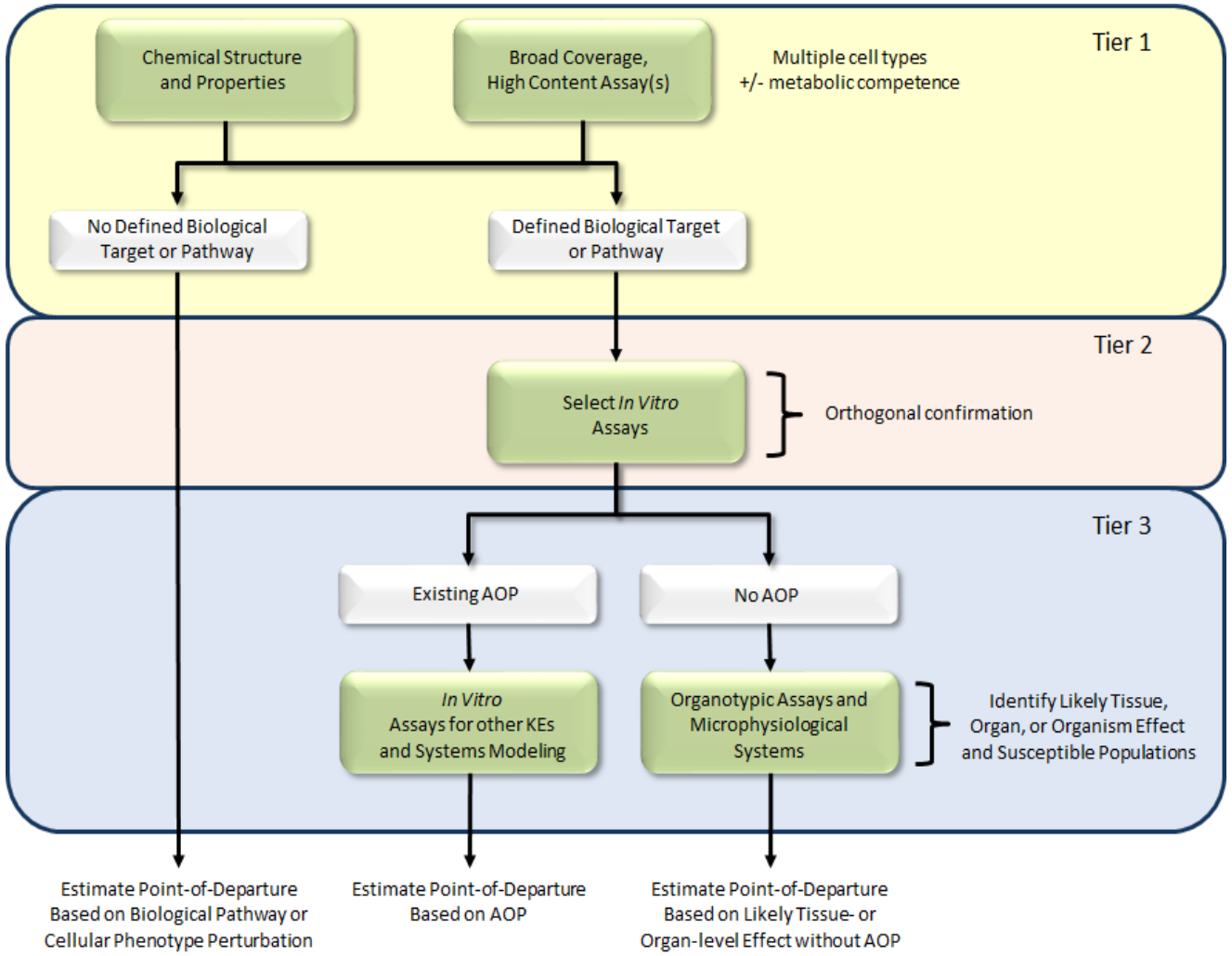
*National Center for Computational Toxicology, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, †National Center for Environmental Assessment, U.S. Environmental Protection Agnecy, Washington, D.C. 20004, ‡National Exposure Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, §Chemical Safety for Sustainability National Research Program, U.S. Environmental Protection Agency, Washington, D.C. 20004, ¶National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, ‖National Center for Environmental Assessment, U.S. Environmental Protection Agency, Cincinnati, OH 45220, ‖National Risk Management Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH 45220, and ‖National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Duluth, MN 55804

[1]To whom correspondence should be addressed at National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, 109 T.W. Alexander Drive, Room D110-D, Mail Code: D143-02, Research Triangle Park, NC 27711. Fax: (919) 541-1194. E-mail: thomas.russell@epa.gov.

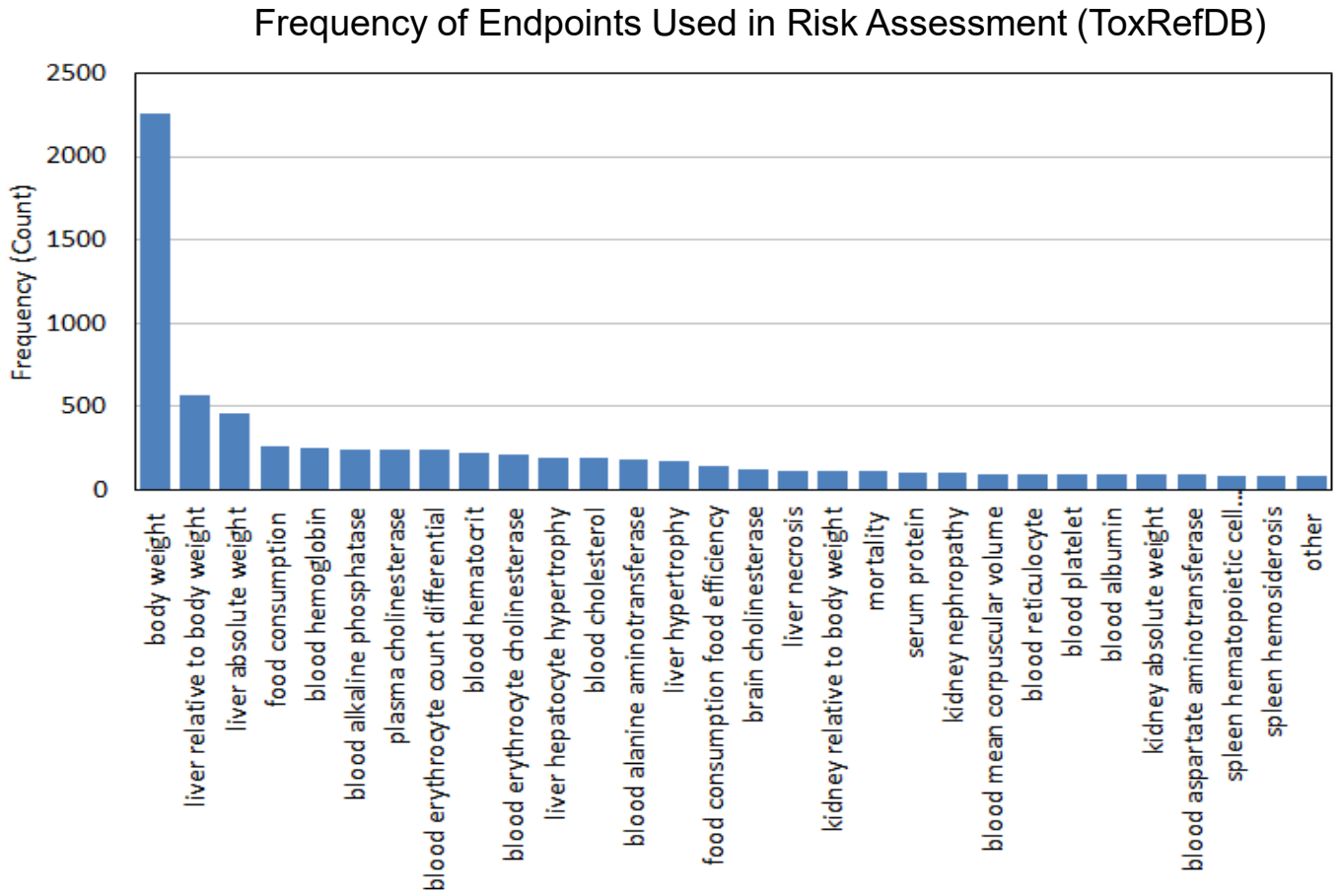
Disclaimer: The U.S. Environmental Protection Agency has provided administrative review and has approved this article for publication. The views expressed in this article are those of the authors and do not necessarily reflect the views of the U.S. Environmental Protection Agency.

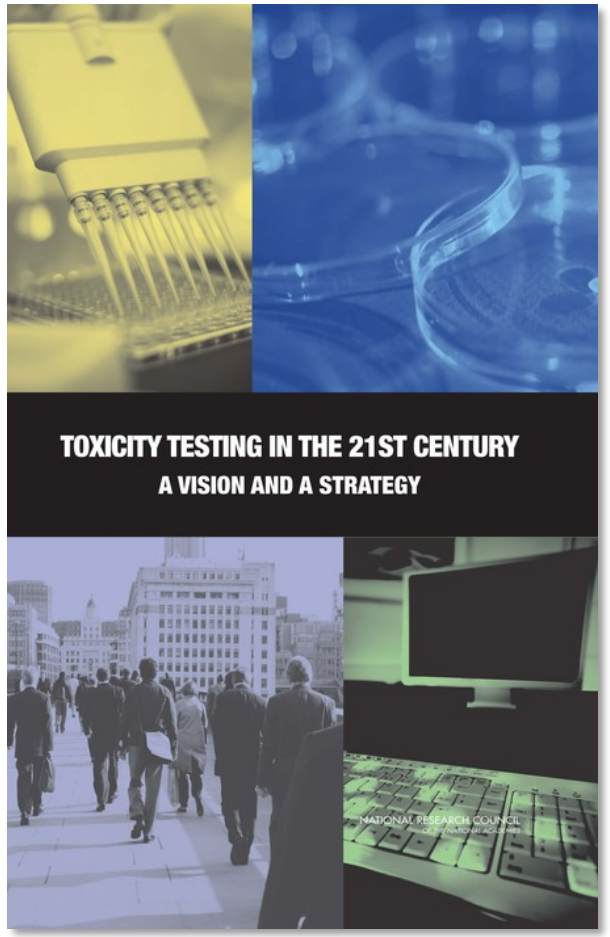
ABSTRACT

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,



Still Transitioning from Apical to Molecular Endpoints

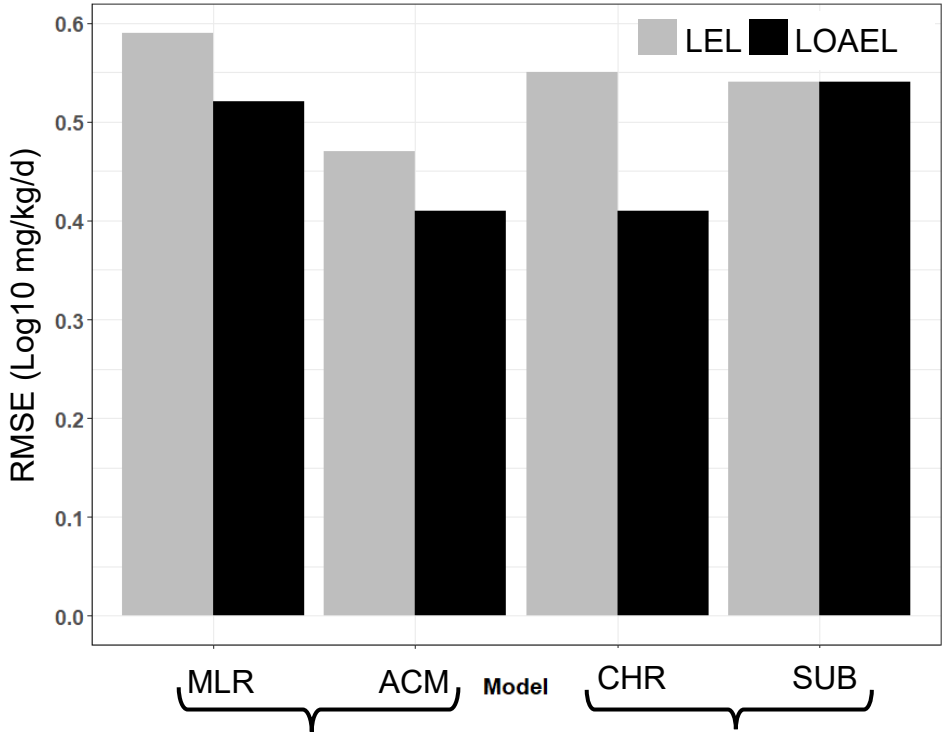




K. Paul-Friedman, Unpublished

Evolving Understanding How to Benchmark Approaches

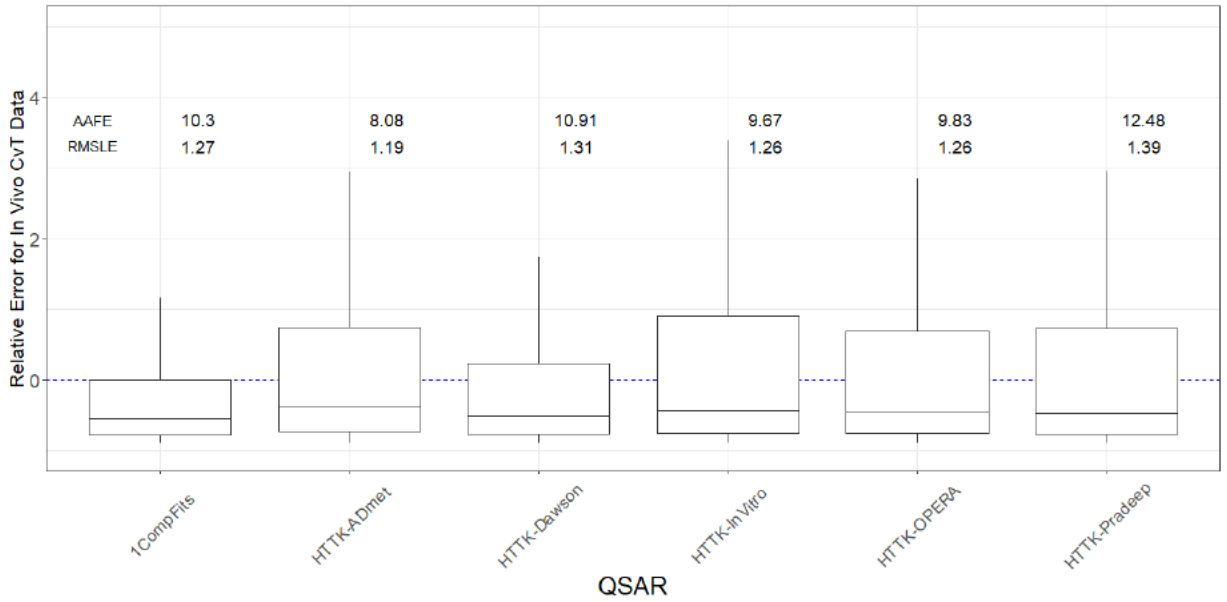
Evaluating LEL/LOAEL Variability in Traditional Toxicity Studies to Set Expectations for NAMs



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

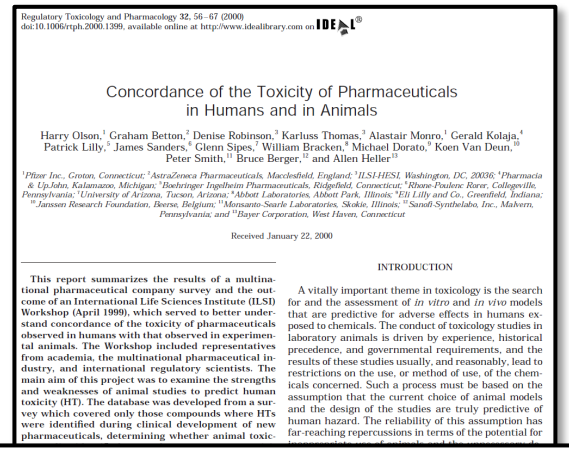
Comparing *In Silico, In Vitro,* and *In Vivo* Data for Toxicokinetic Modeling



Wambaugh et al., QSAR2021 meeting poster

Grappling With the Issue of Protection vs Prediction

Limited Qualitative Concordance of Rodent and Human Toxicological 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]

[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

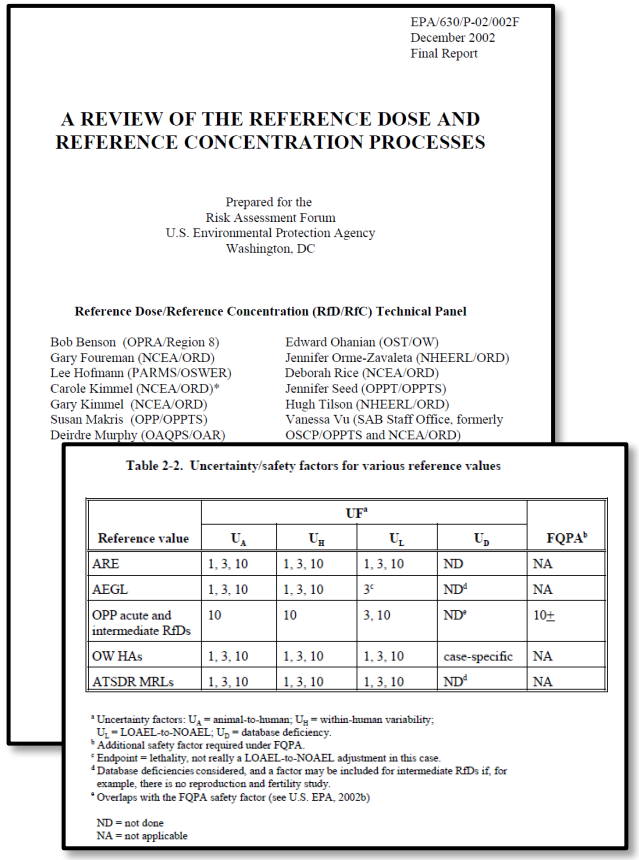
This report summarizes the results of a multinational pharmaceutical company survey and the outcome of an International Life Sciences Institute (ILSI) Workshop (April 1999), which served to better understand concordance of the toxicity of pharmaceuticals observed in humans with that observed in experimental 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 toxic-

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

…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%.**

Current Risk Assessment Practices Geared Towards Protection Not Prediction



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

Reference Dose/Reference Concentration (RfD/RfC) Technical Panel

Bob Benson (OPRA/Region 8)
Gary Foureman (NCEA/ORD)
Lee Hofmann (PARMS/OSWER)
Carole Kimmel (NCEA/ORD)*
Gary Kimmel (NCEA/ORD)
Susan Makris (OPP/OPPTS)
Deirdre Murphy (OAQPS/OAR)
Edward Ohanian (OST/OW)
Jennifer Orme-Zavaleta (NHEERL/ORD)
Deborah Rice (NCEA/ORD)
Jennifer Seed (OPPT/OPPTS)
Hugh Tilson (NHEERL/ORD)
Vanessa Vu (SAB Staff Office, formerly OSCP/OPPTS and NCEA/ORD)

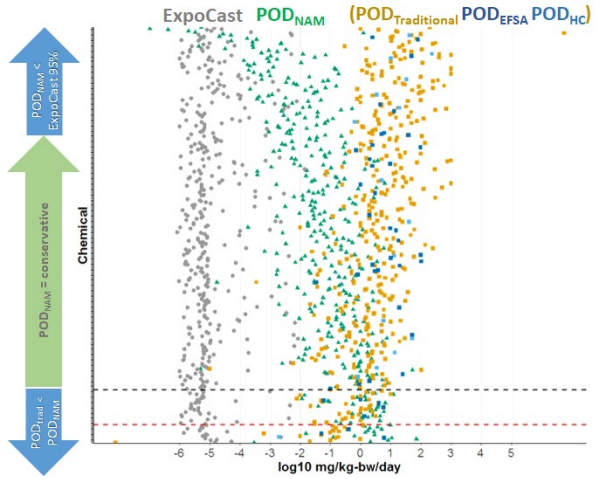
Table 2-2. Uncertainty/safety factors for various reference values

Reference value	UF[a] U_A	U_H	U_L	U_D	FQPA[b]
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

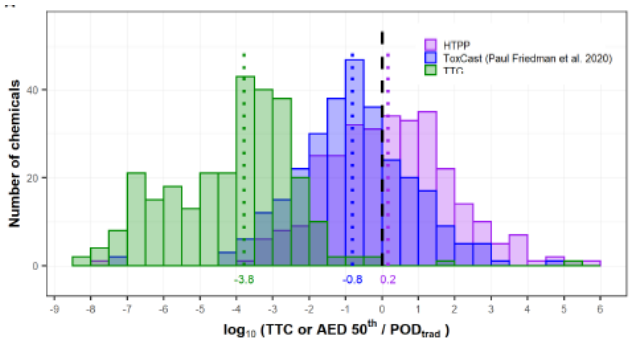
[a] Uncertainty factors: U_A = animal-to-human; U_H = within-human variability; U_L = LOAEL-to-NOAEL; U_D = database deficiency.
[b] Additional safety factor required under FQPA.
[c] Endpoint = lethality, not really a LOAEL-to-NOAEL adjustment in this case.
[d] Database deficiencies considered, and a 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

Case Studies Demonstrating Application of Bioactivity as a Protective POD

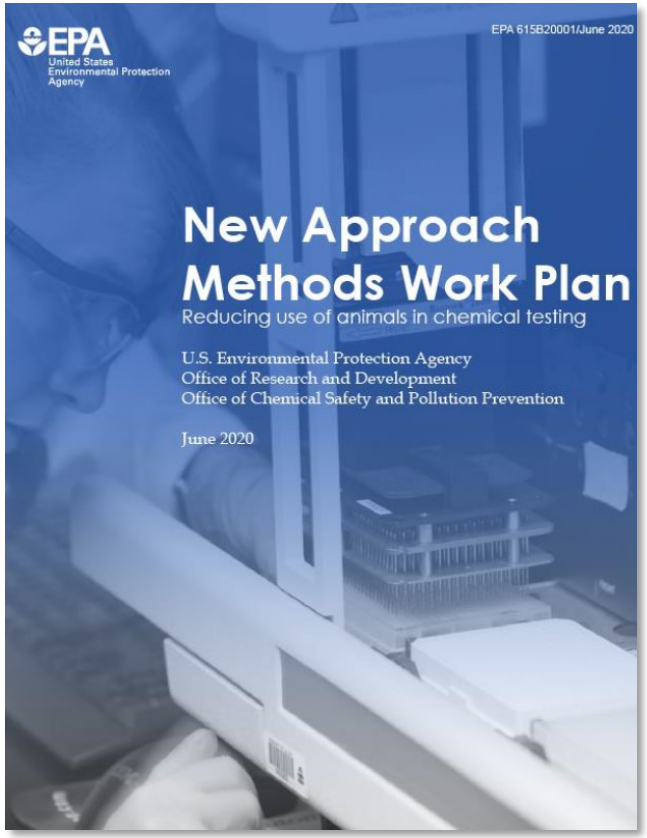


Paul-Friedman et al., 2020



Nyffeler and Harrill, ISMB Poster, 2020

Growing Need for Fit-for-Purpose Validation/ Confidence Frameworks

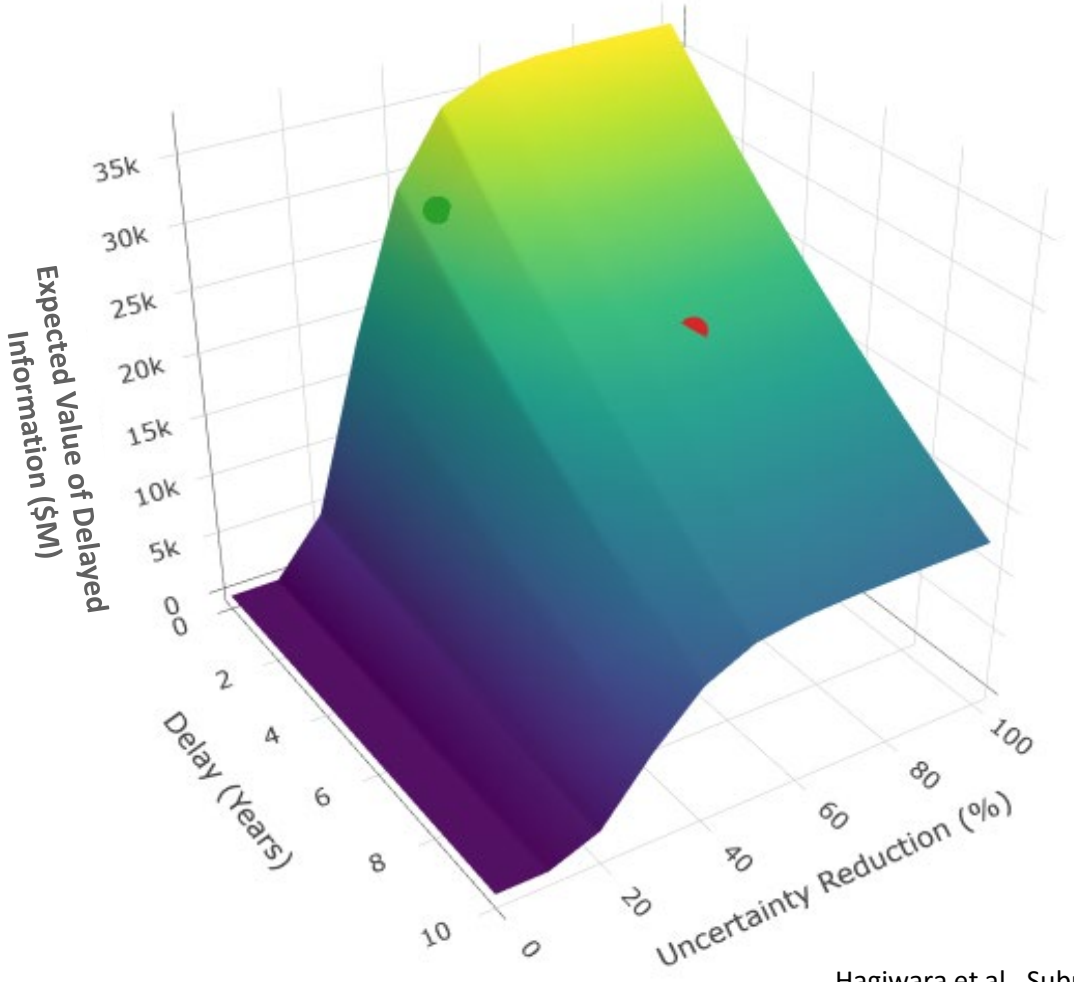


Deliverables:

- US National Academies of Sciences report on uncertainties and utility of existing mammalian toxicity tests in Q4 2022.
- Scientific confidence framework to evaluate the quality, reliability, and relevance of NAMs in Q3 2022.

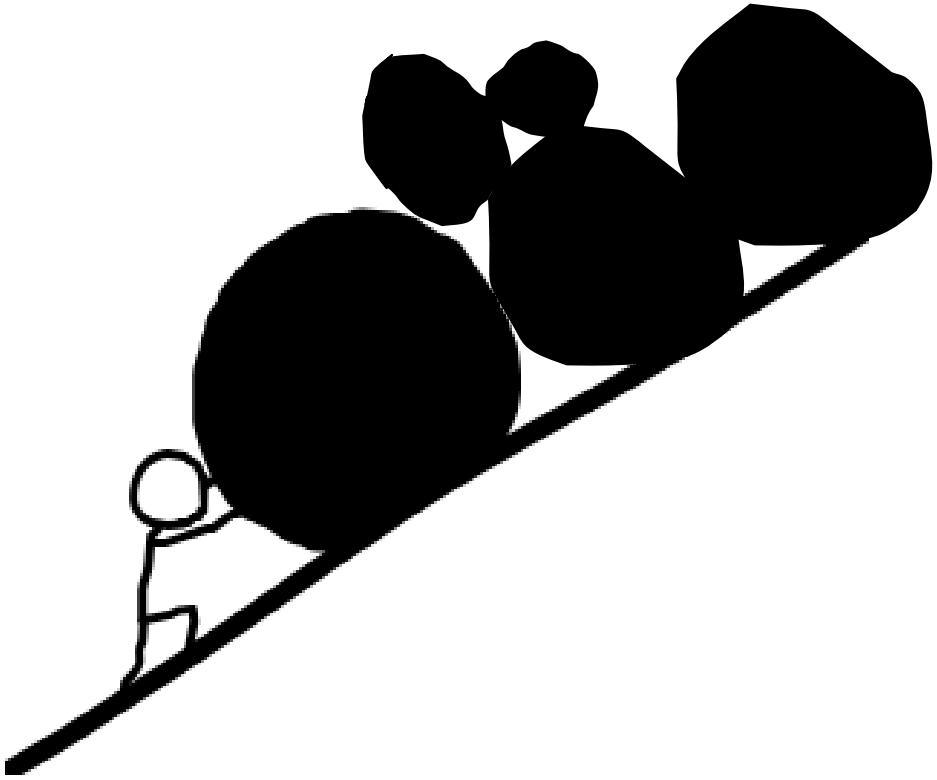
Understanding Public Health and Economic Trade-Offs of Making Decisions Faster vs. Uncertainty

Value of Information Analysis Evaluating the Economic and Health Costs Associated with Different Toxicity Testing Methods



Hagiwara et al., Submitted

Where Do We Go From Here…



In my view, continue to advance the development and application of NAMs holistically in each of these areas (and more) and work across national, sector, and disciplinary boundaries.

EPA
United States
Environmental Protection
Agency

Thank you for your attention!