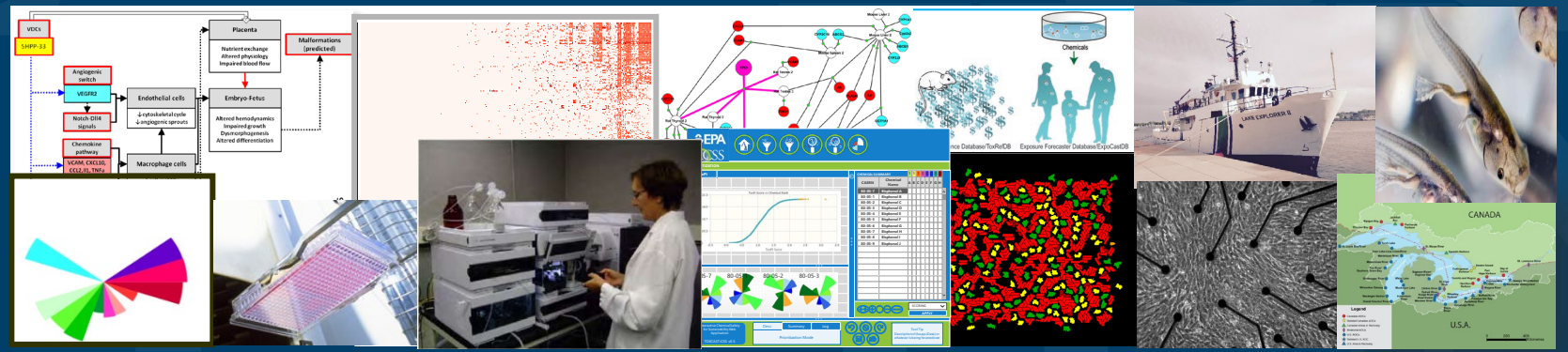
NAMs Paradox

When an Unstoppable Force Meets an Immovable Object



Alliance for Risk Assessment Workshop XIII

February 15, 2022

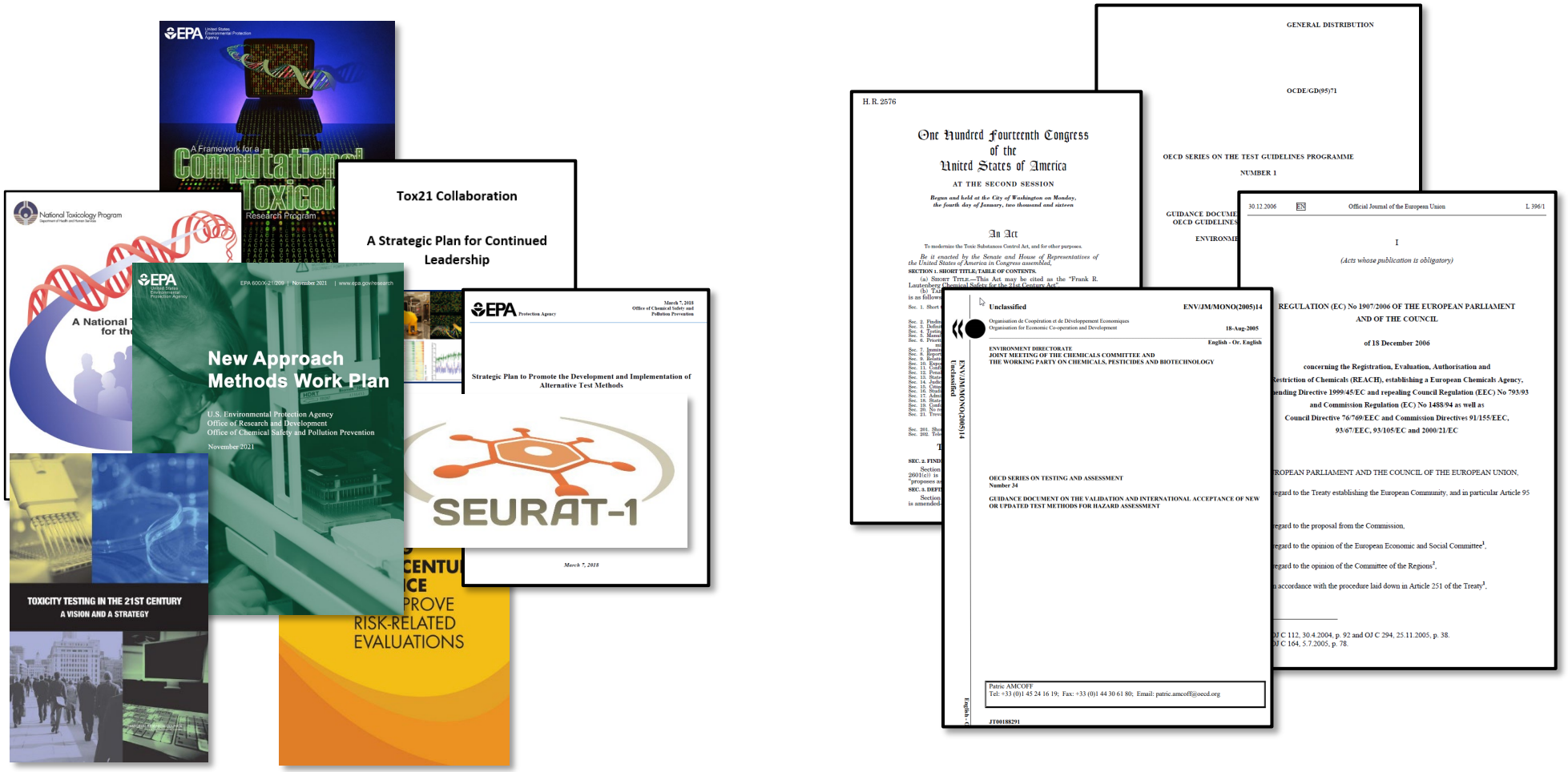
Rusty Thomas
Director
Center for Computational Toxicology and Exposure

EPA United States Environmental Protection Agency

The Original Paradox…

Teumessian fox and the hunting dog Laelaps

The NAM Paradox…



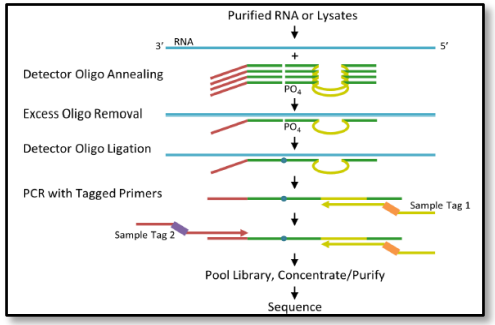
The unstoppable NAM force and the unmovable regulatory systems and processes

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

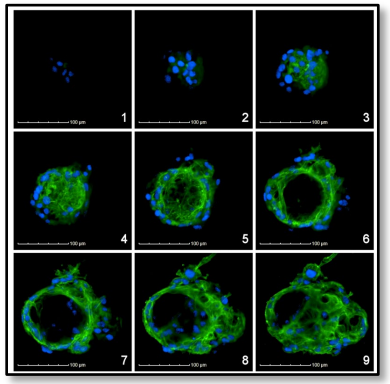
1. Continue to innovate with NAMs while systematically address the limitations (a couple examples…)
2. Accept that there is likely not a primary mechanism/mode of action for most environmental/industrial chemicals
3. Work through how to assemble NAMs in a coherent, practical, fit for purpose testing 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

Step 1: Continue to Innovate and Address Limitations in NAMs

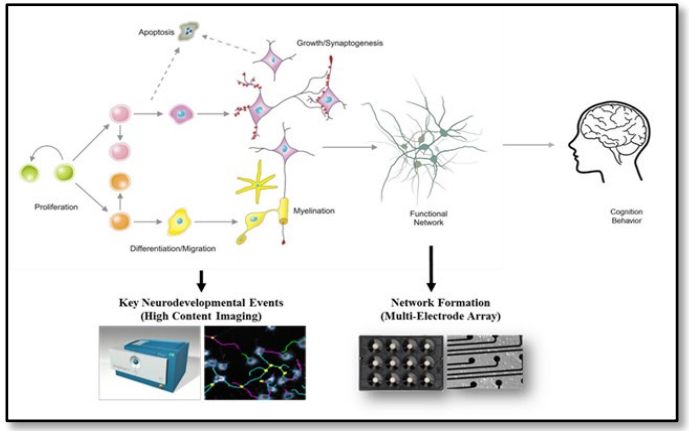
Whole Genome Transcriptomics



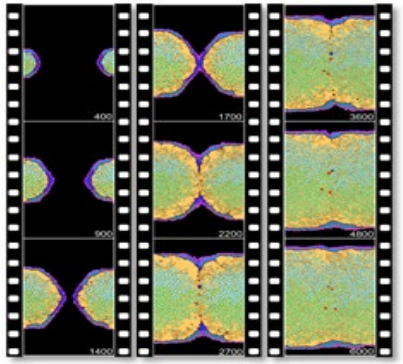
Organotypic Culture Models



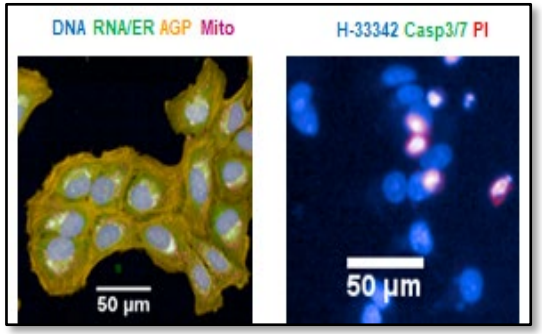
Integrated Approach to Testing and Assessment for DNT



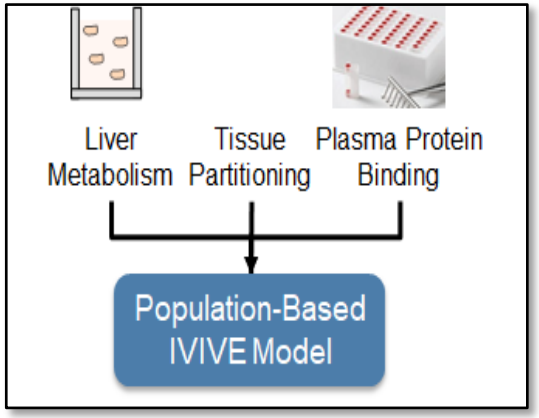
Virtual Tissue Models



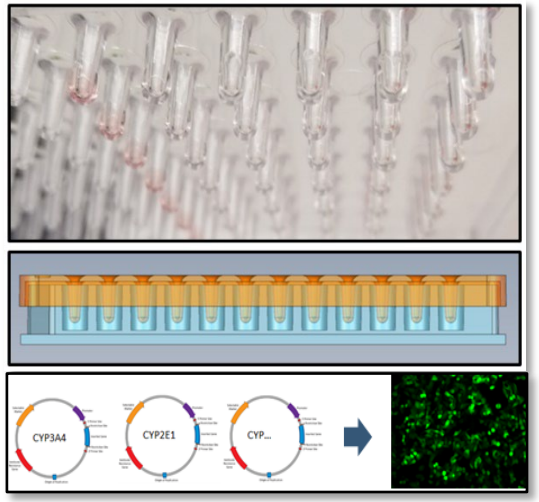
Multi-Parameter Cellular Phenotypic Profiling



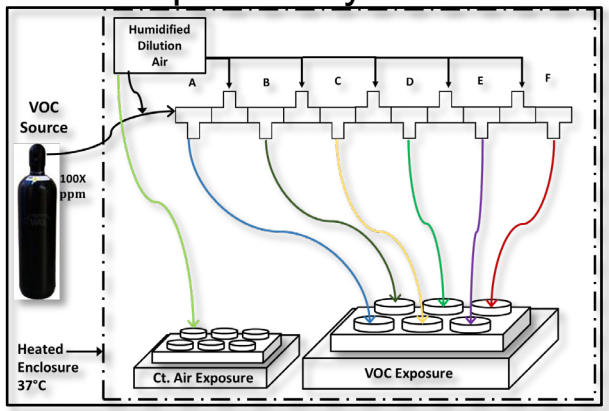
Toxicokinetic Measurements and Modeling



Metabolic Retrofitting

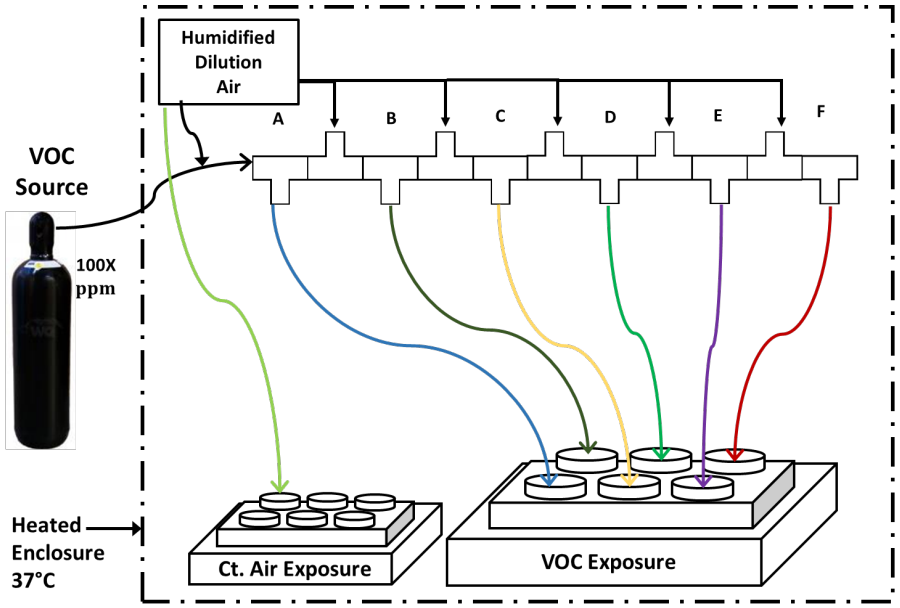


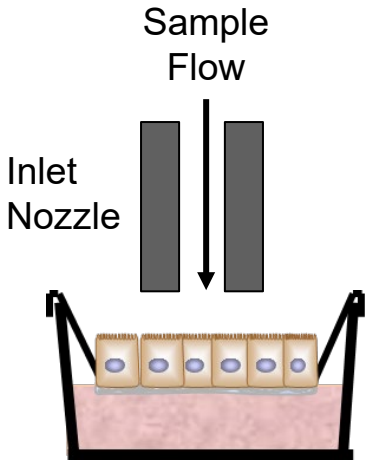
Volatile/Aerosol *In Vitro* Exposure Systems



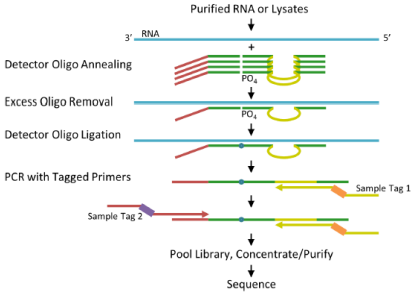
Sequence Alignment to Predict Across Species Susceptibility

Developing *In Vitro* Exposure Systems for Volatile Chemicals

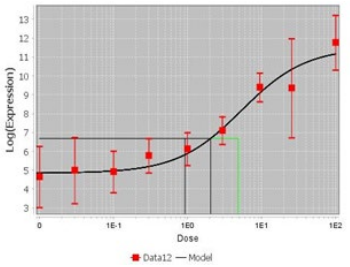




Whole Genome Transcriptomics (HTTr)



Concentration Response Modeling



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

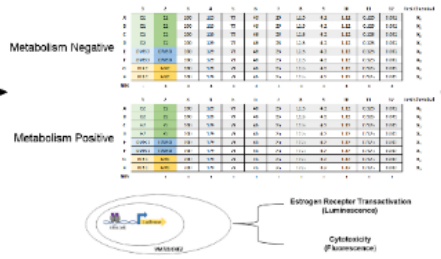
* The ACGIH TLV TWA for 1-bromopropane was updated to 0.1 ppm in 2012. Prior to that the TLV-TWA for 1-bromopropane was 10 ppm.

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

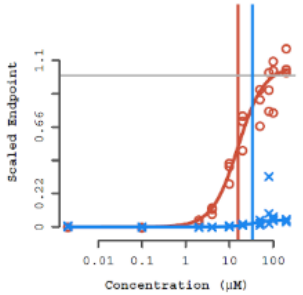
Retrofitting NAMs for Metabolic Competence

AIME Metabolism Assay

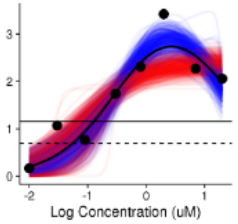
Estrogen Receptor Transactivation Assay



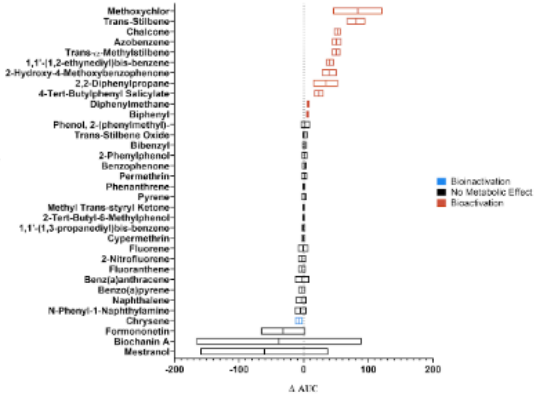
ToxCast Pipeline

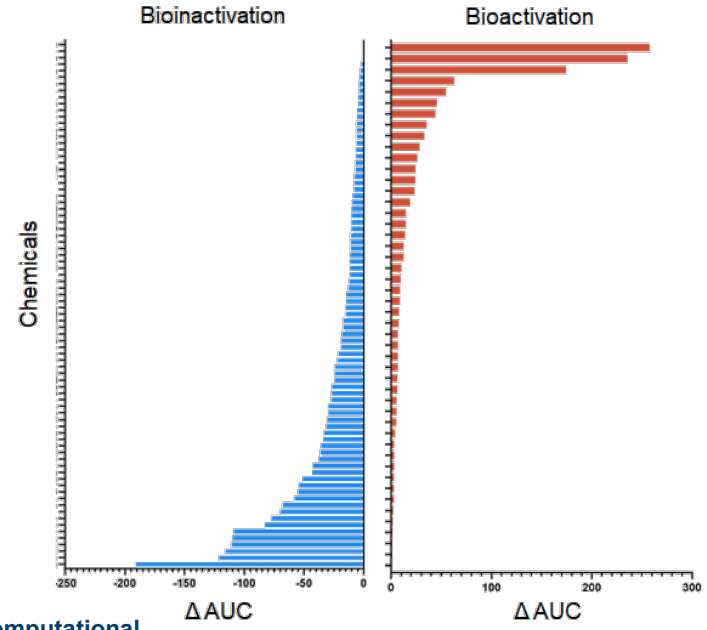


Toxboot Uncertainty Quantification



Rank Metabolism-dependent Bioactivity



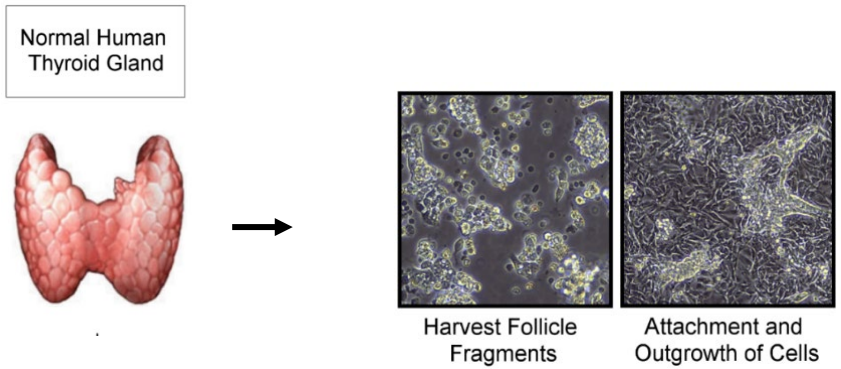


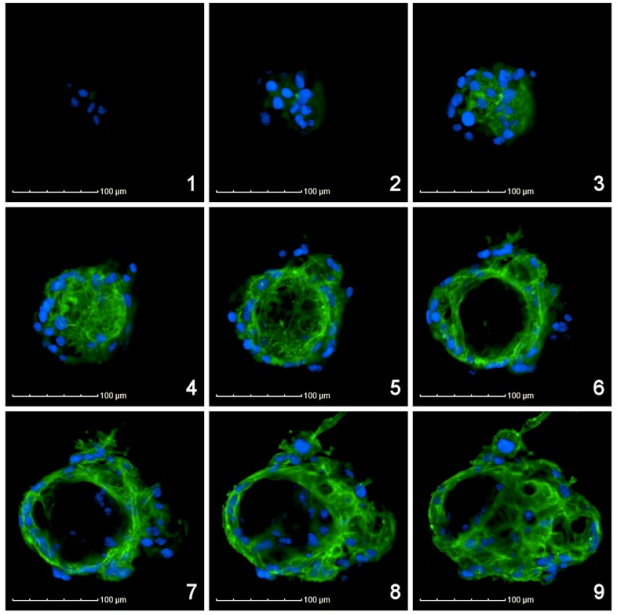
Preliminary Analysis of 768 ToxCast Chemical Screen

- Application of Deisenroth et al., *Toxicol Sci.,* 2020
- 11% of chemicals exhibit metabolism-dependent changes in ER bioactivity. Most are estrogenic ± metabolism.
- False positive and false negative chemicals represent 3.6% of total chemicals screened.
- Profiles of predicted routes of biotransformation and potential metabolites.

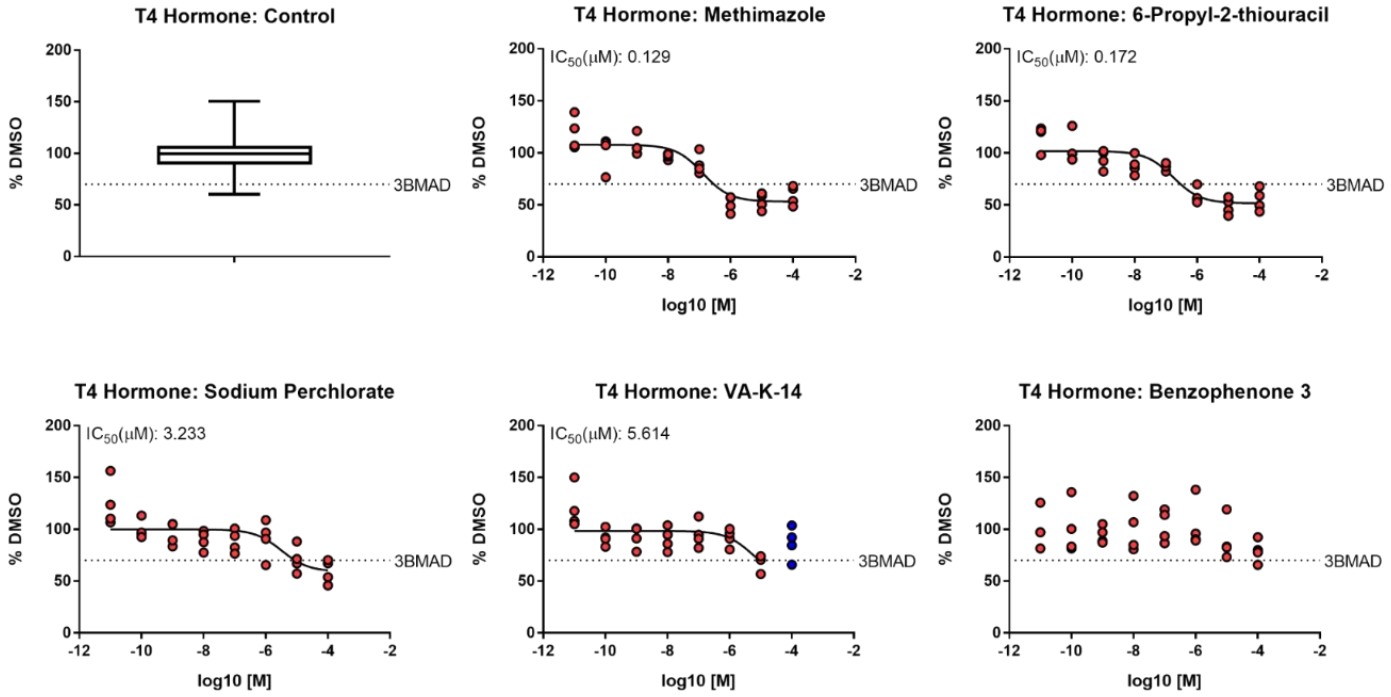
Deisenroth *et al., Toxicol Sci* In Press

Developing Complex Organotypic Culture Models to Evaluate Tissue/Organ Effects



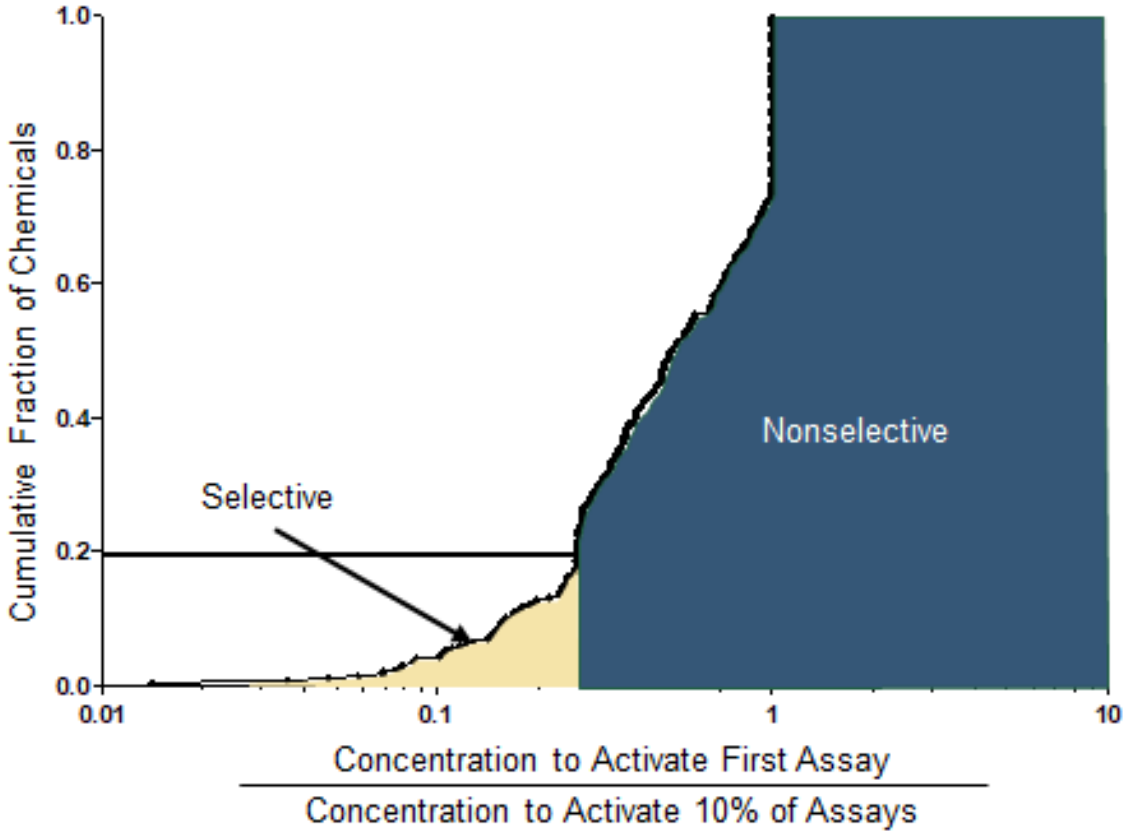


Blue, Hoechst 33342 /DNA
Green, Phalloidin/Actin



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

FORUM

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

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

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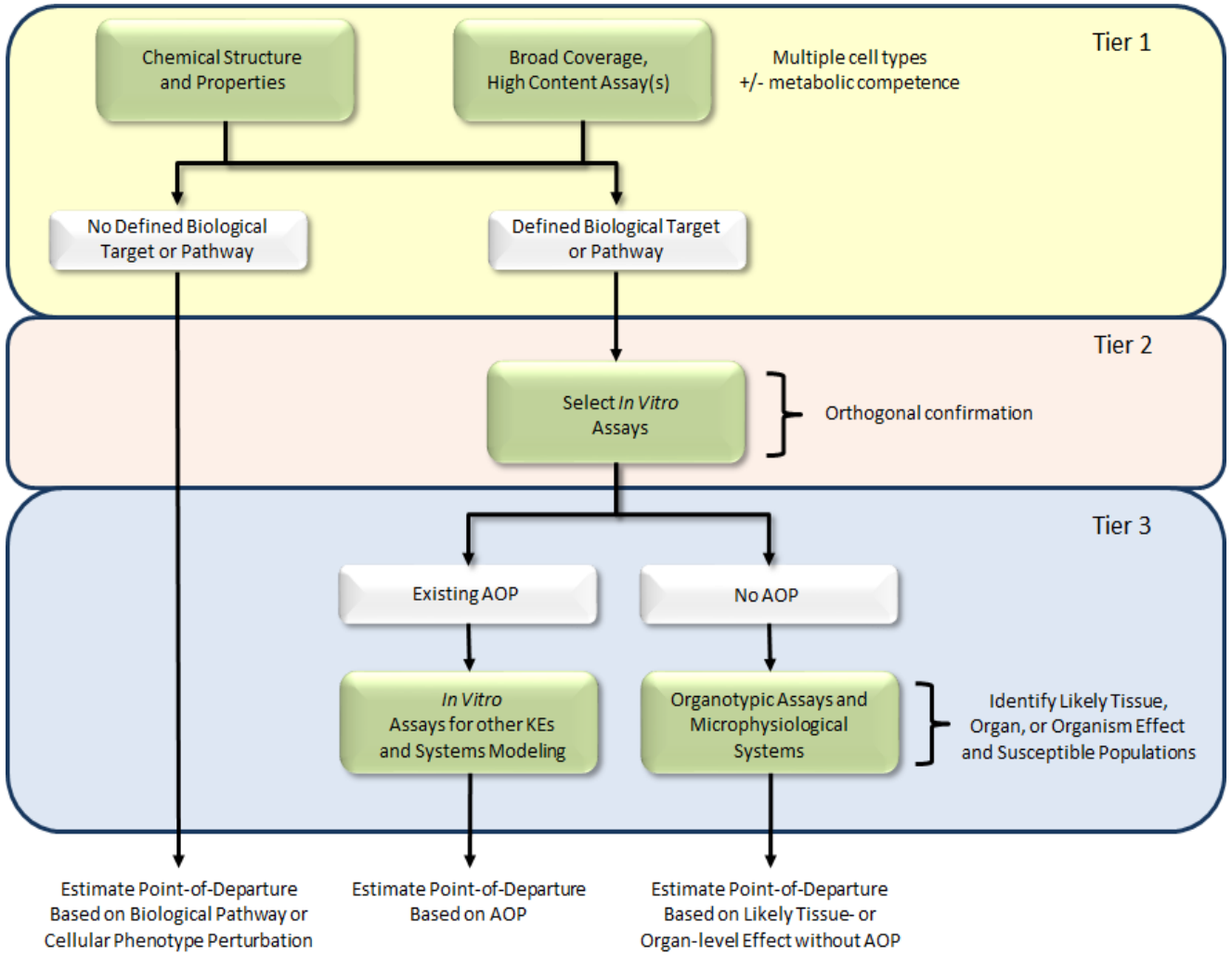
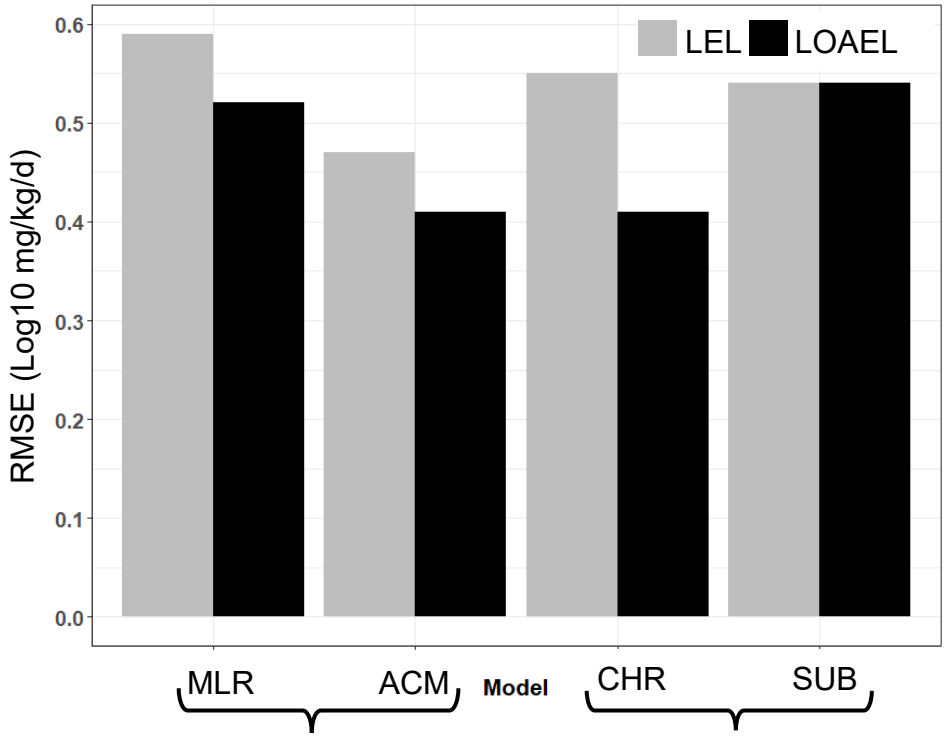
ABSTRACT

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,



Step 4: Understand How to Benchmark Approaches

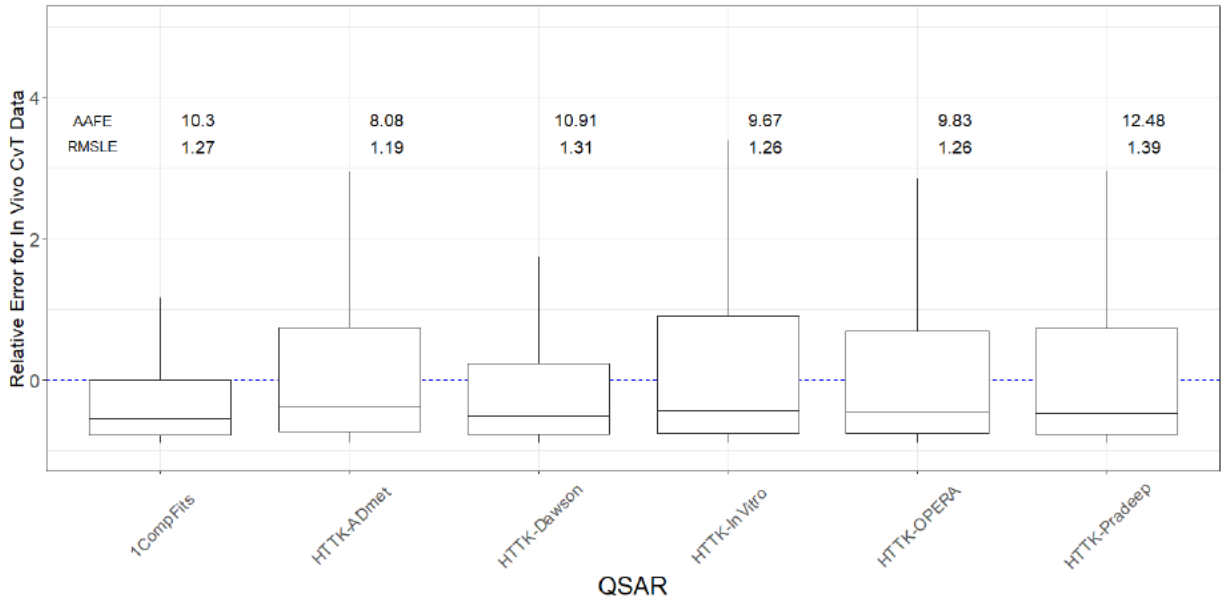
Evaluating LEL/LOAEL Variability in Traditional Toxicity Studies to Set Expectations for NAMs



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

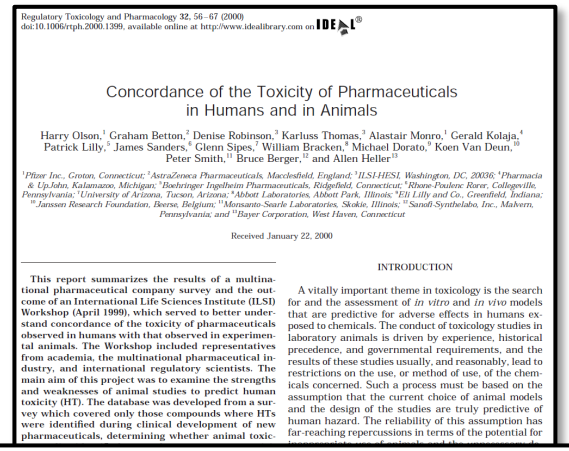
Comparing *In Silico, In Vitro,* and *In Vivo* Data for Toxicokinetic Modeling



Wambaugh et al., QSAR2021 meeting poster

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

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

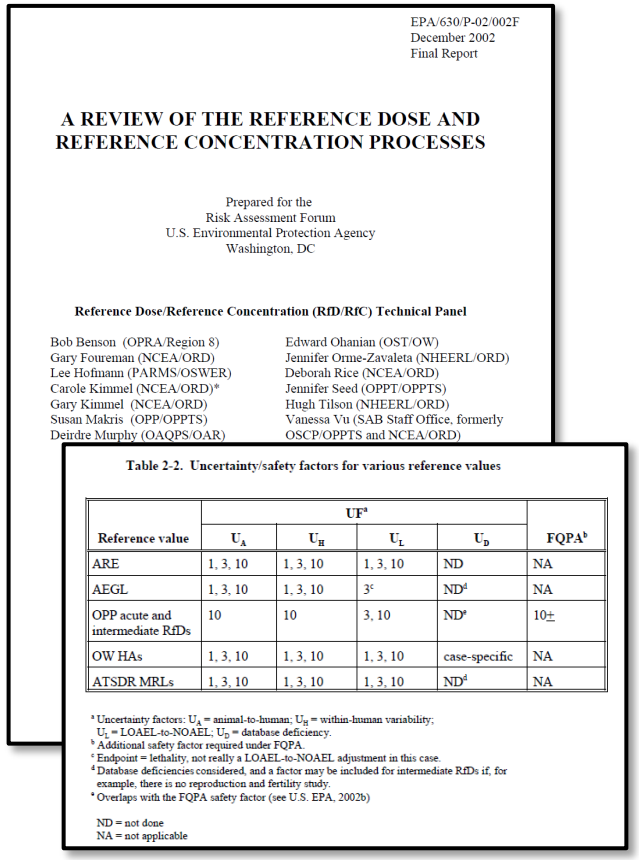
This report summarizes the results of a multinational pharmaceutical company survey and the outcome of an International Life Sciences Institute (ILSI) Workshop (April 1999), which served to better understand concordance of the toxicity of pharmaceuticals observed in humans with that observed in experimental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

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Vanessa Vu (SAB Staff Office, formerly OSCP/OPPTS and NCEA/ORD)

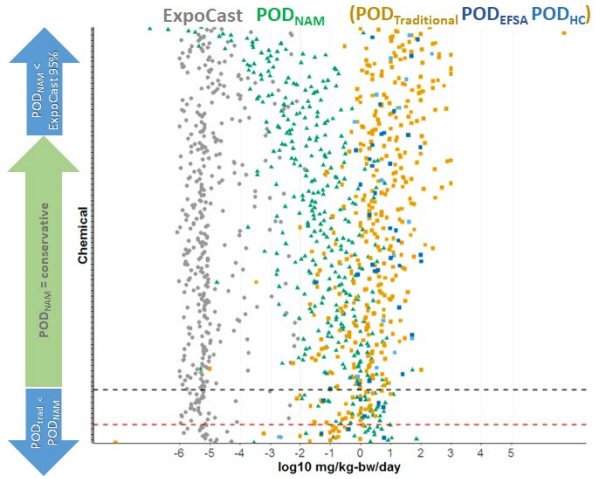
Table 2-2. Uncertainty/safety factors for various reference values

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

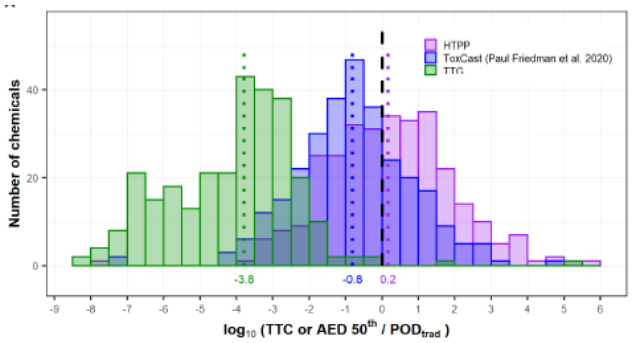
[a] Uncertainty factors: U_A = animal-to-human; U_H = within-human variability; U_L = LOAEL-to-NOAEL; U_D = database deficiency.
[b] Additional safety factor required under FQPA.
[c] Endpoint = lethality, not really a LOAEL-to-NOAEL adjustment in this case.
[d] Database deficiencies considered, and a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

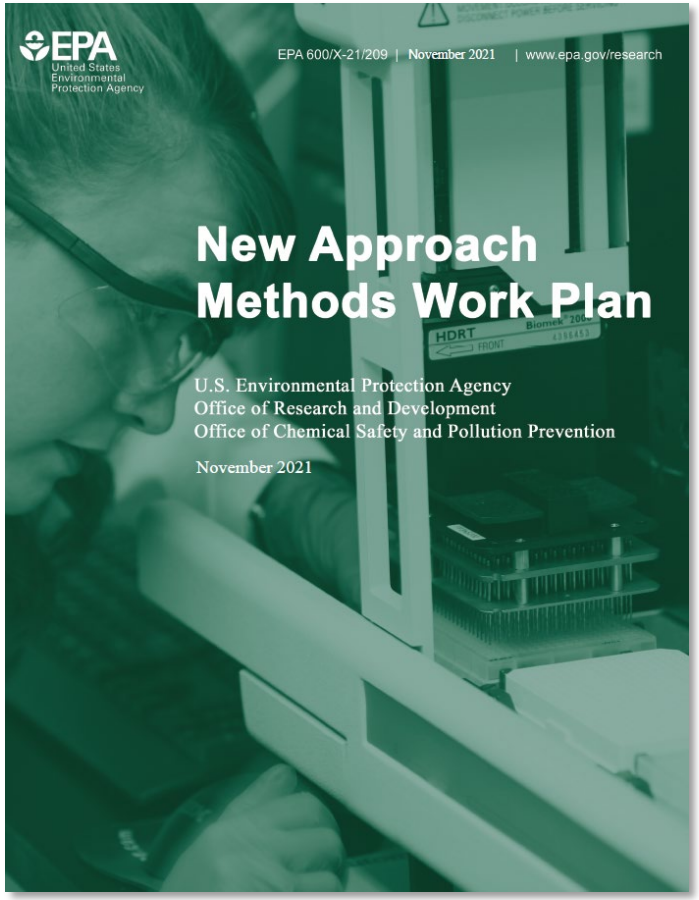


Paul-Friedman et al., 2020



Nyffeler and Harrill, ISMB Poster, 2020

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



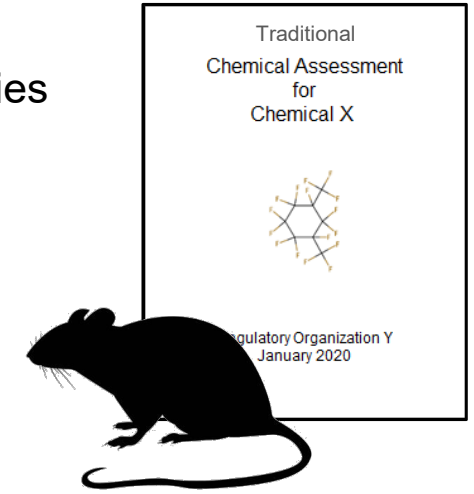
Deliverables:

- 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

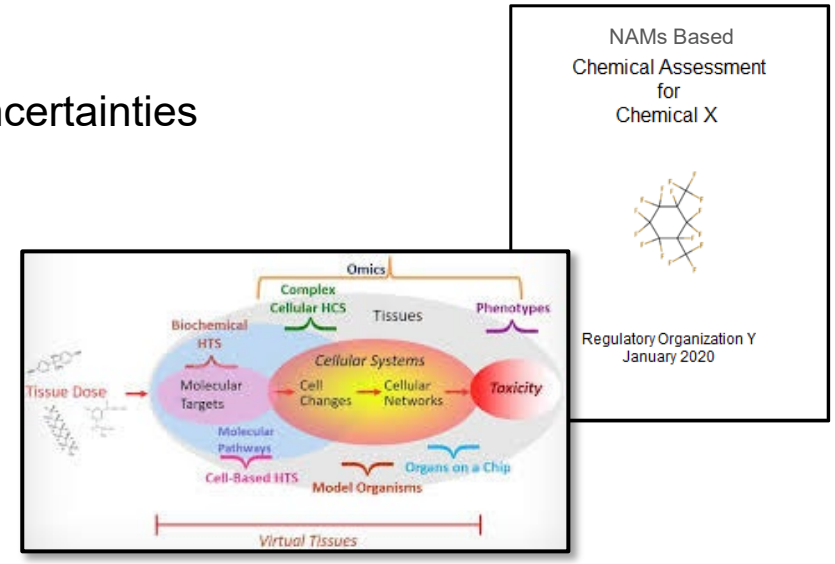
Option 1

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



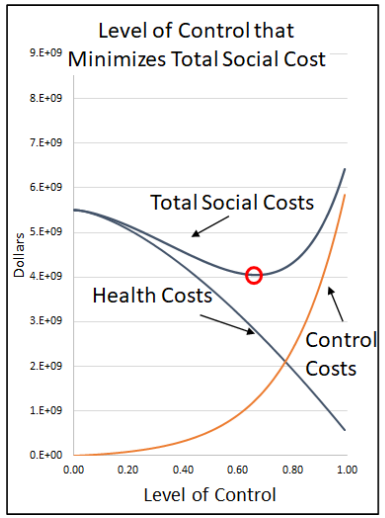
Option 2

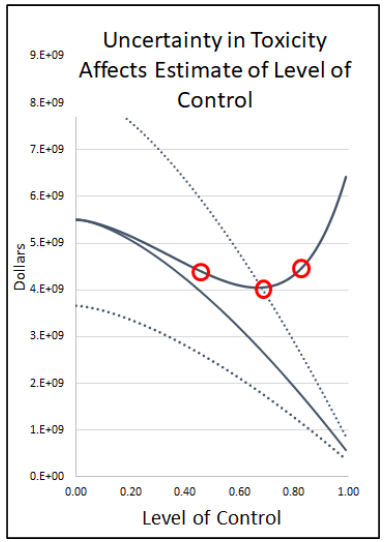
- <1 year
- “Bigger” uncertainties
- $Ks



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)

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General Conclusions From the Value of Information Studies

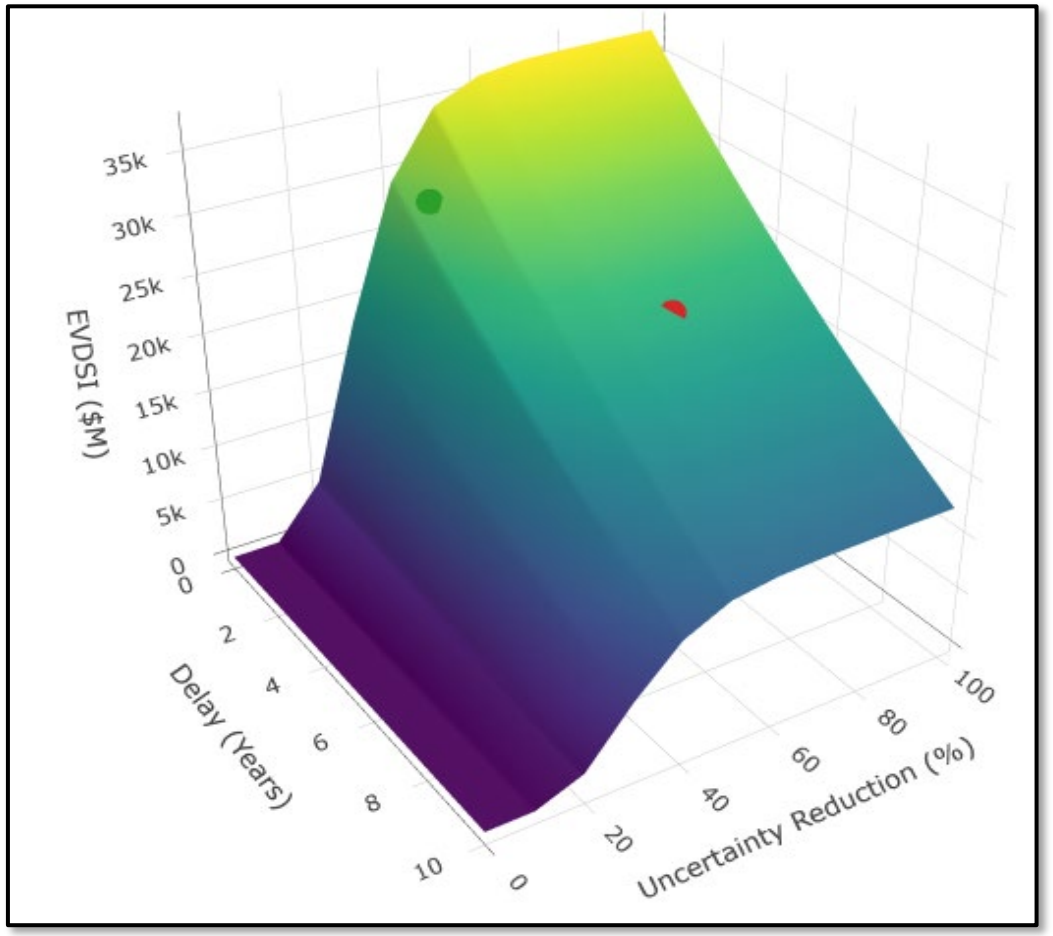
Example Scenarios

- 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)



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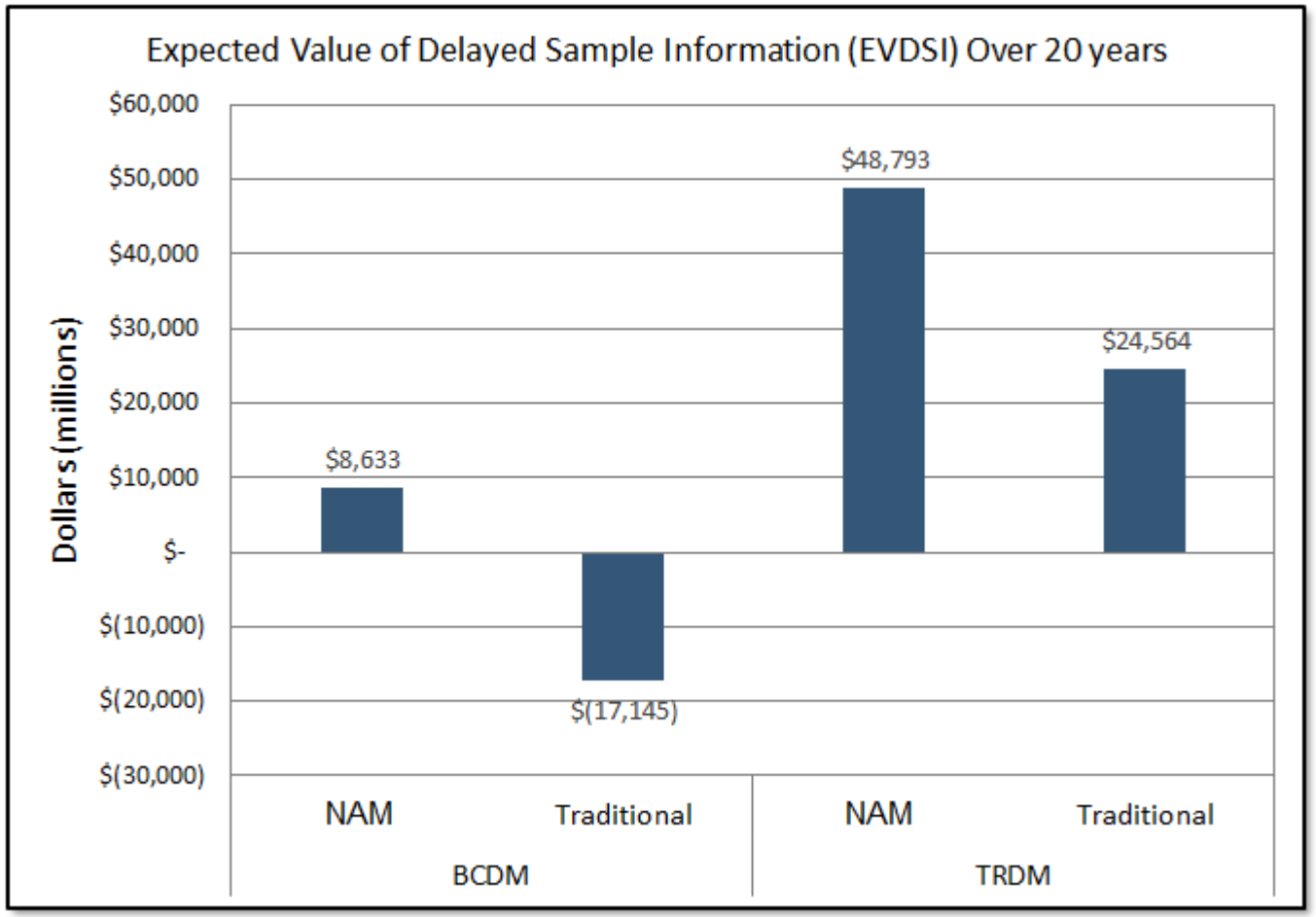
Focused Case Study on Di (2-Ethylhexyl)Phthalate

Parameters

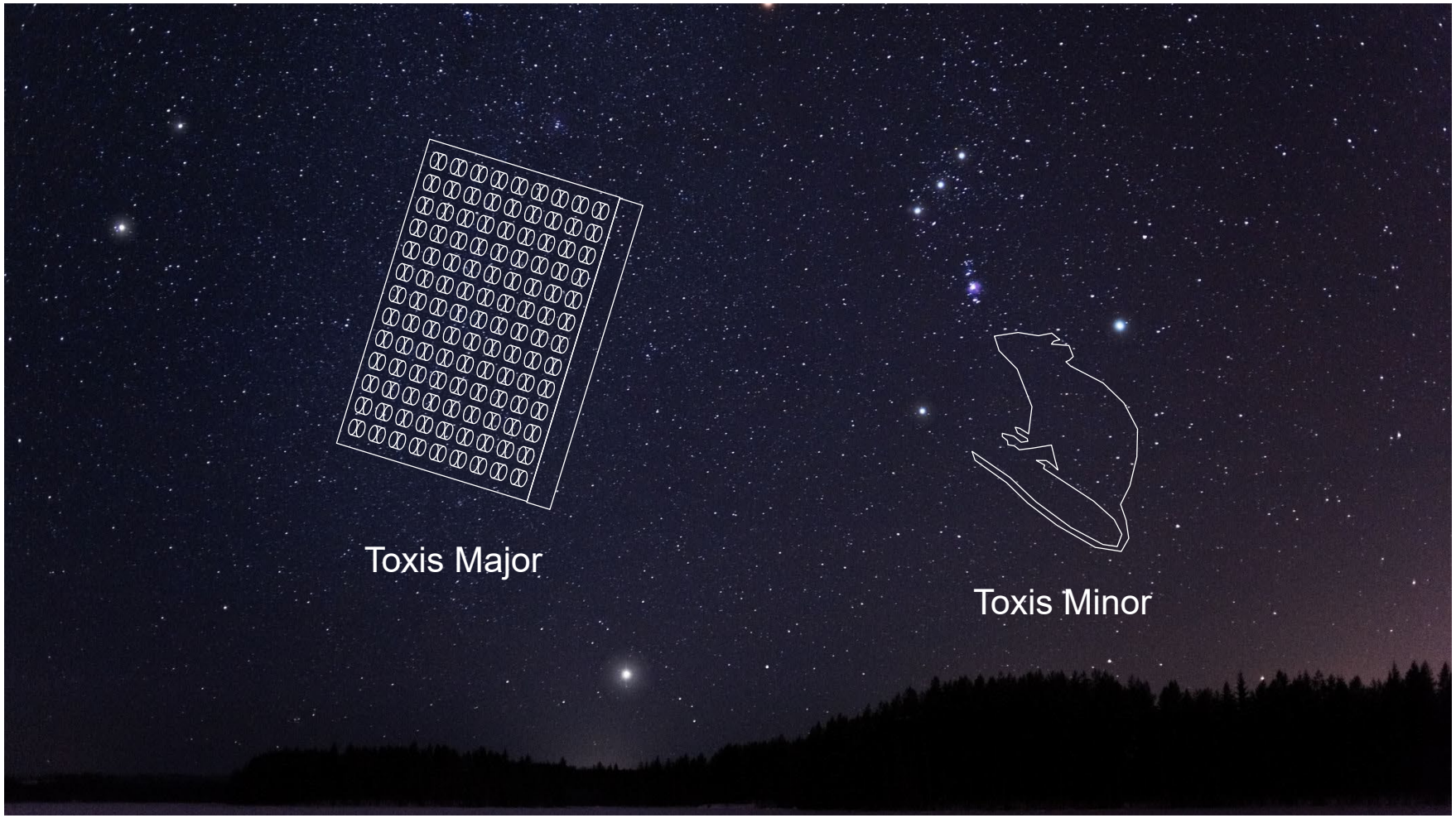
	Values
Toxicity (Prior)	
$Log_{10}\ \mu_{tox}$	1.699
Uncertainty in μ_{tox} (Orders of Magnitude or OM)	7
$Log_{10}\ (\sigma_{tox})$	0.697
Exposure	
$Log_{10}(\mu_{exp})$	-2.87
Uncertainty in μ_{exp} (OM)	1.74
$Log_{10}(\sigma_{exp})$	0.34
Toxicity Post Test A – NAM	
Uncertainty in measured μ_{tox} (OM)	2.74
Delay	1 yrs
Cost	$50,000
Toxicity Post Test B – Traditional	
Uncertainty in measured μ_{tox} (OM)	1.76
Delay	8 yrs
Cost	$5,000,000

- Exposure estimates derived from NHANES biomonitoring data for U.S. adults (Reyes and Price, 2019)
- Toxicity estimates from published standards using methods from Chiu and Slob (2015)
- Evaluated Benefit Cost Decision Maker (BCDM) and Target Risk Decision Maker (TRDM)
- Chronic health effects (mortality)



P. Price, Preliminary Data

Moving from a Paradox to a Practical Solution



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