Growing Up and Leaving Home

Transitioning 21st Century Computational Toxicology and New Approach Methods into Application

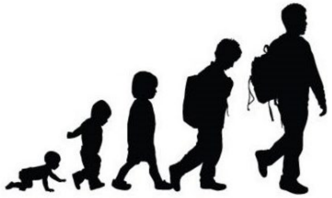
11th World Congress on Alternatives and Animal Use in the Life Sciences

August 23, 2021

Rusty Thomas
Director
Center for Computational Toxicology and Exposure

EPA United States Environmental Protection Agency

The 3Rs are Over 60, but the New Generation of Alternative Approaches are Relatively Young…



1960 | 1970 | 1980 | 1990 | 2000 | 2010 | 2020

1959
3Rs Proposed by Russell and Burch

1976
Increased EPA investment in QSAR development to support TSCA

1981
Center for Alternatives to Animal Testing (CAAT) Established

1993
European ban on sale of animal tested cosmetic products with delayed implementation

1994
Interagency Coordinating Center for the Validation of Alternative Methods (ICCVAM) Established

2003
EPA CompTox Strategic Plan

2004
OECD non-animal alternative tests for dermal absorption, dermal corrosivity, and dermal phototoxicity

2007
NAS Report on Toxicity Testing

2013
European ban on sale of animal tested cosmetic products goes into effect

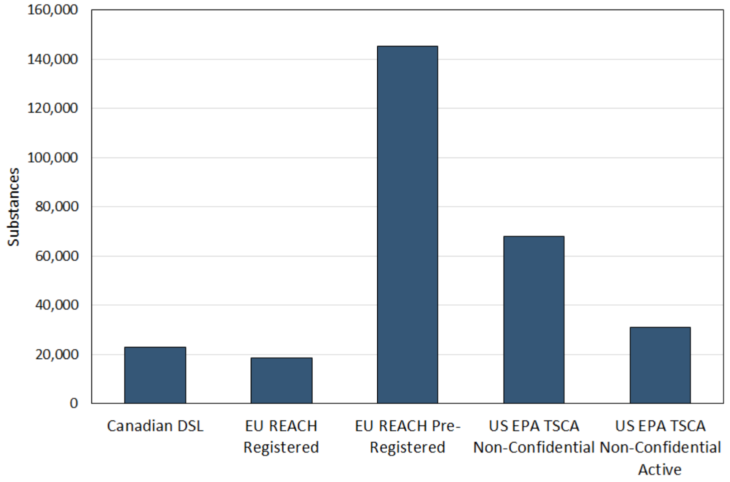
2014
'New Approach Methods' term coined to incorporate many alternative methods

2016
TSCA Amended with Alternative Testing Provisions

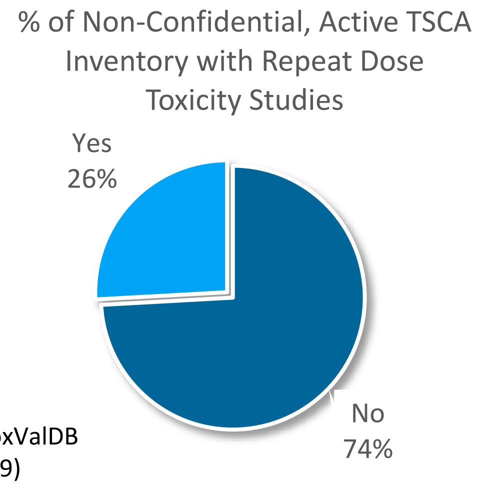
2020
EPA NAM Work Plan

Despite the Range in Ages, the Underlying Drivers Continue to Be the Same…

Number of Substances

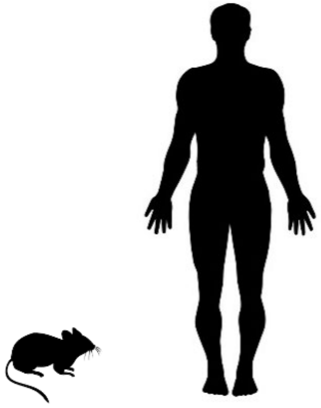


Amount of Data

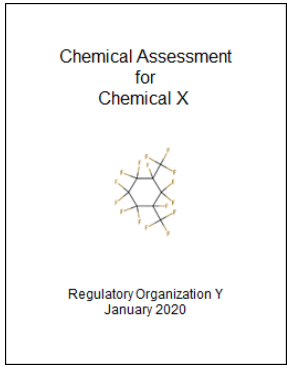


*Data from ToxValDB (Dec 2019)

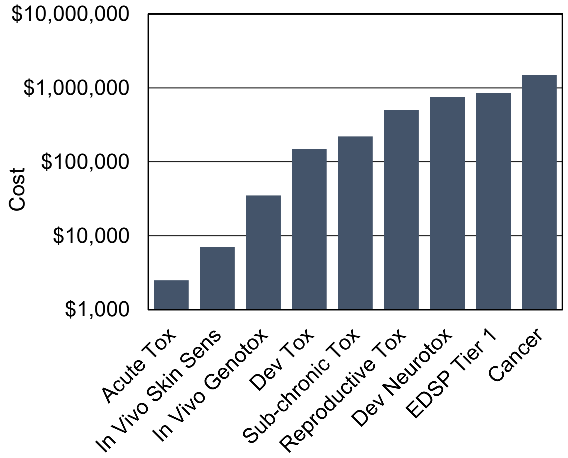
Reliability/Relevance



Time

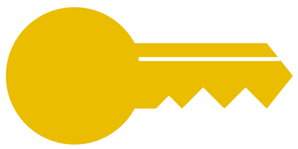


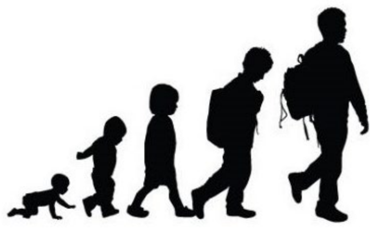
Economics



Ethical and Societal Considerations

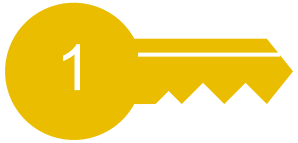
Five Keys to Growing Up and Leaving Home for Computational Toxicology and NAMs



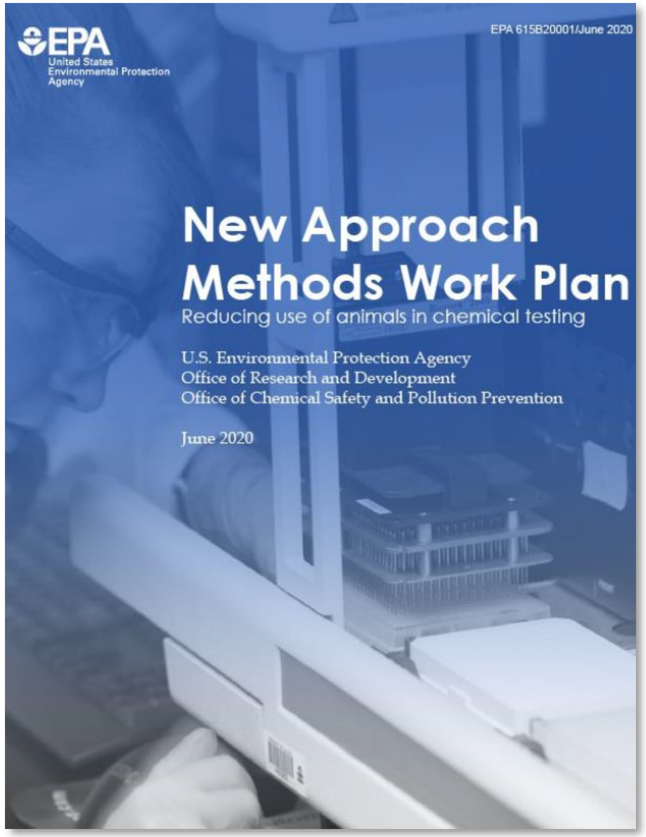


- Know where you want to go and how to get there
- Set expectations for success
- Continue developing and improving the science
- Start small and build on successes
- Communicate, communicate, communicate

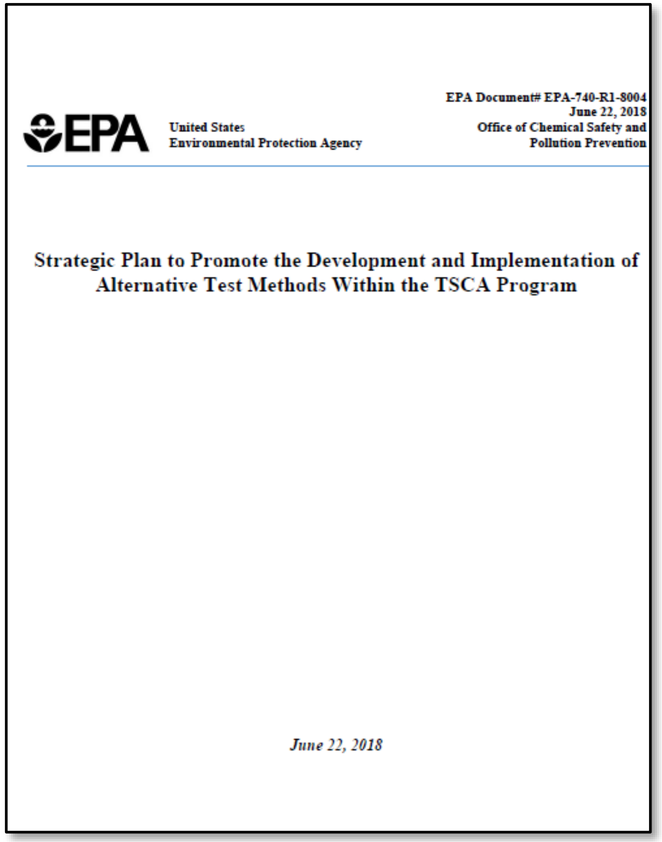
Knowing Where To Go and How to Get There Requires a Plan…



Know Where You Want to Go…



Focused on Agency-wide action



EPA United States Environmental Protection Agency

EPA Document# EPA-740-R1-8004
June 22, 2018
Office of Chemical Safety and Pollution Prevention

Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program

June 22, 2018

Focused on TSCA

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

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

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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,

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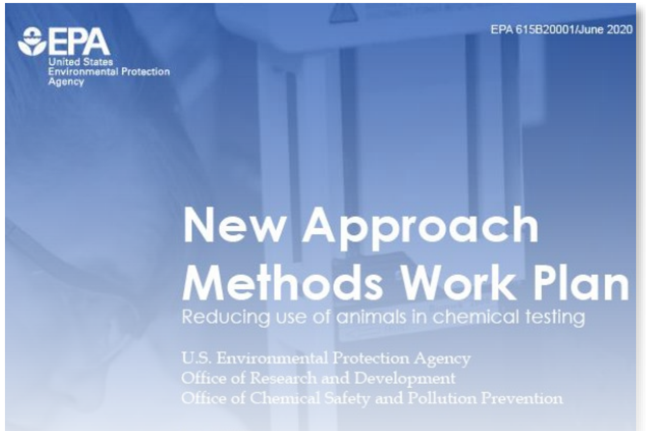
Focused on research

The Plans Contain Similar Strategic Directions and an Operational Blueprint

1

Know Where You Want to Go…


EPA 615B20001/June 2020

United States Environmental Protection Agency

New Approach Methods Work Plan

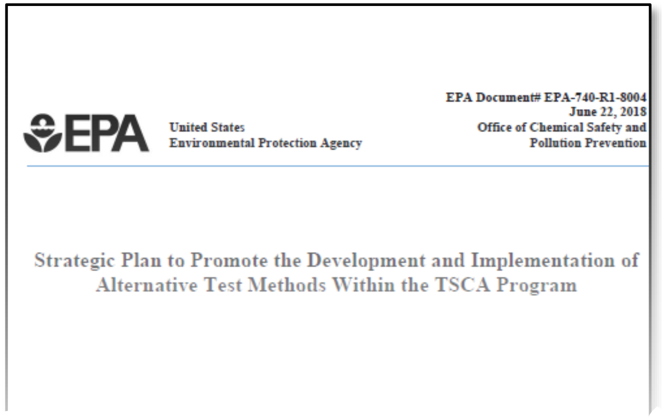
Reducing use of animals in chemical testing

U.S. Environmental Protection Agency
Office of Research and Development
Office of Chemical Safety and Pollution Prevention

June 2020

Primary Objectives

- Evaluate Regulatory Flexibility
- Develop Baselines and Metrics
- Establish Scientific Confidence and Demonstrate Application
- Develop NAMs to Address Information Gaps
- Engage and Communicate with Stakeholders

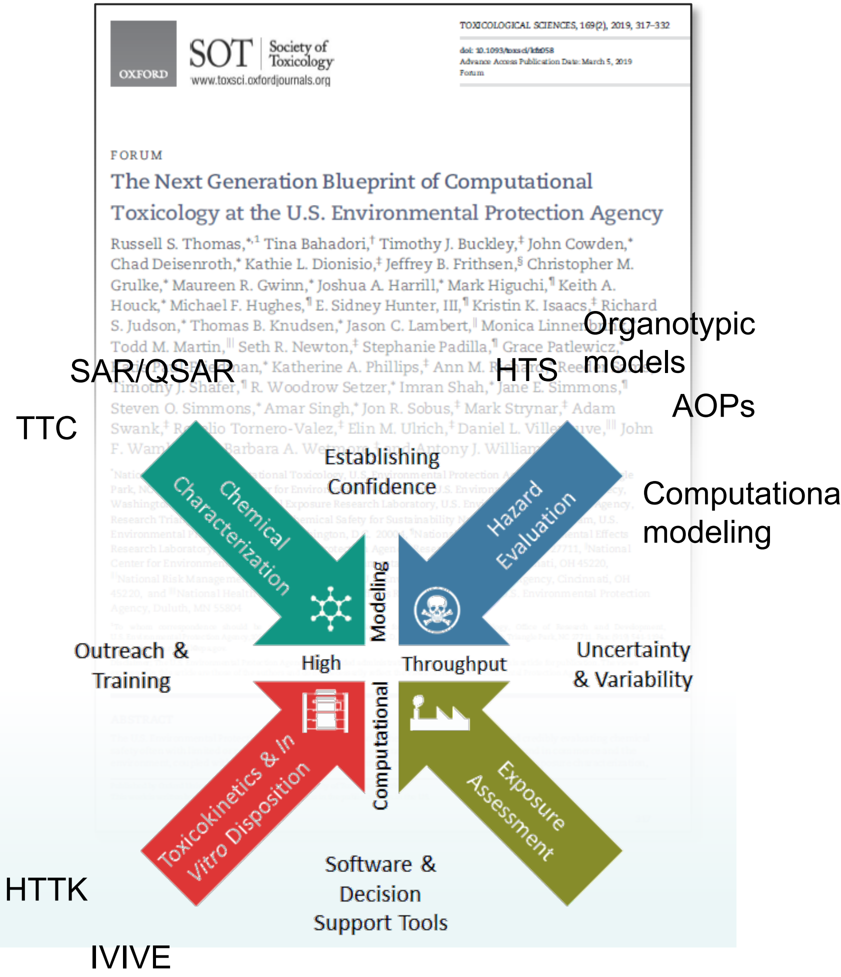

United States Environmental Protection Agency

EPA Document# EPA-740-R1-8004
June 22, 2018
Office of Chemical Safety and Pollution Prevention

Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program

Core Components

- Identifying, Developing, and Integrating NAMs
- Building Confidence that NAMs are Scientifically Reliable and Relevant
- Implementing the Reliable and Relevant NAMs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FORUM

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

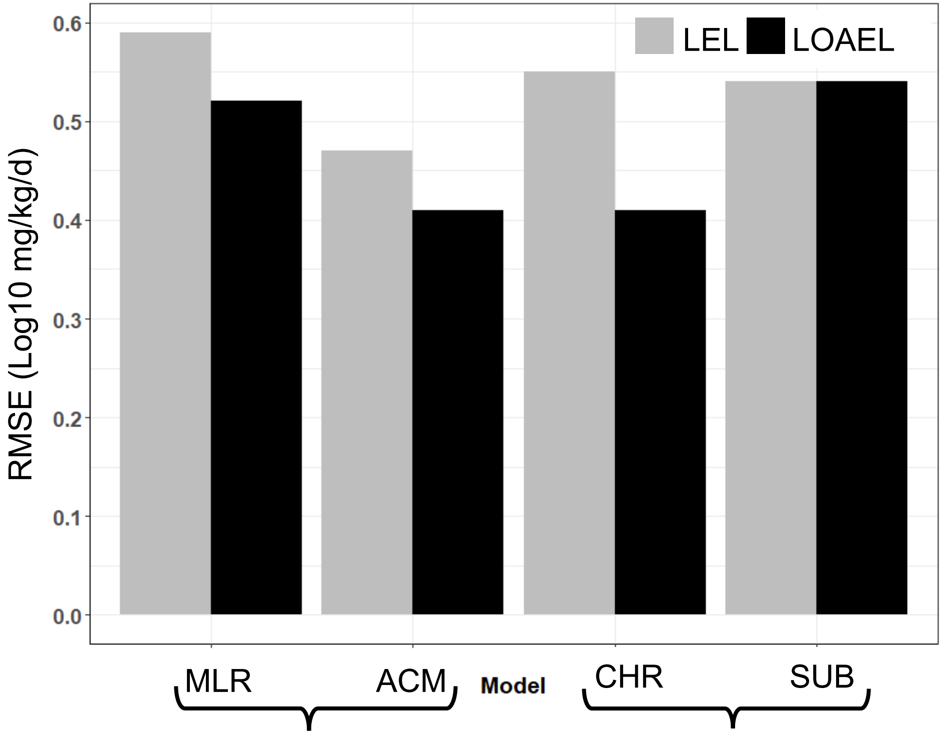
United States Environmental Protection Agency

Setting Expectations for NAMs Requires Data

2

Set Expectations for Success…

Evaluating LEL/LOAEL Variability in Traditional Toxicity Studies by Mining Legacy Data for ~1,200 Chemicals



Different statistical methods

Different study types

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 Target Organ Variability in Traditional Toxicity Studies by Mining Legacy Data for ~1,200 Chemicals

Organ	Species	Repeated negative	Mixed effects	Repeated positive	% Concordance
Liver	dog	20	26	46	71.7
	mouse	30	40	69	71.2
	rat	42	71	132	71.0
Kidney	dog	49	33	10	64.1
	mouse	61	51	27	63.3
	rat	60	105	80	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

Paul-Friedman, Unpublished

EPA United States Environmental Protection Agency

Literature Review and Expert Committee Report to Inform Expectations for NAMs

2

Set Expectations for Success…

The National Academies of SCIENCES ENGINEERING MEDICINE

SEARCH

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Variability and Relevance of Current Laboratory Mammalian Toxicity Tests and Expectations for New Approach Methods (NAMs) for use in Human Health Risk Assessment

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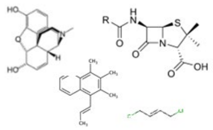
Animal testing is often used to evaluate the potential risks, uses, and environmental impacts of chemicals. New Approach Methodologies (NAMs) are technologies and approaches that can potentially provide the same hazard and risk assessment information without the use of animal testing. To further establish scientific confidence in these approaches, this study will review the variability and relevance of existing mammalian toxicity tests, specifically when it comes to human health risk assessment. The goal of this study is to to set data-driven and science-based expectations for NAMs based on the variability and relevance of the traditional toxicity testing models.

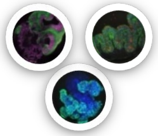
Provide feedback on this project

High-Content Technologies are Being Applied to Increase Biological Coverage

3 Continue Improving the Science…

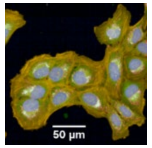
Broad-Based Testing Using High-Content Technologies



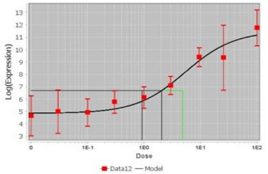


Lots of Chemicals X Multiple Cell Types

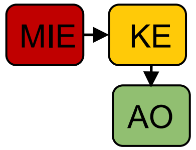
Transcriptomics



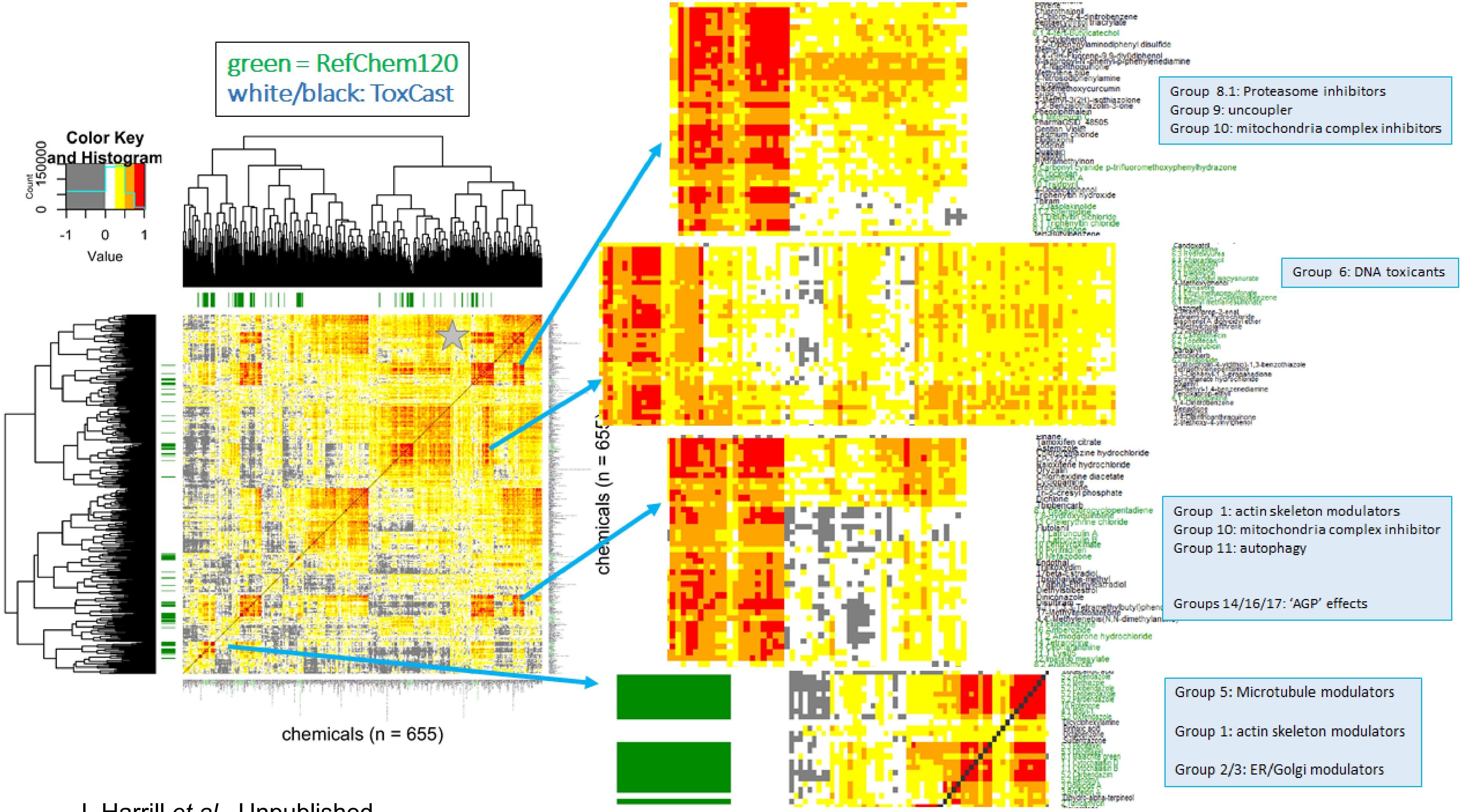
Phenotypic Profiling



Concentration Response



Molecular Target Identification and Grouping



J. Harrill *et al.*, Unpublished

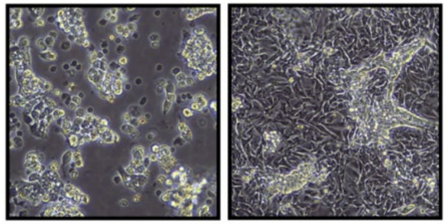
EPA United States Environmental Protection Agency

Improving Organotypic Culture Models to Translate Molecular Events into Tissue Effects

3

Continue Improving the Science…

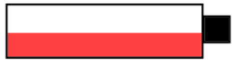
Normal Human Thyroid Gland



Harvest Follicle Fragments

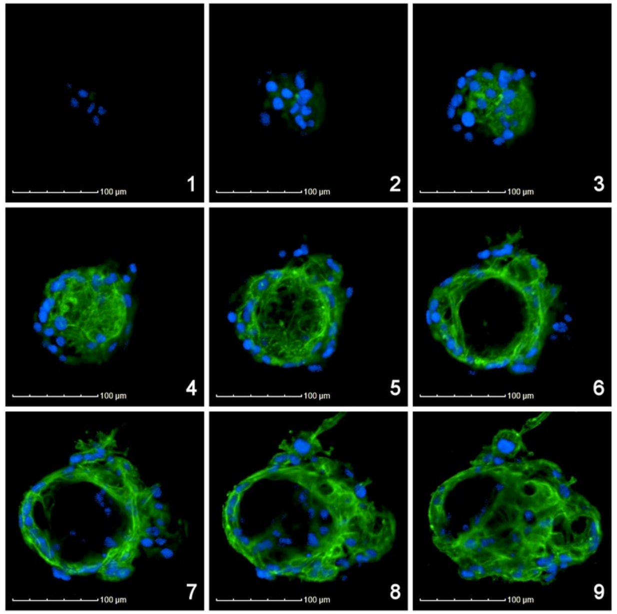
Attachment and Outgrowth of Cells

2D Cell Expansion

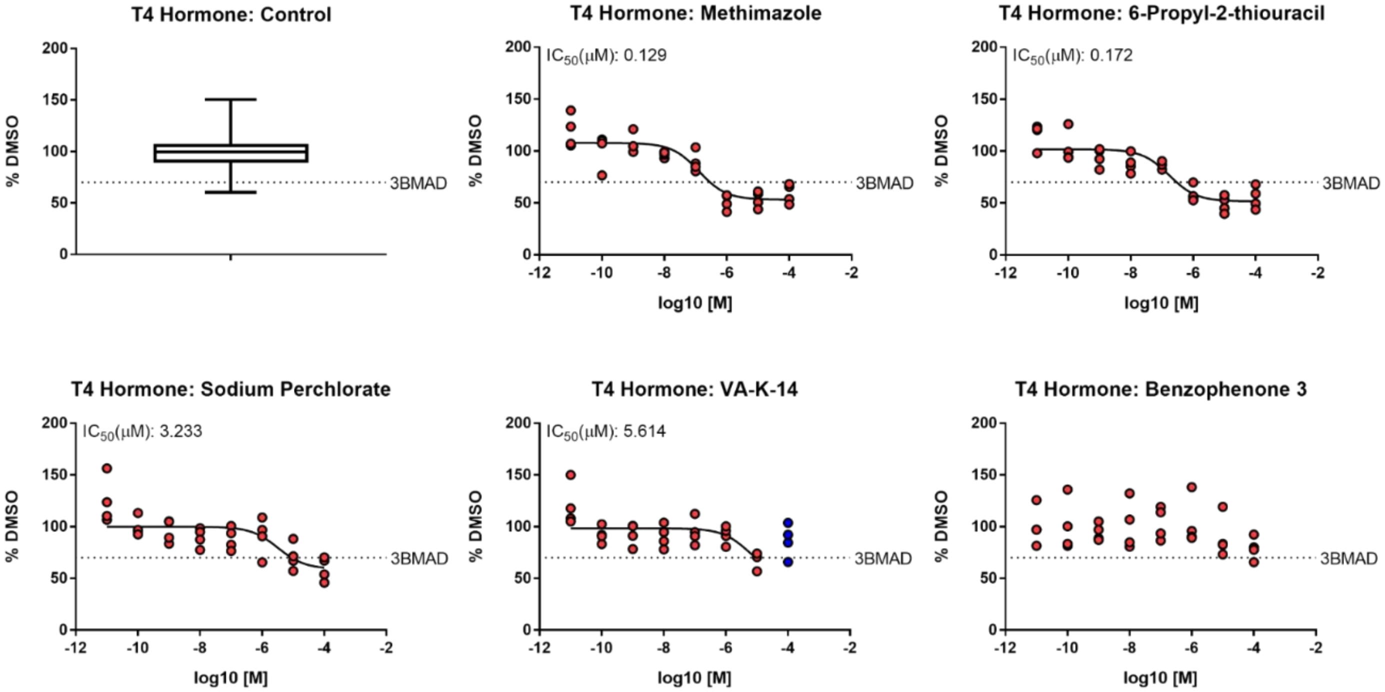


2D Monolayer Culture

3D Sandwich Culture

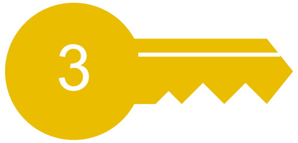


Blue, Hoechst 33342 /DNA
Green, Phalloidin/Actin

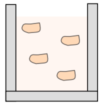


Deisenroth *et al.*, *Toxicol Sci*, 2020

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



Continue Improving the Science…

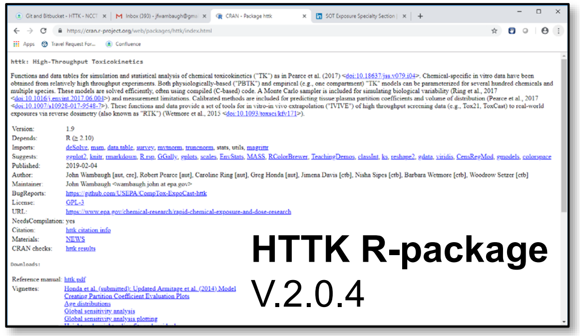


Liver Metabolism

Tissue Partitioning

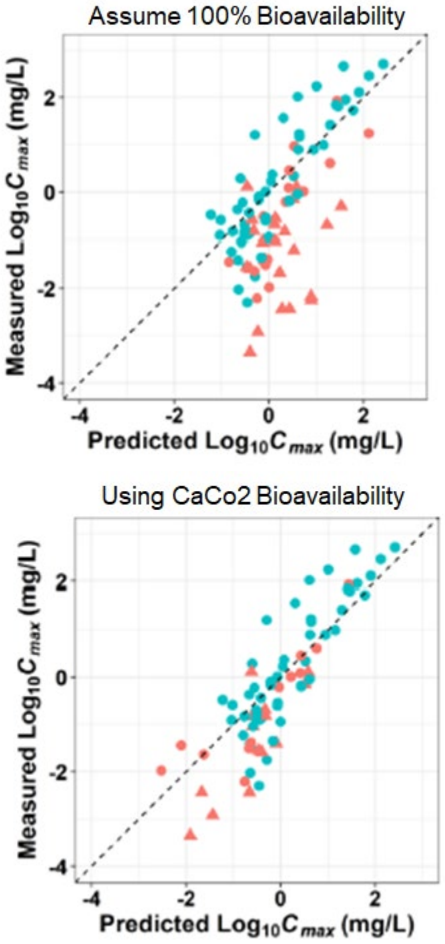
Plasma Protein Binding

HT-TK and PBTK models



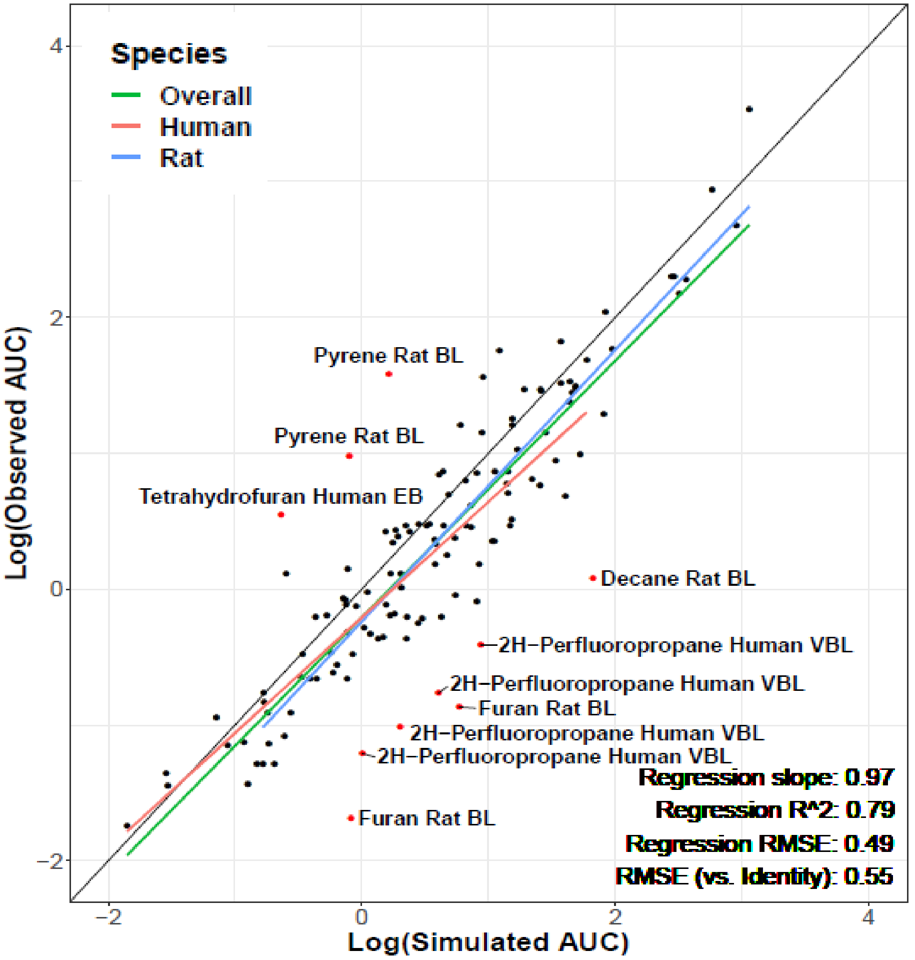
Rotroff *et al., Tox Sci.*, 2010
Wetmore *et al., Tox Sci.*, 2012
Wetmore *et al., Tox Sci.*, 2015
Wambaugh *et al.,Tox Sci.*, 2018
Wambaugh *et al.,Tox Sci.*, 2019
Linakis *et al., J Expo Sci Environ Epidemiol.* 2020

Experimental Models for Bioavailability



Wambaugh et al., Unpublished

Generic PBTK Model for Inhalation Exposure

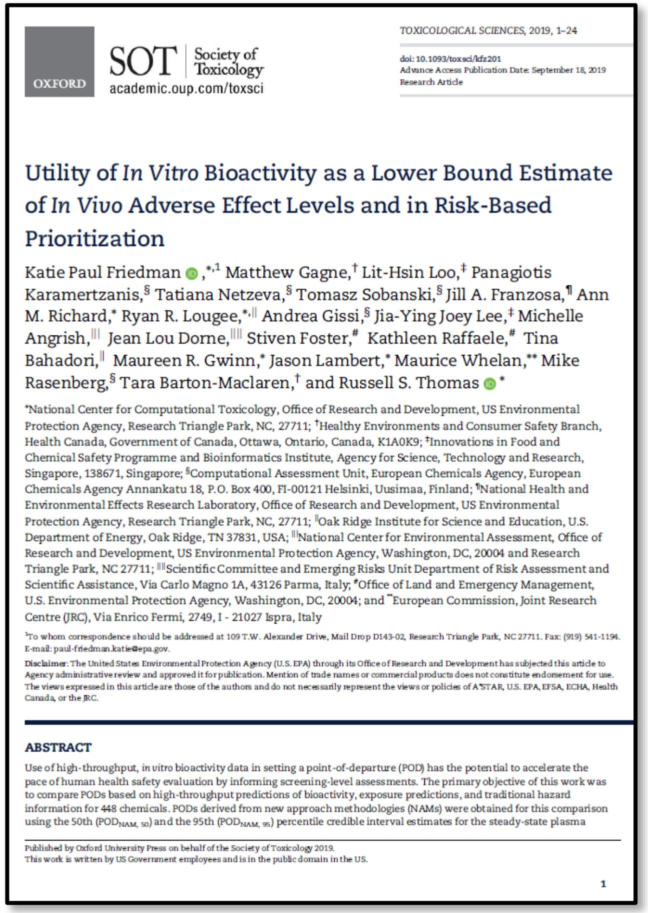


Linakis et al., 2020

Case Study to Demonstrate Application of NAMs To Screening Level Assessments

4

Start Small and Build on Successes…



TOXICOLOGICAL SCIENCES, 2019, 1–24

doi: 10.1093/toxsci/kfz201
Advance Access Publication Date: September 18, 2019
Research Article

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Utility of *In Vitro* Bioactivity as a Lower Bound Estimate of *In Vivo* Adverse Effect Levels and in Risk-Based Prioritization

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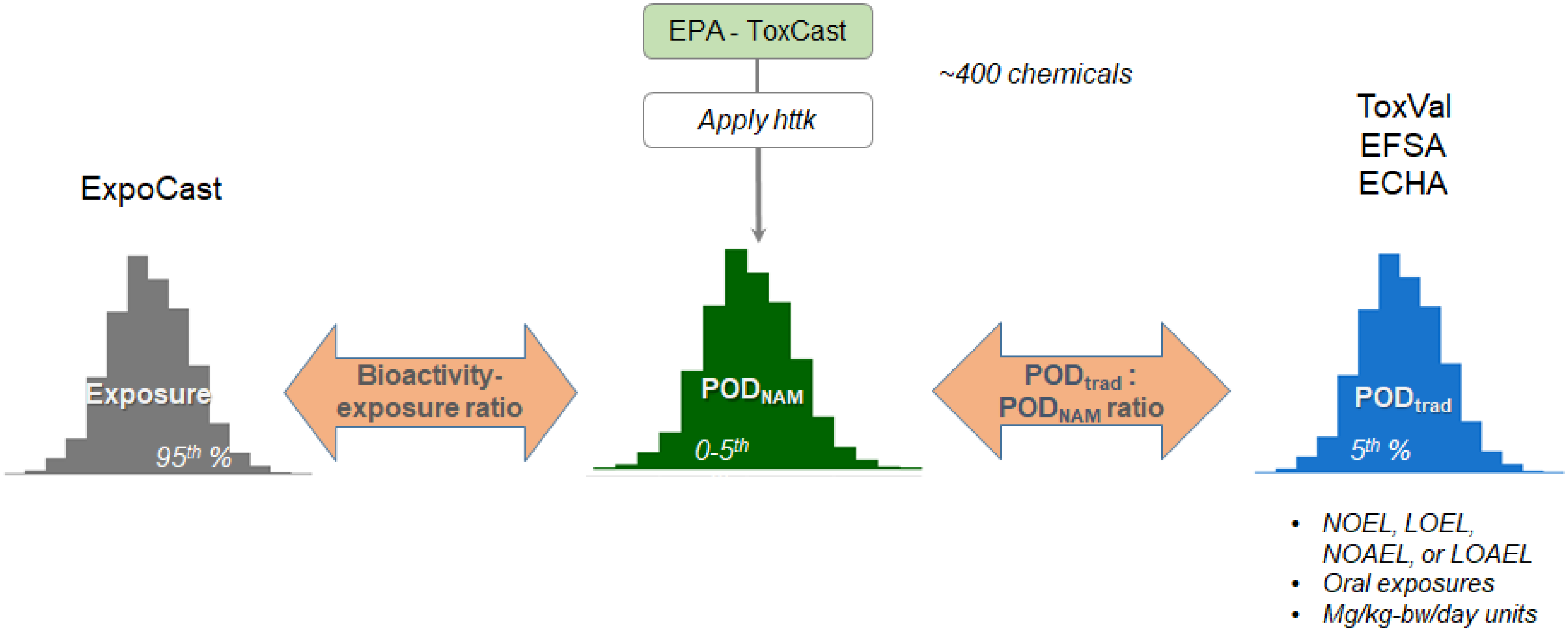
ABSTRACT

Use of high-throughput, *in vitro* bioactivity data in setting a point-of-departure (POD) has the potential to accelerate the pace of human health safety evaluation by informing screening-level assessments. The primary objective of this work was to compare PODs based on high-throughput predictions of bioactivity, exposure predictions, and traditional hazard information for 448 chemicals. PODs derived from new approach methodologies (NAMs) were obtained for this comparison using the 50th ($POD_{NAM, 50}$) and the 95th ($POD_{NAM, 95}$) percentile credible interval estimates for the steady-state plasma

1

Paul-Friedman et al., 2020



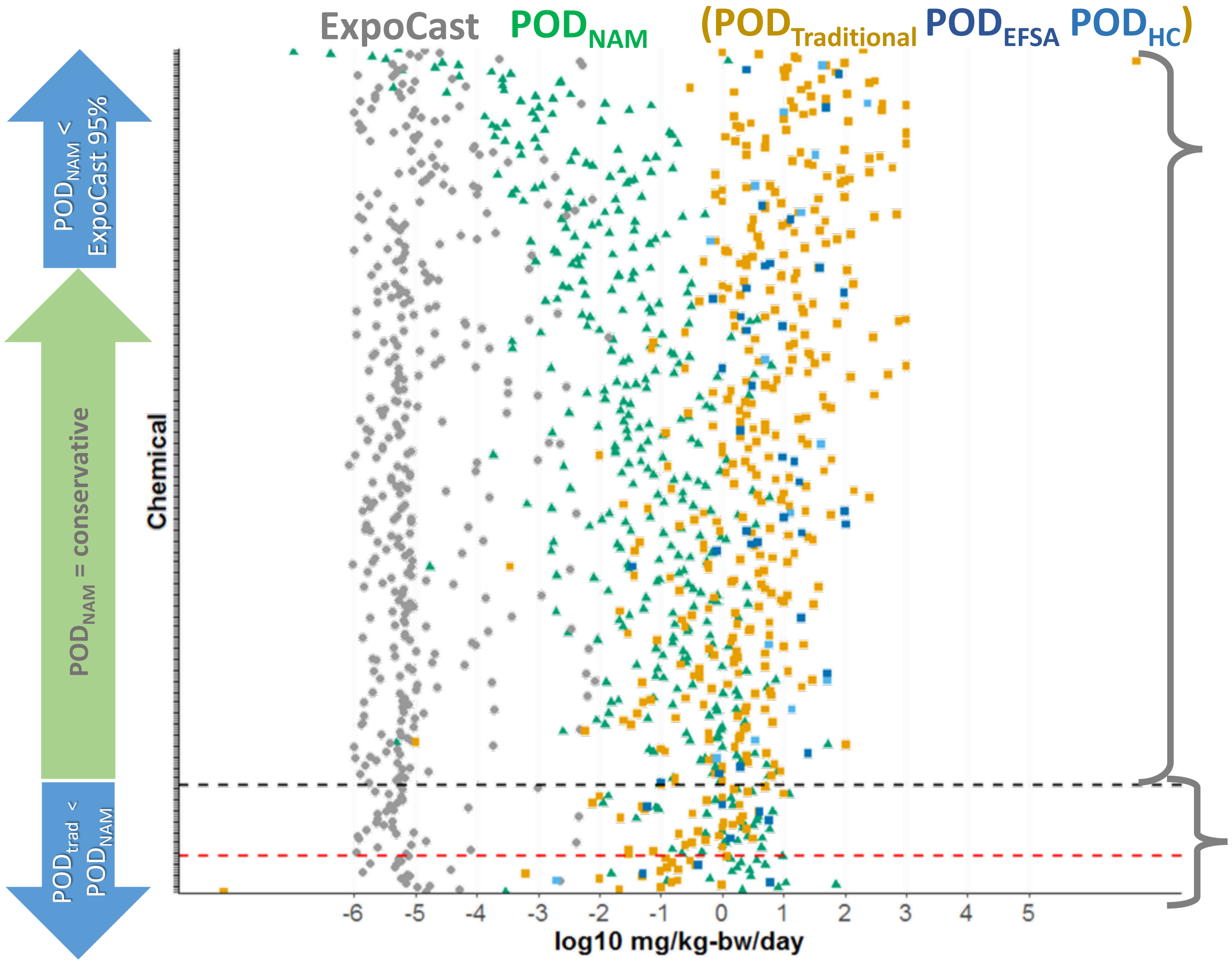
Goal: Determine whether *in vitro* bioactivity from broad-based NAMs can be used as a conservative point-of-departure and when compared with exposure estimates serve to prioritize chemicals for future study or as lower tier risk assessment.

United States Environmental Protection Agency

Case Study to Demonstrate Application of NAMs To Screening Level Assessments

4

Start Small and Build on Successes…



For ~89% of the chemicals, POD_{NAM} was conservative.

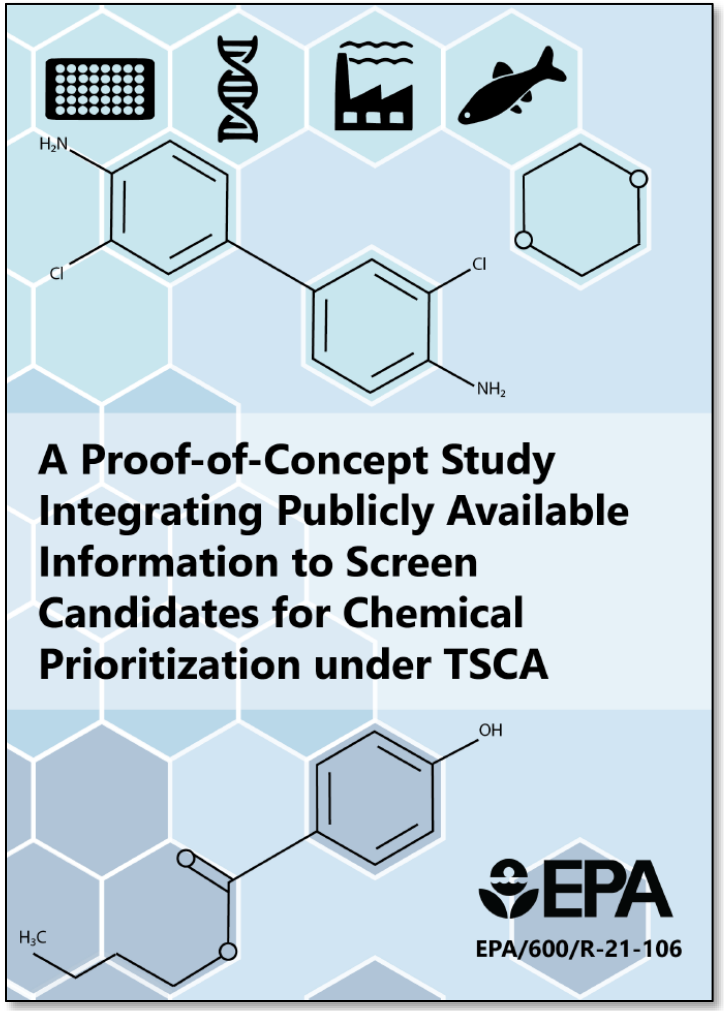
(~100-fold on average), but less conservative than a TTC

Chemicals where POD_{NAM} was not conservative enriched in OPs/carbamates

Building on the Concept for Regulatory and Product Development Decisions

4

Start Small and Build on Successes…



Science Approach Document

Bioactivity Exposure Ratio:
Application in Priority Setting and Risk Assessment

Health Canada

March 2021

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journal homepage: www.elsevier.com/locate/comtox

Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients

Matthew Dent[a,*], Renata Teixeira Amaral[b], Pedro Amores Da Silva[b], Jay Ansell[c], Fanny Boisleve[d], Masato Hatao[e], Akihiko Hirose[f], Yutaka Kasai[g], Petra Kern[h], Reinhard Kreiling[i], Stanley Milstein[j], Beta Montemayor[k], Julcemara Oliveira[l], Andrea Richarz[m], Rob Taalman[n], Eric Vaillancourt[o], Rajeshwar Verma[j], Nashira Vieira O'Reilly Cabral Posada[l], Craig Weiss[p], Hajime Kojima[f]

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[h] Procter and Gamble Services Company NV, Temselaan 100, B-1853 Strombeek-Bever, Belgium
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ABSTRACT

Consumer safety is a prerequisite for any cosmetic product. Worldwide, there is an ever-increasing desire to bring safe products to market without animal testing, which requires a new approach to consumer safety. 'Next Generation Risk Assessment' (NGRA), defined as an exposure-led, hypothesis driven risk assessment approach that integrates *in silico*, *in chemico* and *in vitro* approaches, provides such an opportunity. The customized nature of each NGRA means that the development of a prescriptive list of tests to assure safety is not possible, or appropriate. The International Cooperation on Cosmetics Regulation (ICCR) therefore tasked a group of scientists from regulatory authorities and the Cosmetic Industry to agree on and outline the principles for incorporating these new approaches into risk assessments for cosmetic ingredients. This ICCR group determined the overall goals of NGRA (to be human-relevant, exposure-led, hypothesis-driven and designed to prevent harm); how an NGRA should be conducted (using a tiered and iterative approach, following an appropriate literature search and evaluation of the available data, and using robust and relevant methods and strategies); and how the assessment should be documented (transparent and explicit about the logic of the approach and sources of uncertainty). Those working on the risk assessment of cosmetics have a unique opportunity to lead progress in the application of novel approaches, and cosmetic risk assessors are encouraged to consider these key principles when conducting or evaluating such assessments.

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United States Environmental Protection Agency

Case Study on Application of NAMs for Developmental Neurotoxicity

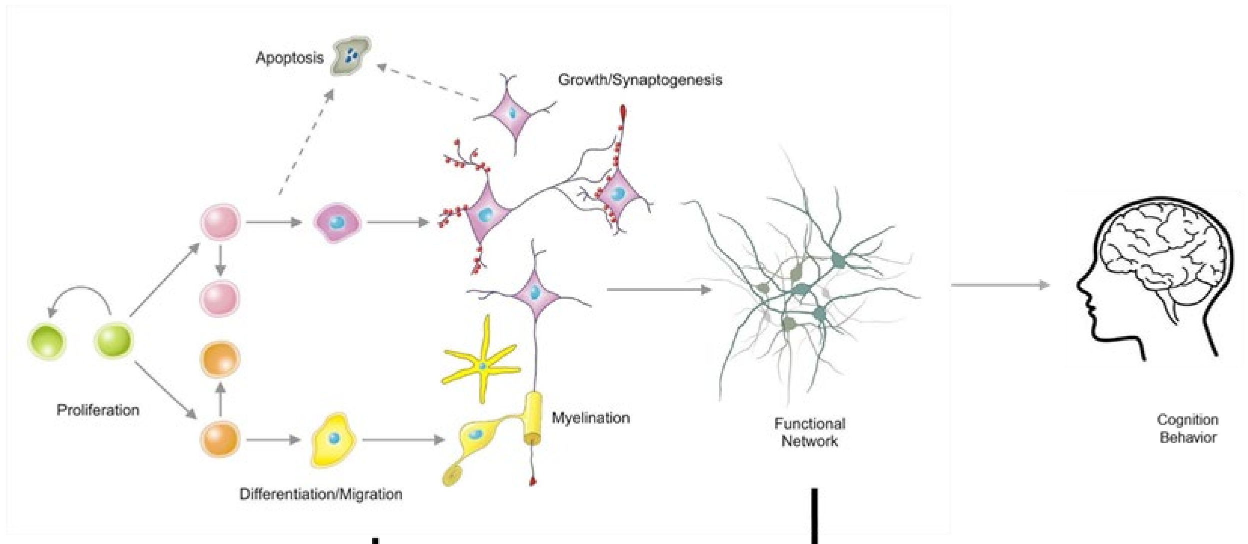
4

Start Small and Build on Successes…

Agency Issue Paper:

Use of New Approach Methodologies to Derive Extrapolation Factors and Evaluate Developmental Neurotoxicity for Human Health Risk Assessment

July 2020



Key Neurodevelopmental Events (High Content Imaging)

Network Formation (Multi-Electrode Array)

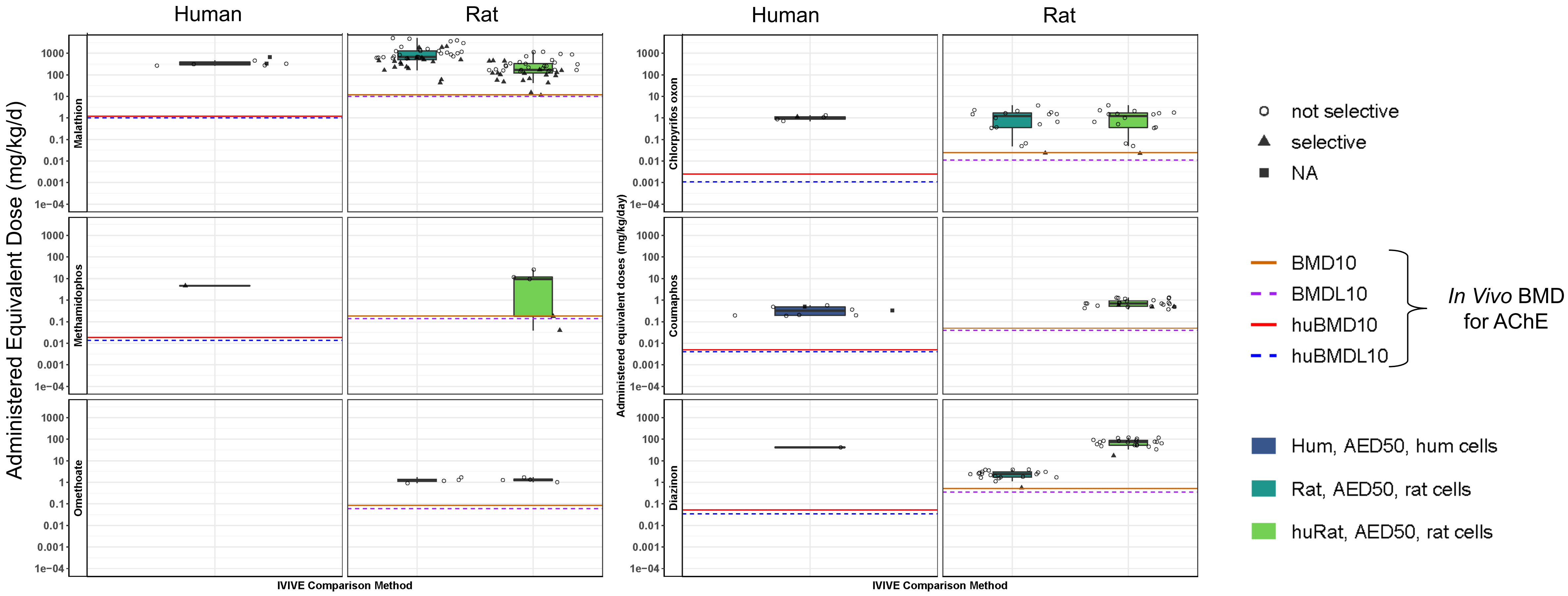
Key Question: How do NAMs for key cellular events and processes relevant to developmental neurotoxicity compare to *in vivo* AChE changes in rats on an administered dose basis for organophosphate pesticides (i.e., is AChE protective of potential DNT effects)?

EPA United States Environmental Protection Agency

Case Study on Application of NAMs for Developmental Neurotoxicity

4

Start Small and Build on Successes…



Administered dose equivalents for NAMs relevant to developmental neurotoxicity are general higher or in some cases approaching the doses associated with significant *in vivo* changes in AChE activity.

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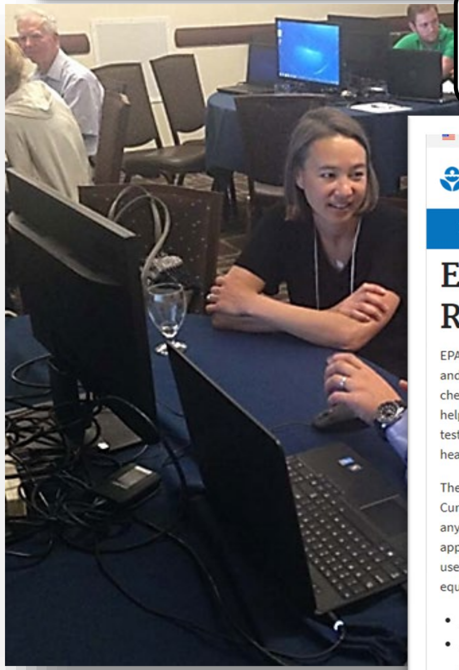
Communicate and Share the Results With the Broader Community

5

Communicate, Communicate…

Tailored Training for Specific User Groups

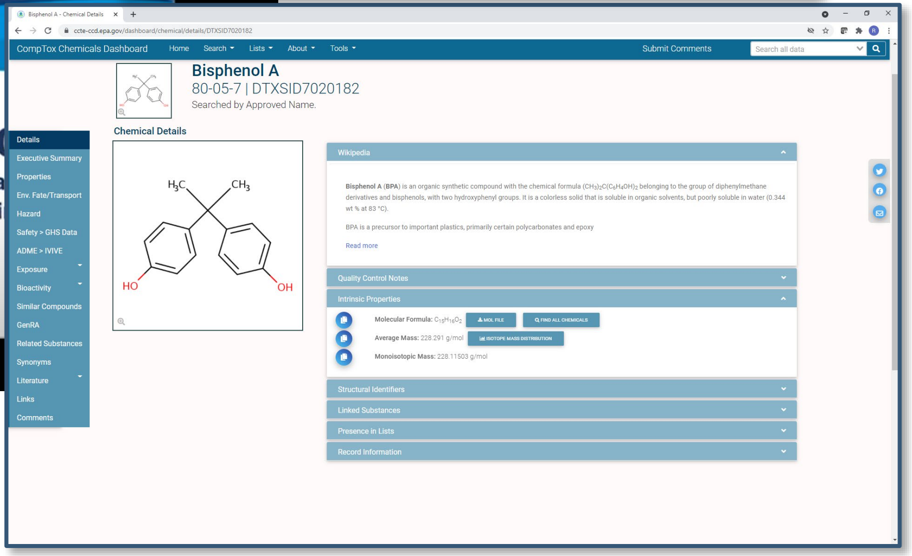


Public Websites with Consolidated Information on NAMs

https://www.epa.gov/nam

Scientific Conferences and Webinars

Data Dashboards and Decision Support Tools



https://comptox.epa.gov/dashboard

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Take Home Messages…

1. Know Where You Want to Go…
2. Set Expectations for Success…
3. Continue Improving the Science…
4. Start Small and Build on Successes…
5. Communicate, Communicate…

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