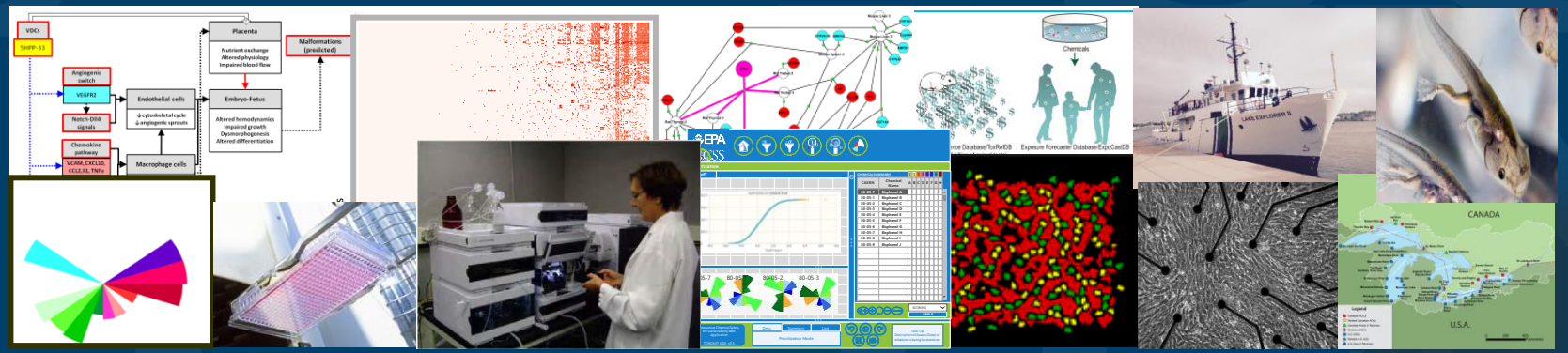
Moving Past Measuring Adversity in an Intact Organism

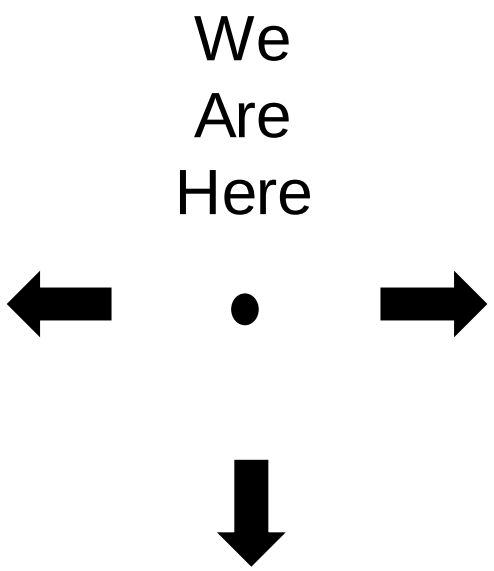


ECHA NAM Workshop

May 31, 2023

Rusty Thomas
Director
Center for Computational Toxicology and Exposure

Moving Past Adversity in Intact Organisms Implies We Don't Want to Stay Where We Are…



But, This Requires We Know The Direction We Want to Go and What It Looks Like When We Get There…

We Are Here

•

B

•

Prediction

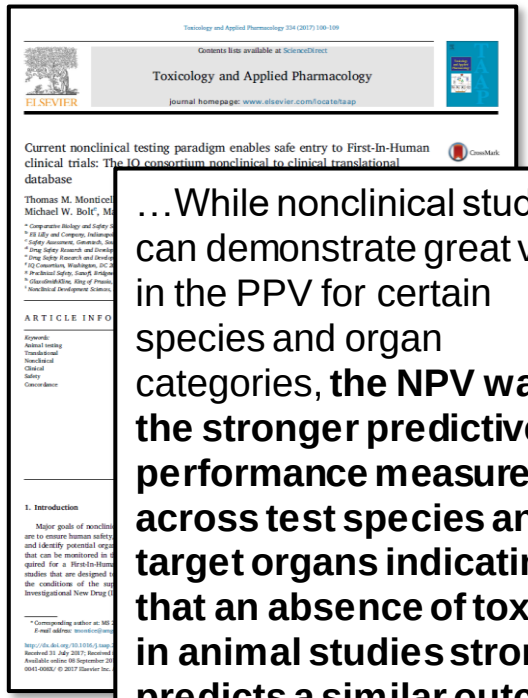
Protection

B

•

Current Data Suggest Rodents Serve as Protective Rather Than Predictive Models of Human Toxicity

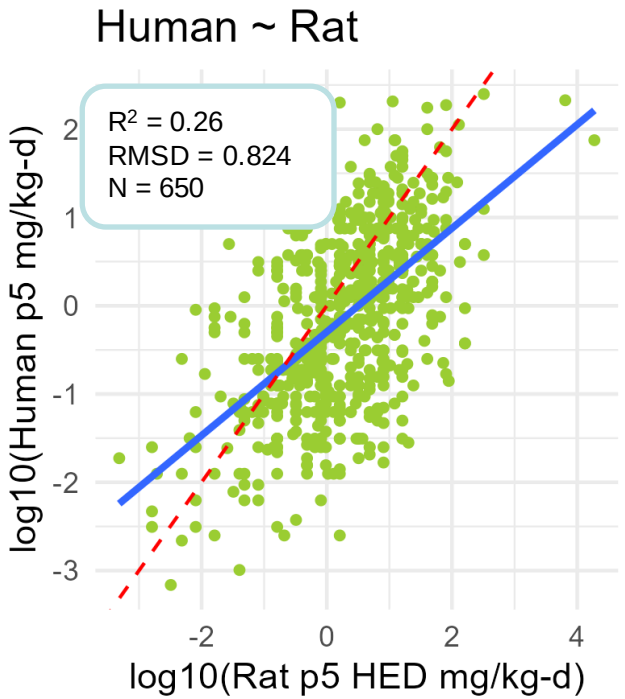
Qualitative Concordance Between Rodent and Human Toxicological Responses

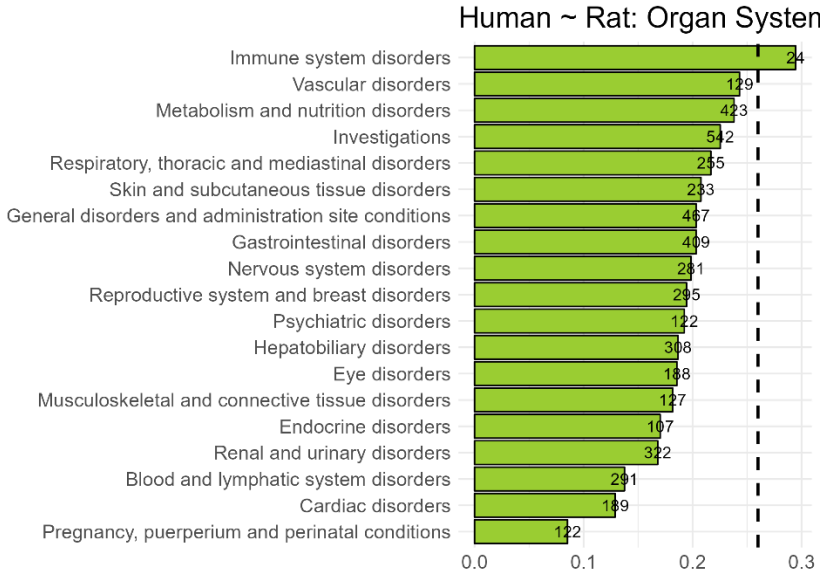

Toxicology and Applied Pharmacology

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

…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.**

Quantitative Concordance Between Rodent and Human Toxicological Responses



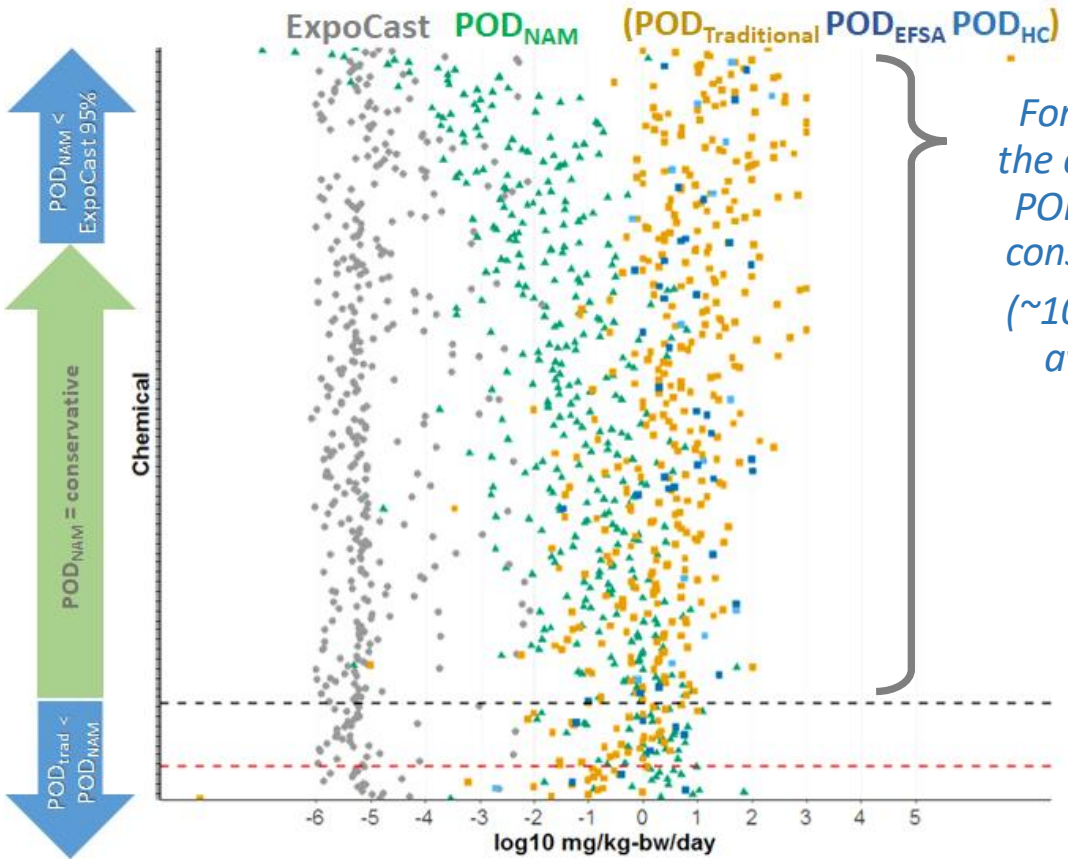


R^2: log10(Human p50) ~ log10(Rat p50)

New APCRA Case Study, Preliminary Results

In Vitro Bioactivity Can Provide Similar or Higher Levels of Protection Compared with Rodent Models

ToxCast Assay Battery

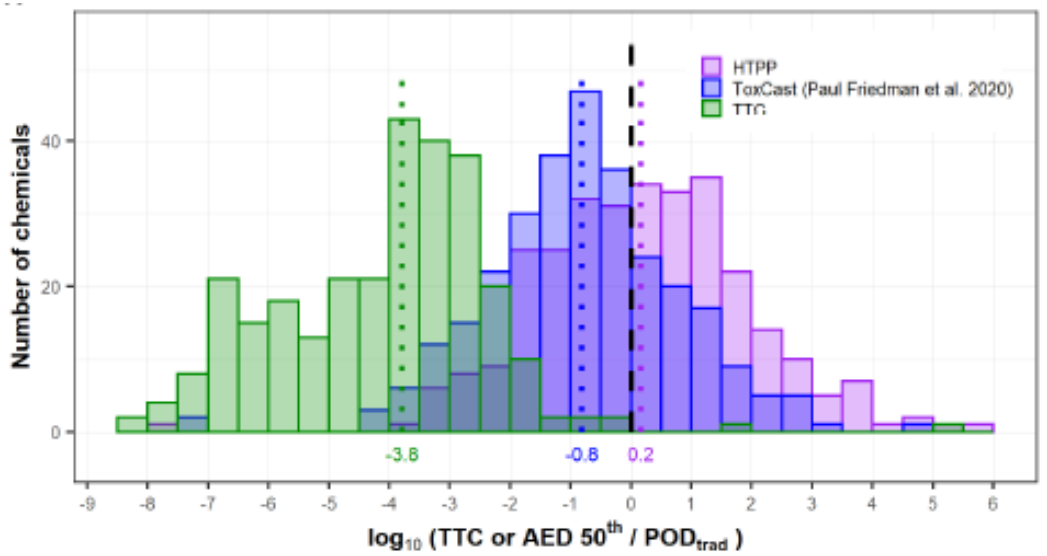


For ~90% of the chemicals, POD_{NAM} was conservative.

(~100-fold on average)

Paul-Friedman et al., 2020

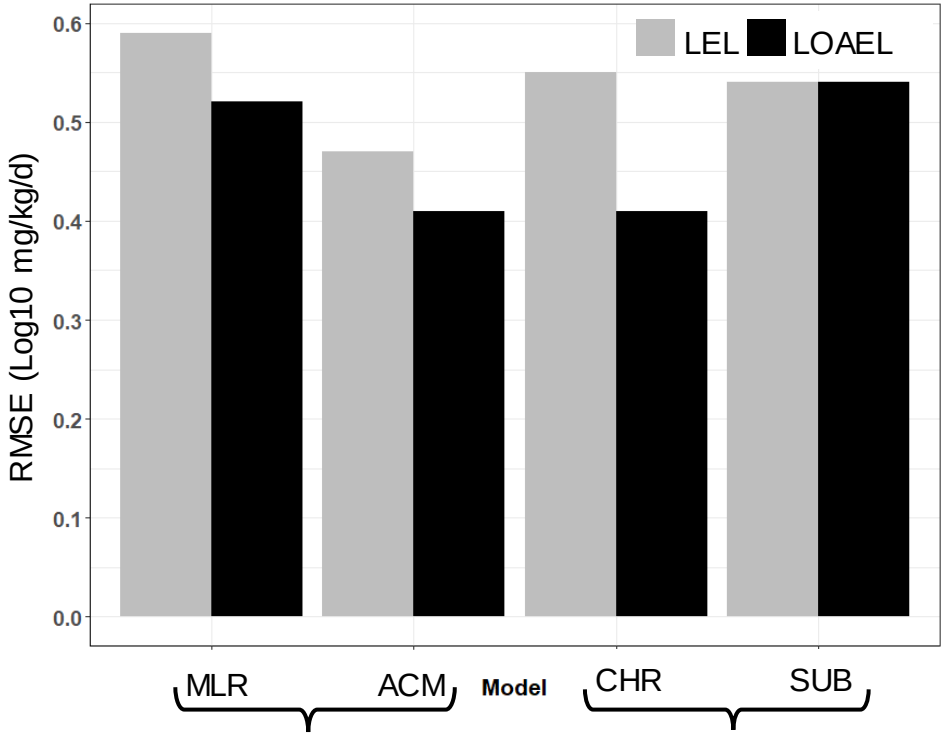
High-Throughput Phenotypic Profiling Assay



Nyffeler and Harrill, ISMB Poster, 2020

Characterizing Variability in Current Toxicity Tests is Important to Set Expectations

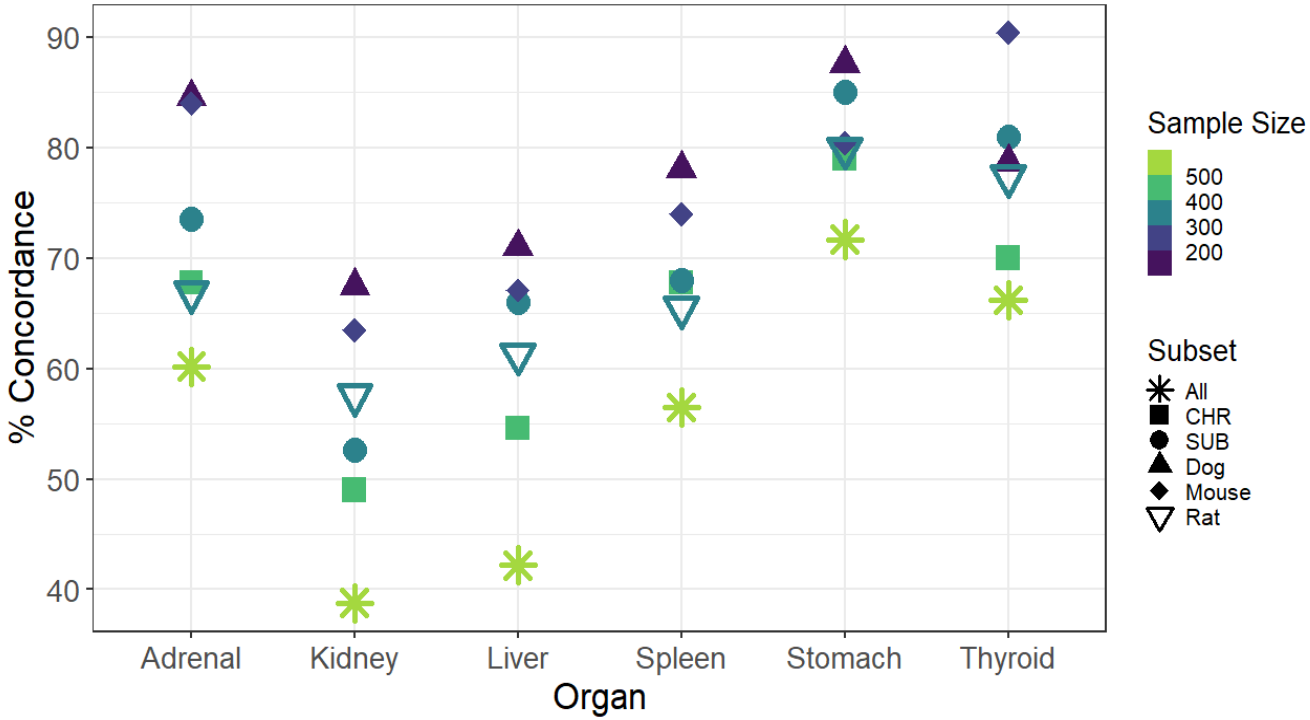
Evaluating Quantitative Variability in Traditional Repeat Dose Toxicity Studies



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)

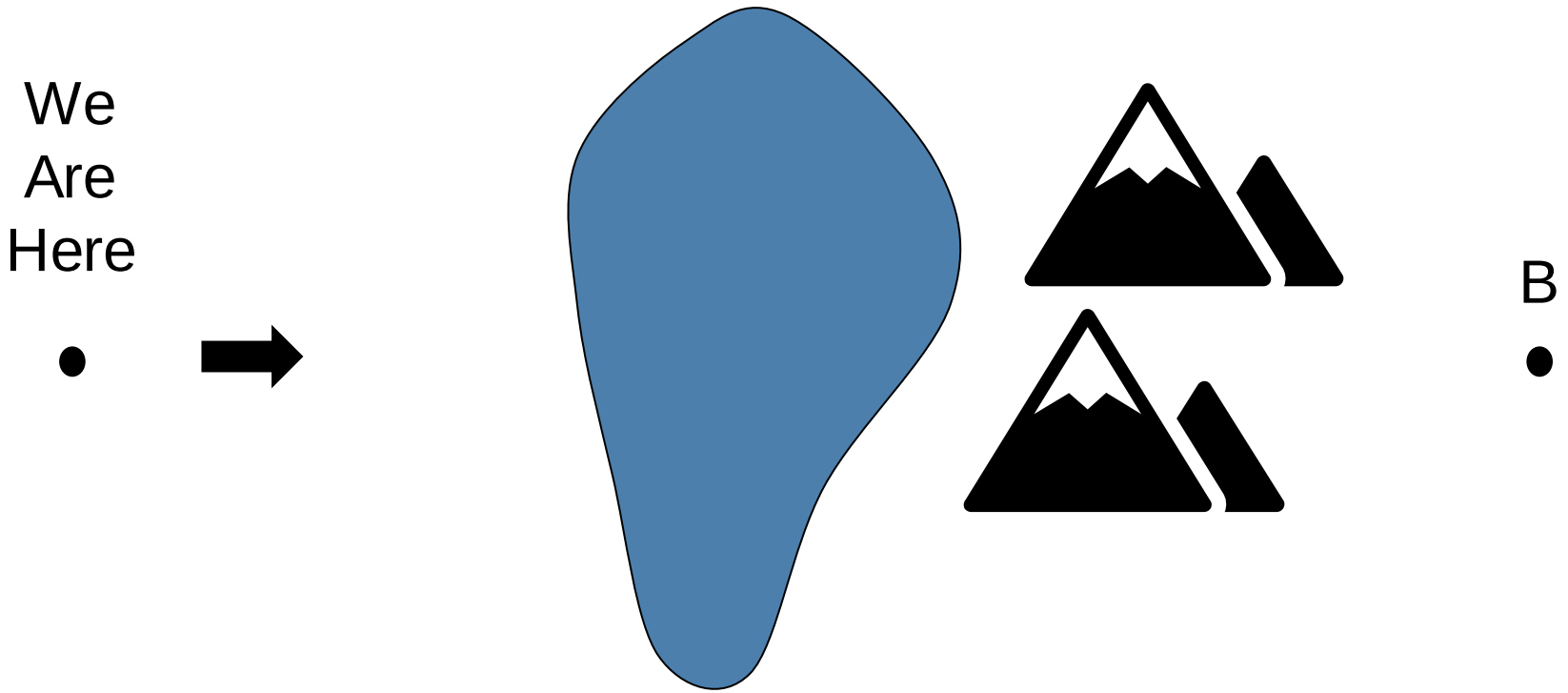
Pham et al., Comp Toxicol., 2020

Evaluating Qualitative Concordance in Target Organ Toxicity

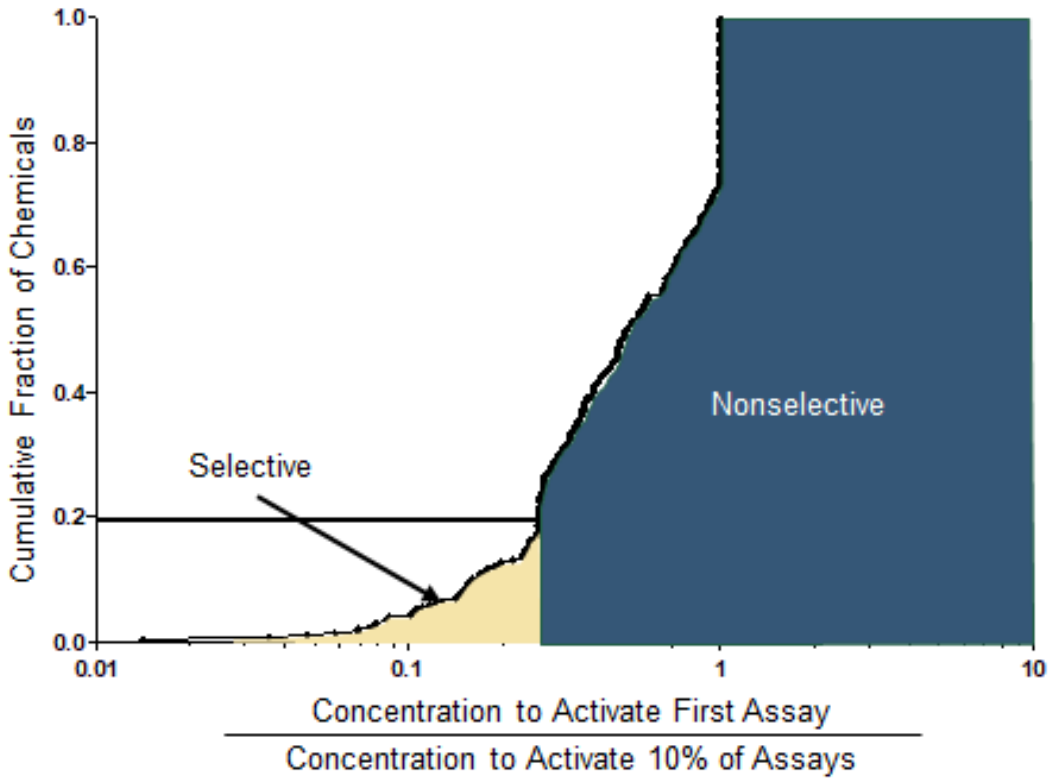


Paul-Friedman, Unpublished

Understanding the Landscape May Impact Your Mode of Transport or Route to Destination



The Chemical Landscape of Interest Generally Interacts Non-Selectively with Biological Systems

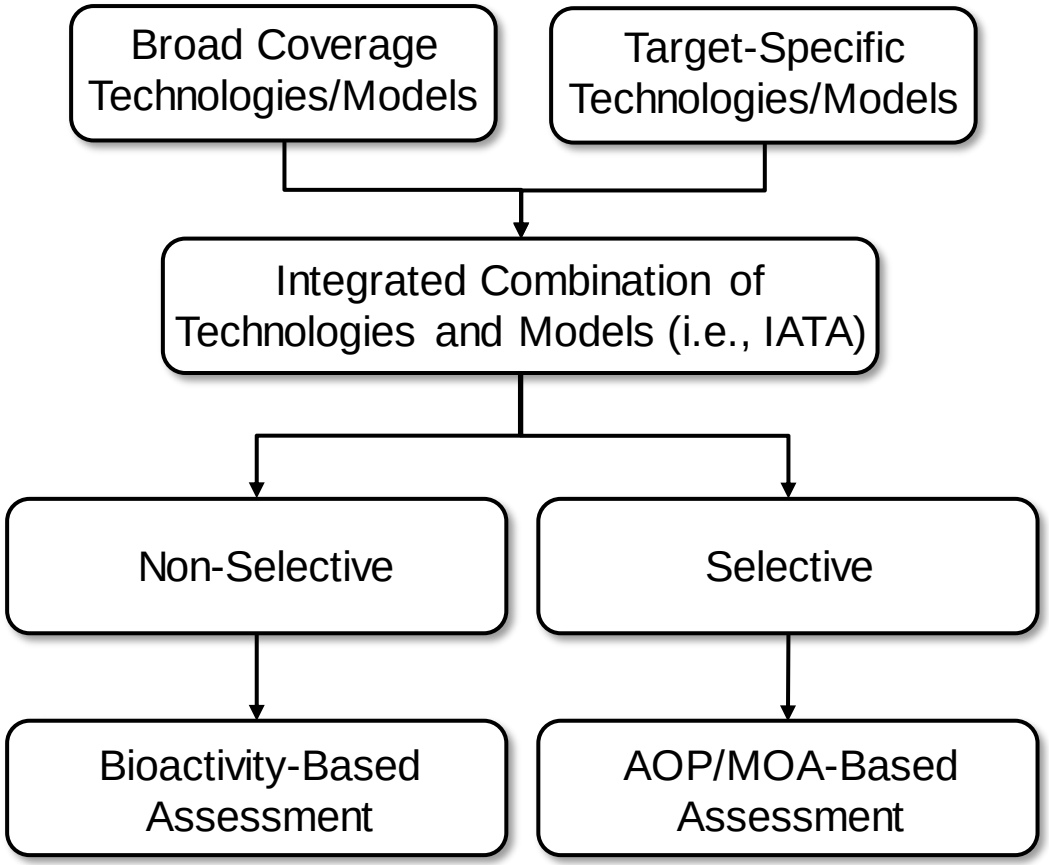


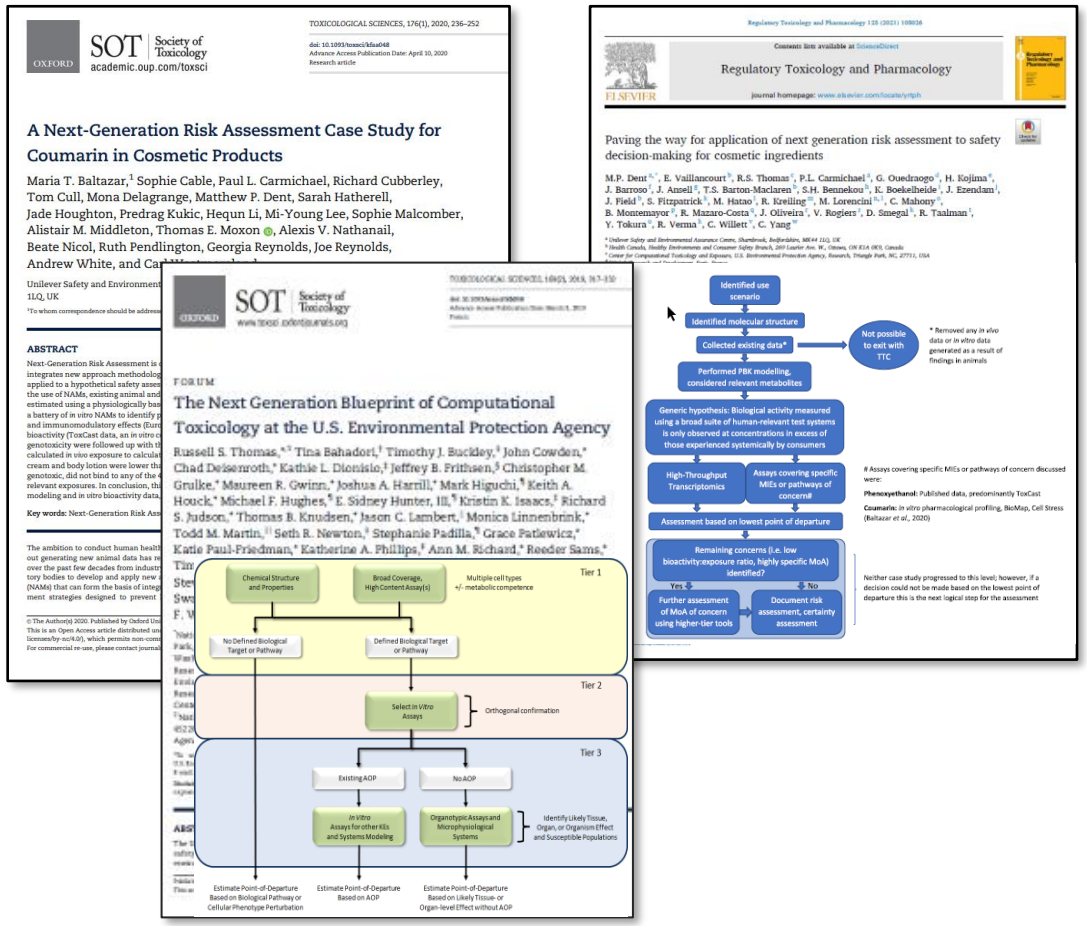
- No matter how good the technology, identifying a predominant mechanism for a non-selective chemical is impractical.
- Supports the use of bioactivity (*in vitro* or *in vivo*) can be a good surrogate for potential adverse effects in chemical assessments.
- Similar to established concepts in ecotoxicology with specific-acting and non-specific acting (i.e., narcosis) classes

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

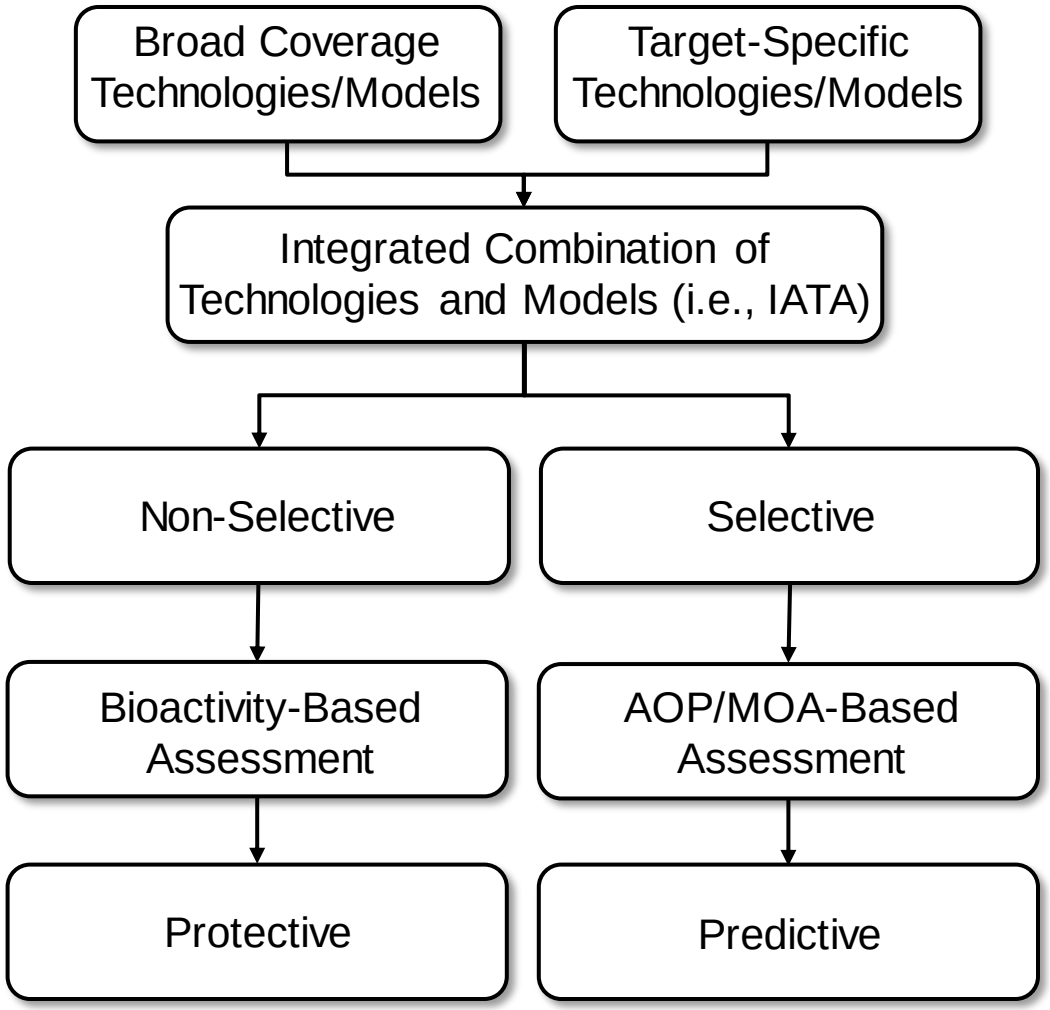
Proposed Toxicity Testing and Assessment Processes Should Align With Chemical Selectivity

Conceptual Testing and Assessment Paradigm for Many NGRA-Based Approaches

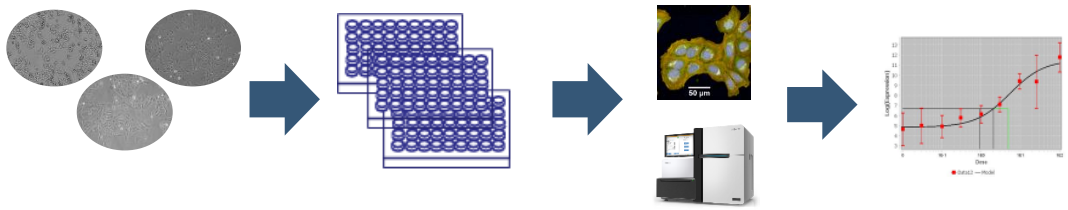




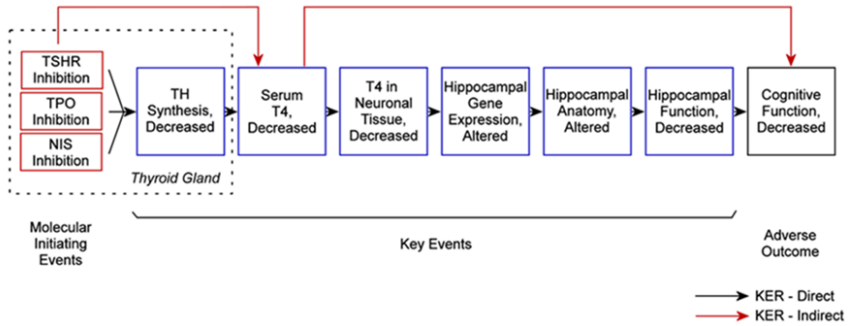
Extend Definition of Hazard to Upstream Key Events and Integrated Measures of Bioactivity



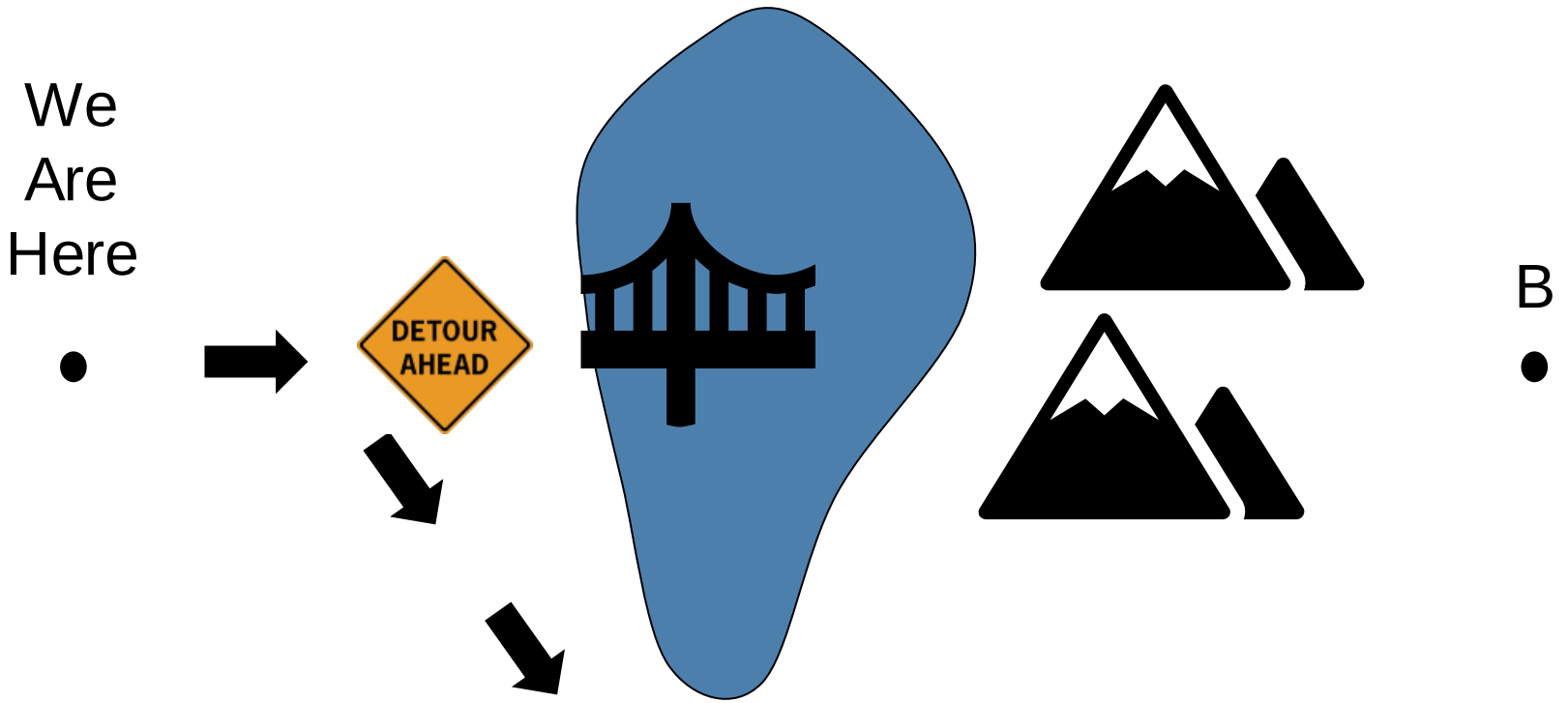
Broad Coverage Assays → Integrated Bioactivity → Protective



Target-Specific Assays → Specific Hazards → Predictive

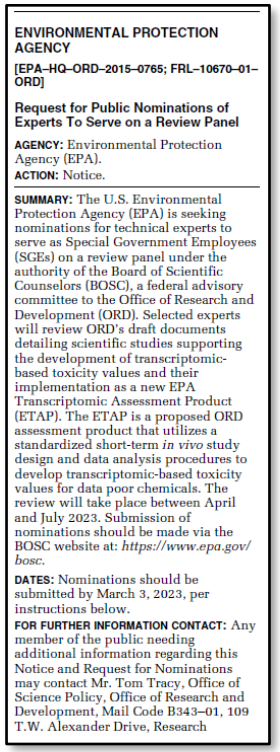


Appreciate That Until New Roads and Bridges Are Built Detours May Be Inevitable



EPA Announced Proposed Release of a New Human Health Assessment Product Based on Transcriptomics

EPA released public notice for upcoming scientific peer-review and public comment on a new draft ORD human health assessment product for data poor chemicals.



ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–ORD–2015–0765; FRL–10670–01–ORD]

Request for Public Nominations of Experts To Serve on a Review Panel

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: The U.S. Environmental Protection Agency (EPA) is seeking nominations for technical experts to serve as Special Government Employees (SGEs) on a review panel under the authority of the Board of Scientific Counselors (BOSC), a federal advisory committee to the Office of Research and Development (ORD). Selected experts will review ORD's draft documents detailing scientific studies supporting the development of transcriptomic-based toxicity values and their implementation as a new EPA Transcriptomic Assessment Product (ETAP). The ETAP is a proposed ORD assessment product that utilizes a standardized short-term *in vivo* study design and data analysis procedures to develop transcriptomic-based toxicity values for data poor chemicals. The review will take place between April and July 2023. Submission of nominations should be made via the BOSC website at: *https://www.epa.gov/bosc.*

DATES: Nominations should be submitted by March 3, 2023, per instructions below.

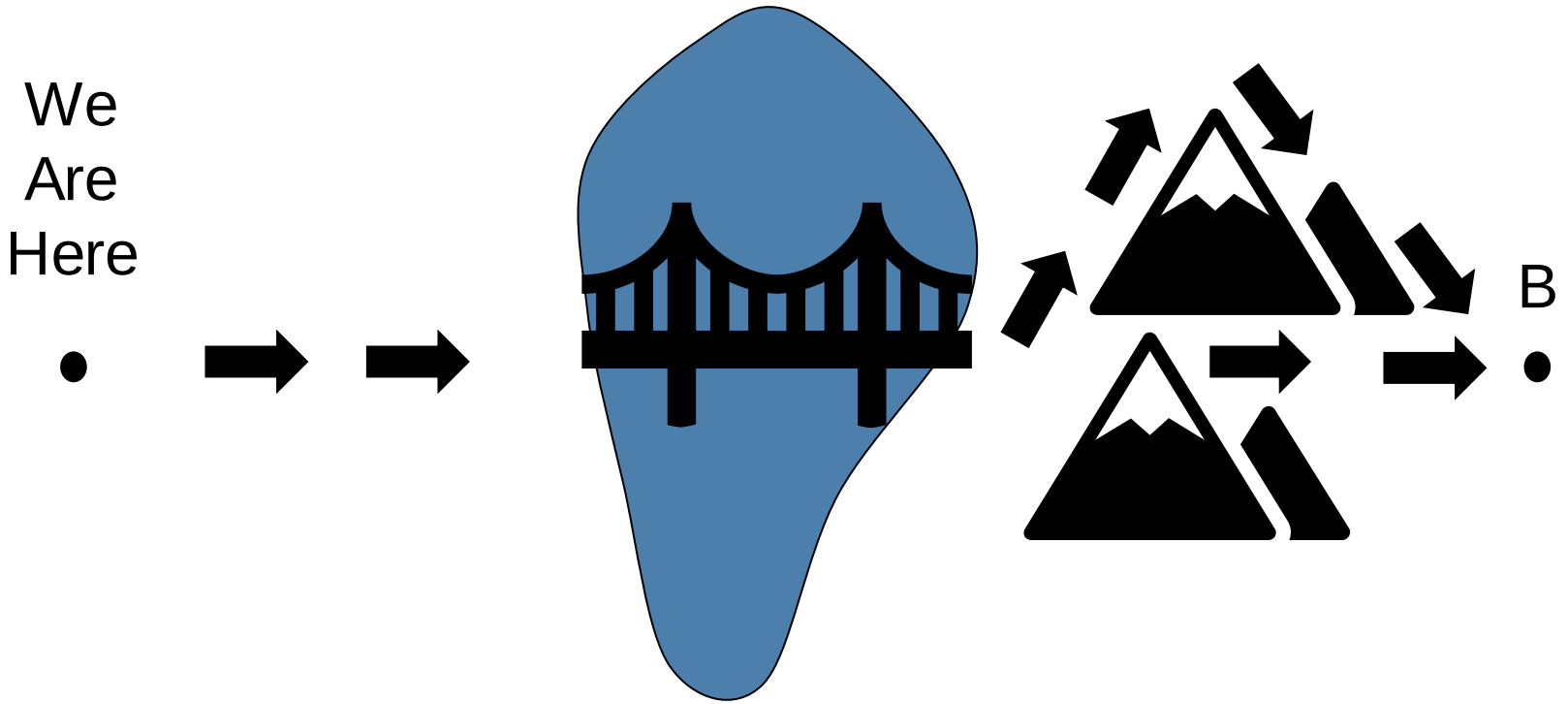
FOR FURTHER INFORMATION CONTACT: Any member of the public needing additional information regarding this Notice and Request for Nominations may contact Mr. Tom Tracy, Office of Science Policy, Office of Research and Development, Mail Code B343–01, 109 T.W. Alexander Drive, Research

EPA Transcriptomic Assessment Product (ETAP) *ad hoc* Board of Scientific Counselors FRN

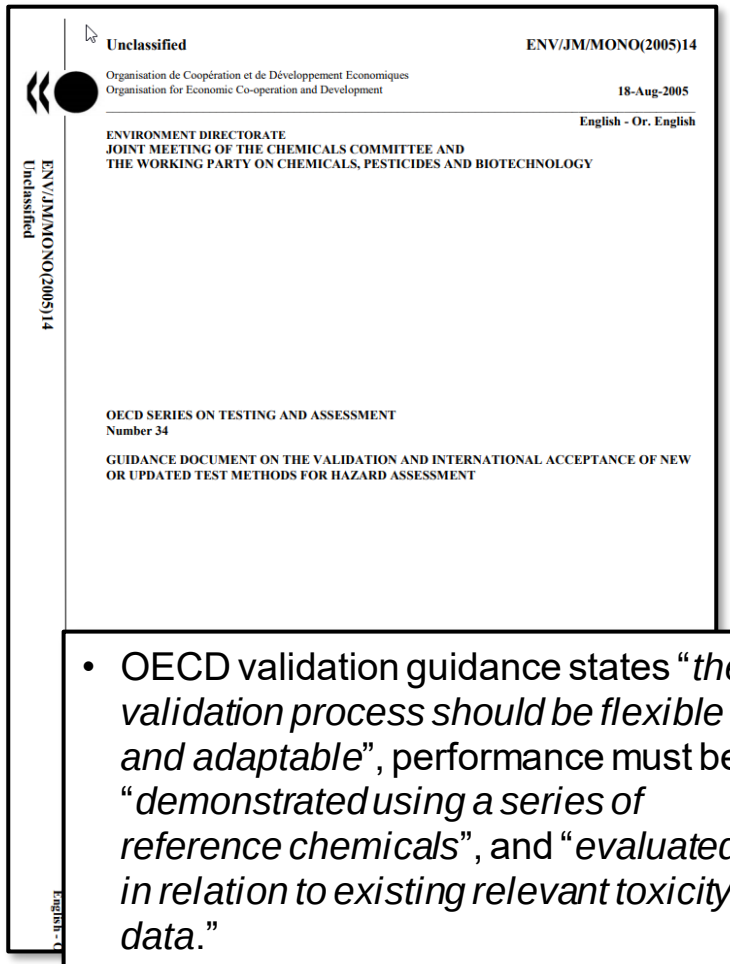
- Development of transcriptomic points-of-departure from short-term *in vivo* studies
- Derivation of transcriptomic reference values for chronic toxicity; and
- Incorporation of transcriptomic reference values into a new standardized assessment product intended for data poor chemicals.
- Example application of the ETAP to a data poor per- and polyfluoroalkyl substance (PFAS).

https://www.federalregister.gov/documents/2023/02/15/2023-03194/request-for-public-nominations-of-experts-to-serve-on-a-review-panel

The Route May Not Be The Same For Everyone



Validation or Qualification Process Should Evolve to be Flexible and Performance-Based



Unclassified ENV/JM/MONO(2005)14

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development 18-Aug-2005

English - Or. English

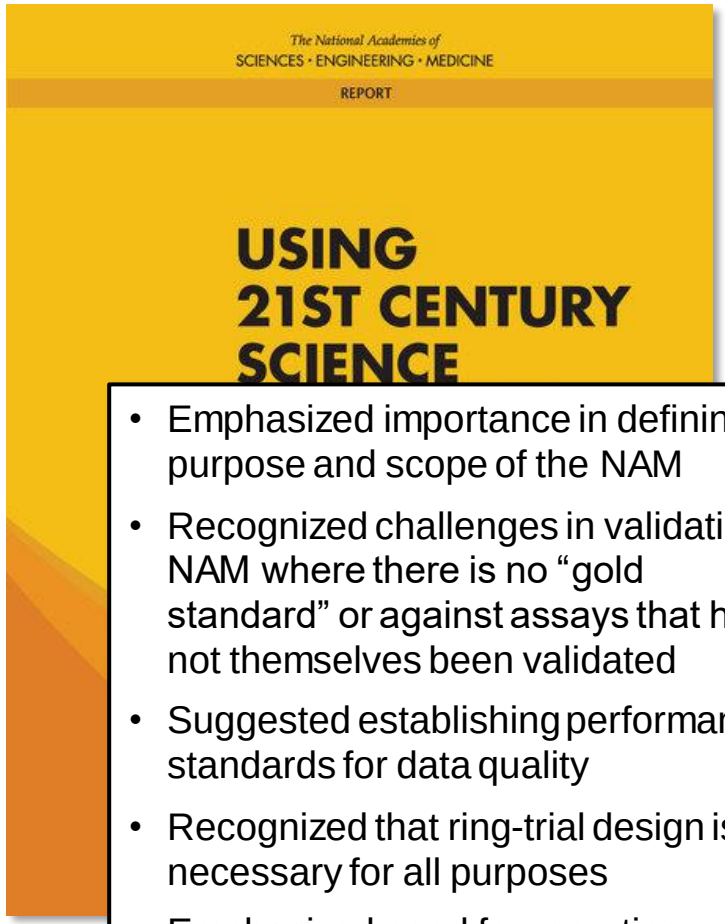
ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ENV/JM/MONO(2005)14
Unclassified

OECD SERIES ON TESTING AND ASSESSMENT
Number 34

GUIDANCE DOCUMENT ON THE VALIDATION AND INTERNATIONAL ACCEPTANCE OF NEW OR UPDATED TEST METHODS FOR HAZARD ASSESSMENT

- OECD validation guidance states "*the validation process should be flexible and adaptable*", performance must be "*demonstrated using a series of reference chemicals*", and "*evaluated in relation to existing relevant toxicity data*."



The National Academies of
SCIENCES · ENGINEERING · MEDICINE

REPORT

USING 21ST CENTURY SCIENCE

- Emphasized importance in defining purpose and scope of the NAM
- Recognized challenges in validating a NAM where there is no "gold standard" or against assays that have not themselves been validated
- Suggested establishing performance standards for data quality
- Recognized that ring-trial design is not necessary for all purposes
- Emphasized need for reporting standards and transparency

Archives of Toxicology
https://doi.org/10.1007/s00204-022-03365-4

REVIEW ARTICLE

A framework for establishing scientific confidence in new approach methodologies

Anna J. van der Zalm[1] · João Barroso[2] · Patience Browne[3] · Warren Casey[4] · John Gordon[5] · Tala R. Henry[6] · Nicole C. Kleinstreuer[7] · Anna B. Lowit[6] · Monique Perron[8] · Amy J. Clippinger[1]

Received: 17 May 2022 / Accepted: 11 August 2022
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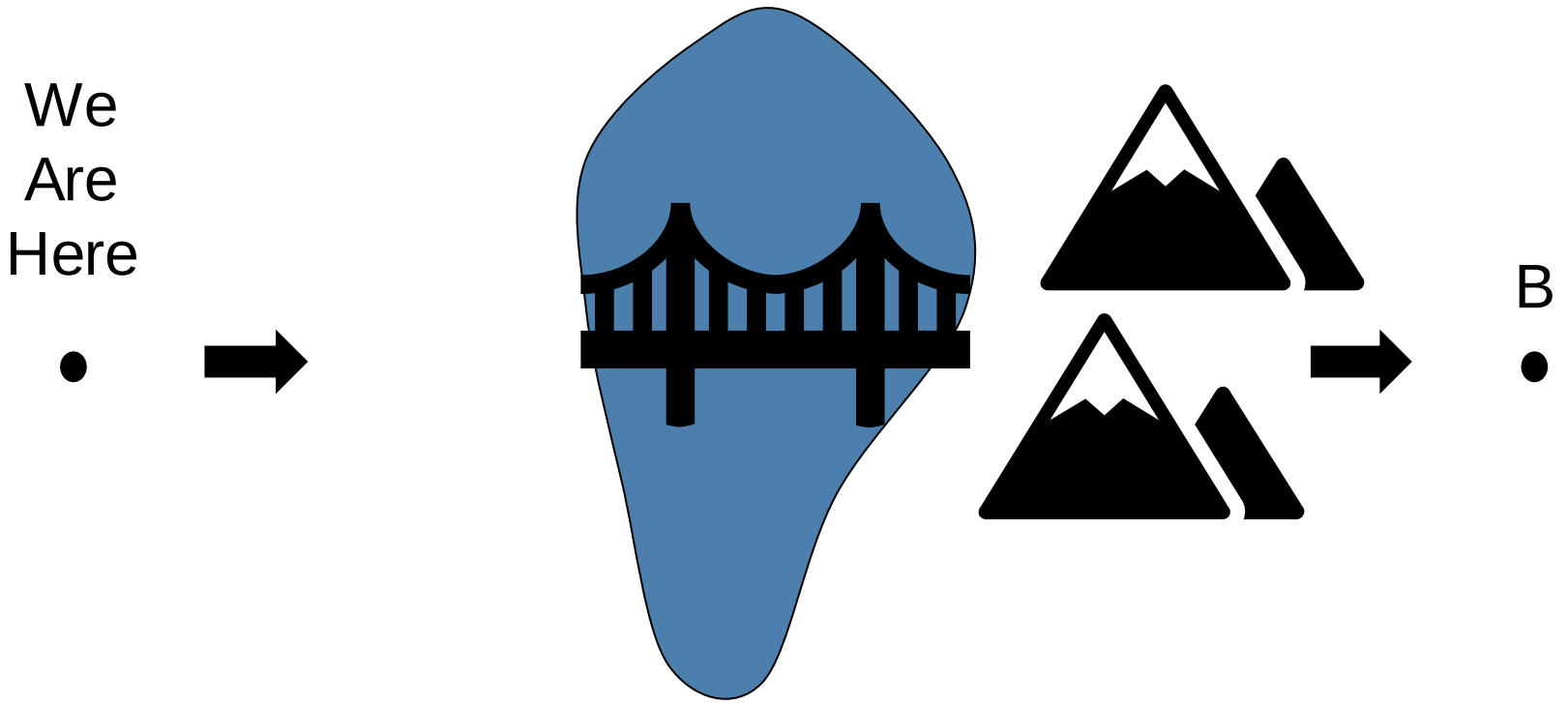
Abstract
Robust and efficient processes are needed to establish scientific confidence in new approach methodologies (NAMs) if they are to be considered for regulatory applications. NAMs need to be fit for purpose, reliable and, for the assessment of human health effects, provide information relevant to human biology. They must also be independently reviewed and transparently communicated. Ideally, NAM developers should communicate with stakeholders such as regulators and industry to identify the question(s), and specified purpose that the NAM is intended to address, and the context in which it will be used. Assessment of the biological relevance of the NAM should focus on its alignment with human biology, mechanistic understanding, and ability to provide information that leads to health protective decisions, rather than solely comparing NAM-based chemical testing results with those from traditional animal test methods. However, when NAM results are compared to historical animal test results, the variability observed within animal test method results should be used to inform performance benchmarks. Building on previous efforts, this paper proposes a framework comprising five essential elements to establish scientific confidence in NAMs for regulatory use: fitness for purpose, human biological relevance, technical characterization, data integrity and transparency, and independent review. Universal uptake of this framework would facilitate the timely development and use of NAMs by the international community. While this paper focuses on NAMs for assessing human health effects of pesticides and industrial chemicals, many of the suggested elements are expected to apply to other types of chemicals and to ecotoxicological effect assessments.

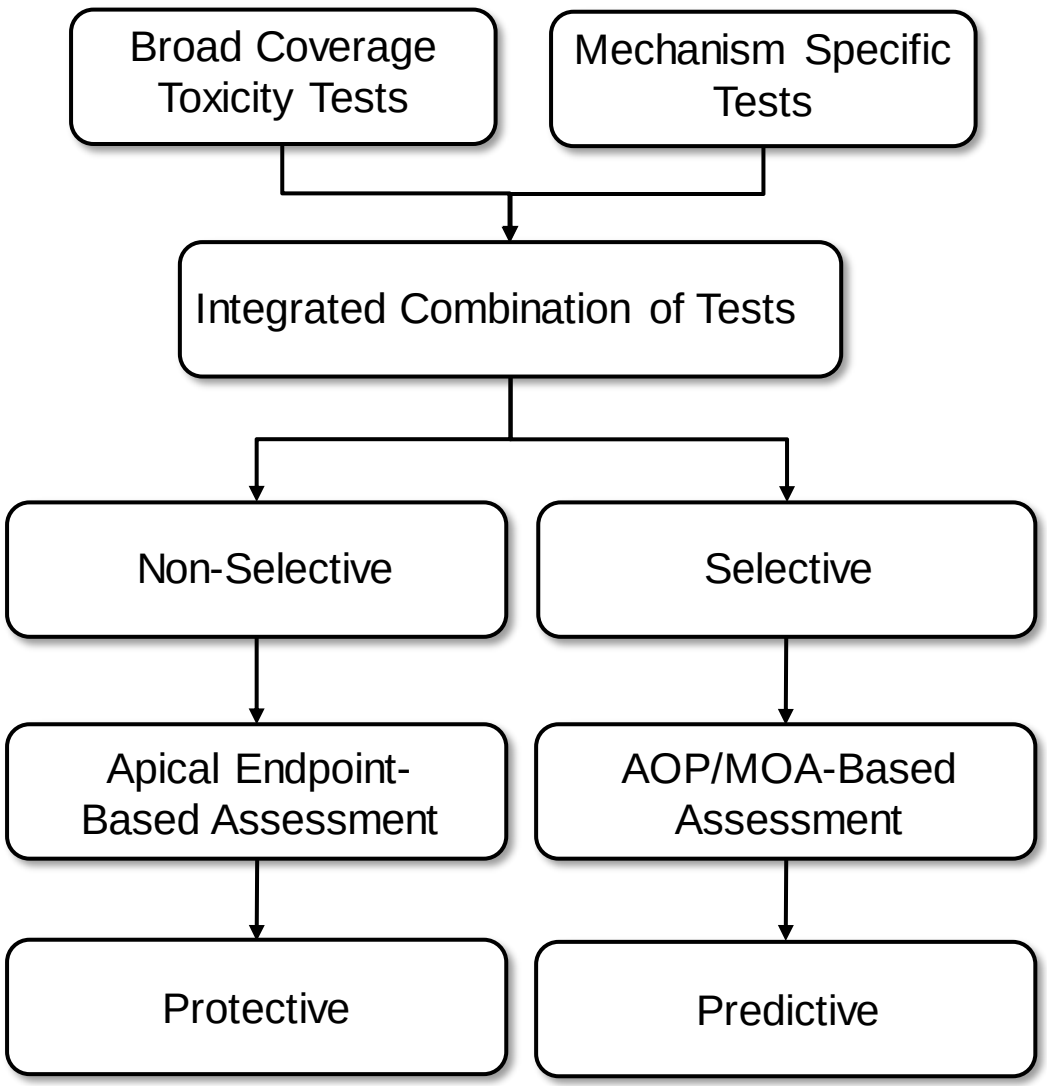
Keywords Validation · Framework · NAMs · New approach methodologies · Human health · Regulatory

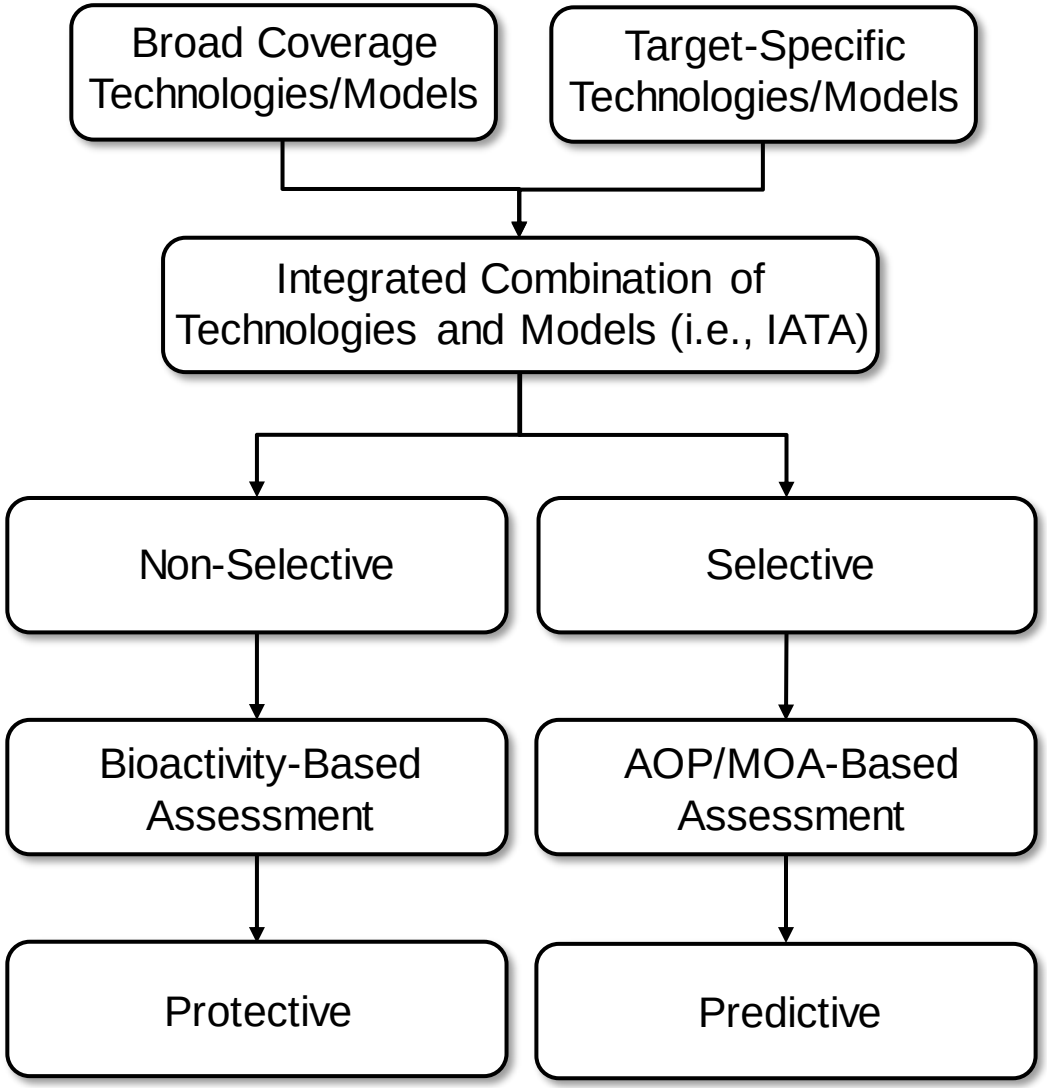
Introduction
Data from traditional animal toxicity test methods have been used for many years to inform human health hazard identification and risk assessment. However, studies relying on animals to characterize effects of chemicals can be of questionable or limited biological relevance to human effects (Bracken 2009; Krewski et al. 2010; Leist and Hartung 2013; Hoffmann 2015; Akhtar 2015; Cohen 2017; Paparella et al.

When We Arrive…



The View May Not Be That Different After All





Acknowledgements

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- CESER
- OCSPP

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- A*STAR
- JRC
- ECHA
- EFSA
- Health Canada

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