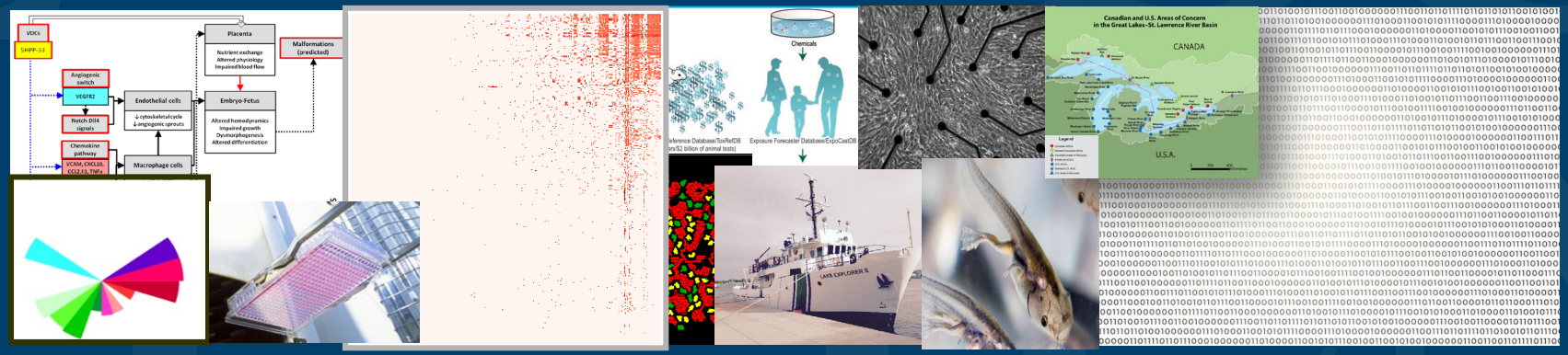
Understanding the Impacts of Chemicals in Environmental Health

A Need for Data or Change in Perspective?

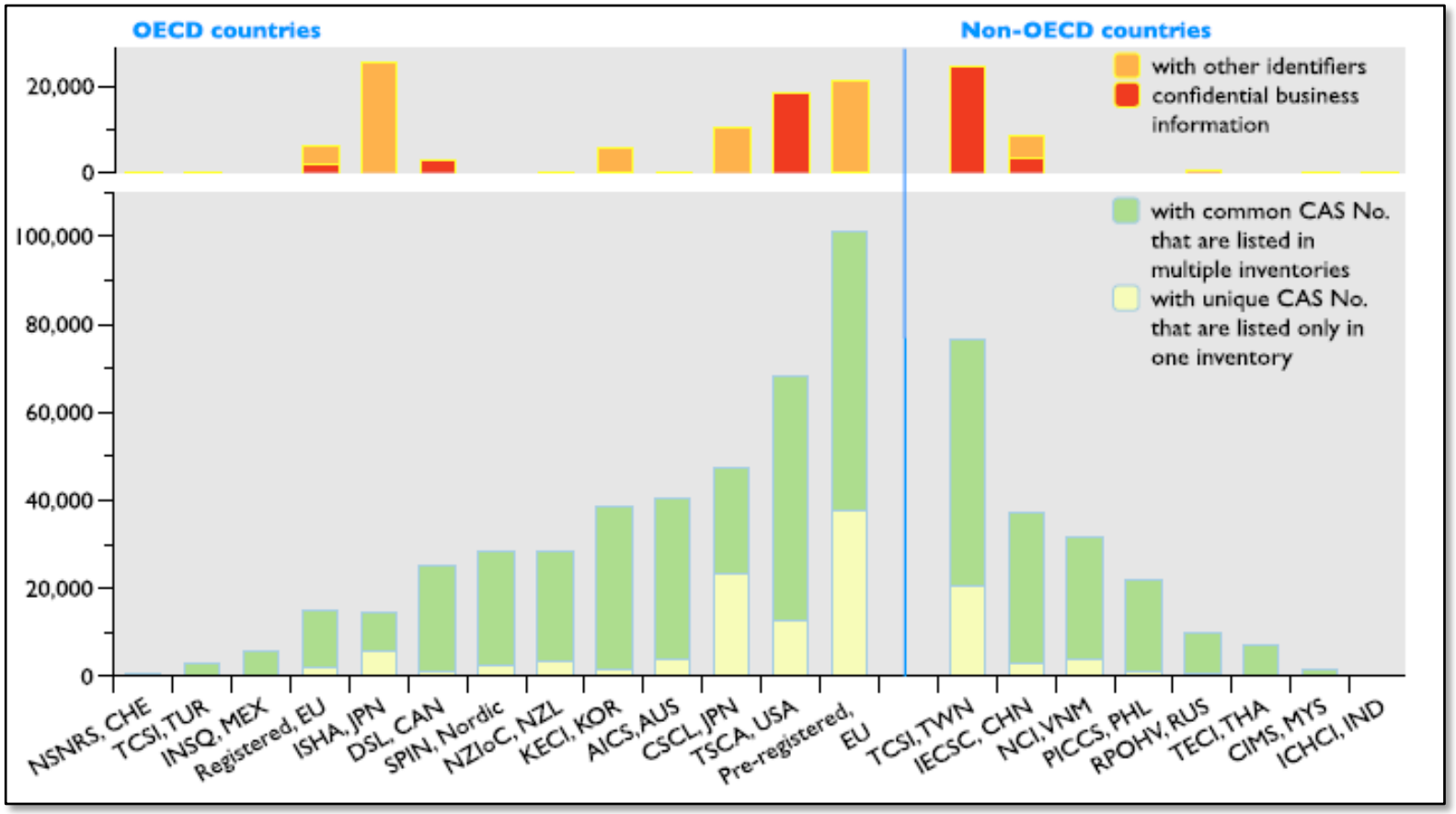


NC Symposium on Life/Data Sciences, Precision Medicine and Environmental Health

May 8, 2023

Rusty Thomas
Director
Center for Computational Toxicology and Exposure

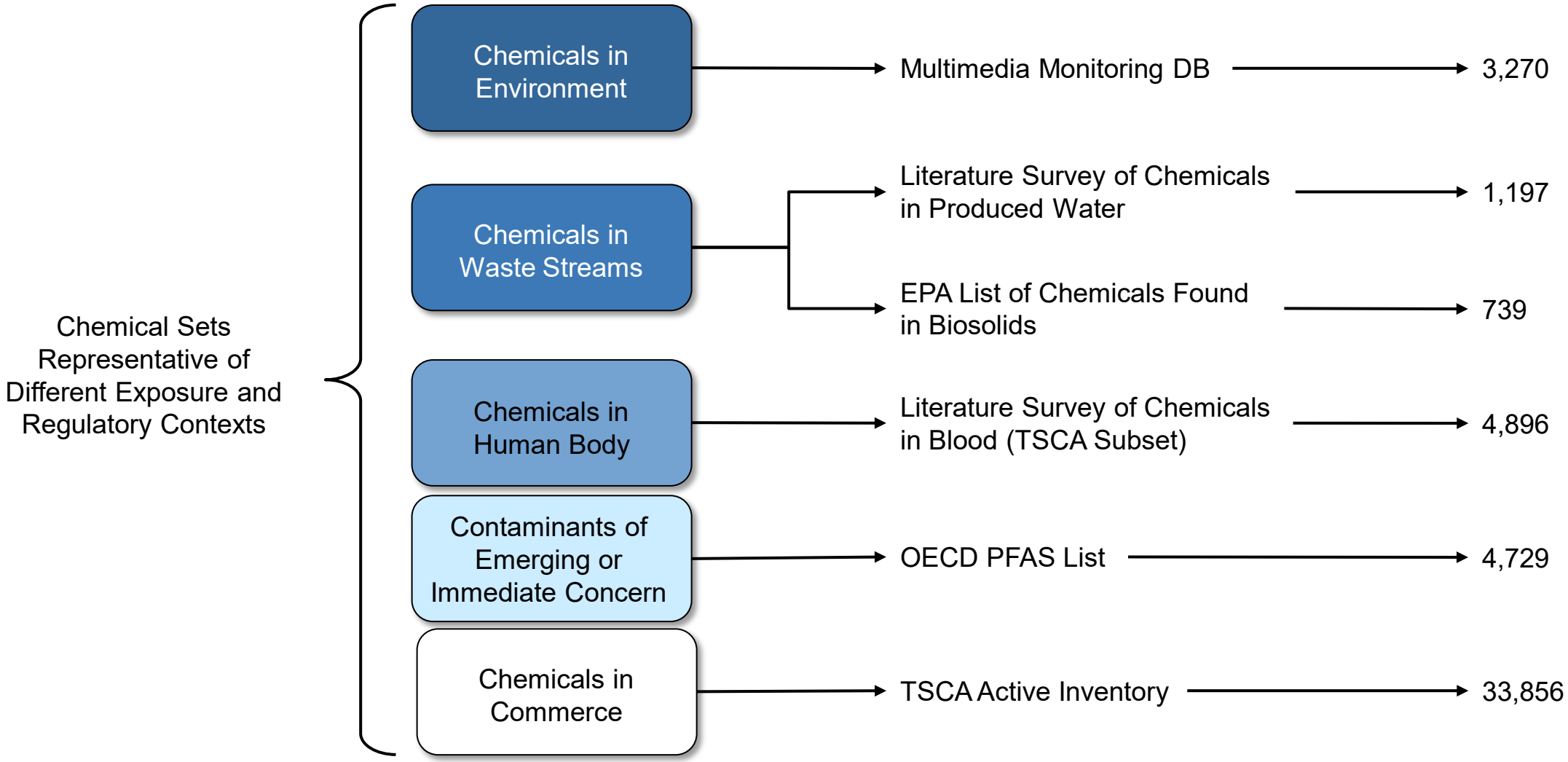
Magnitude of the Worldwide Chemical Inventory



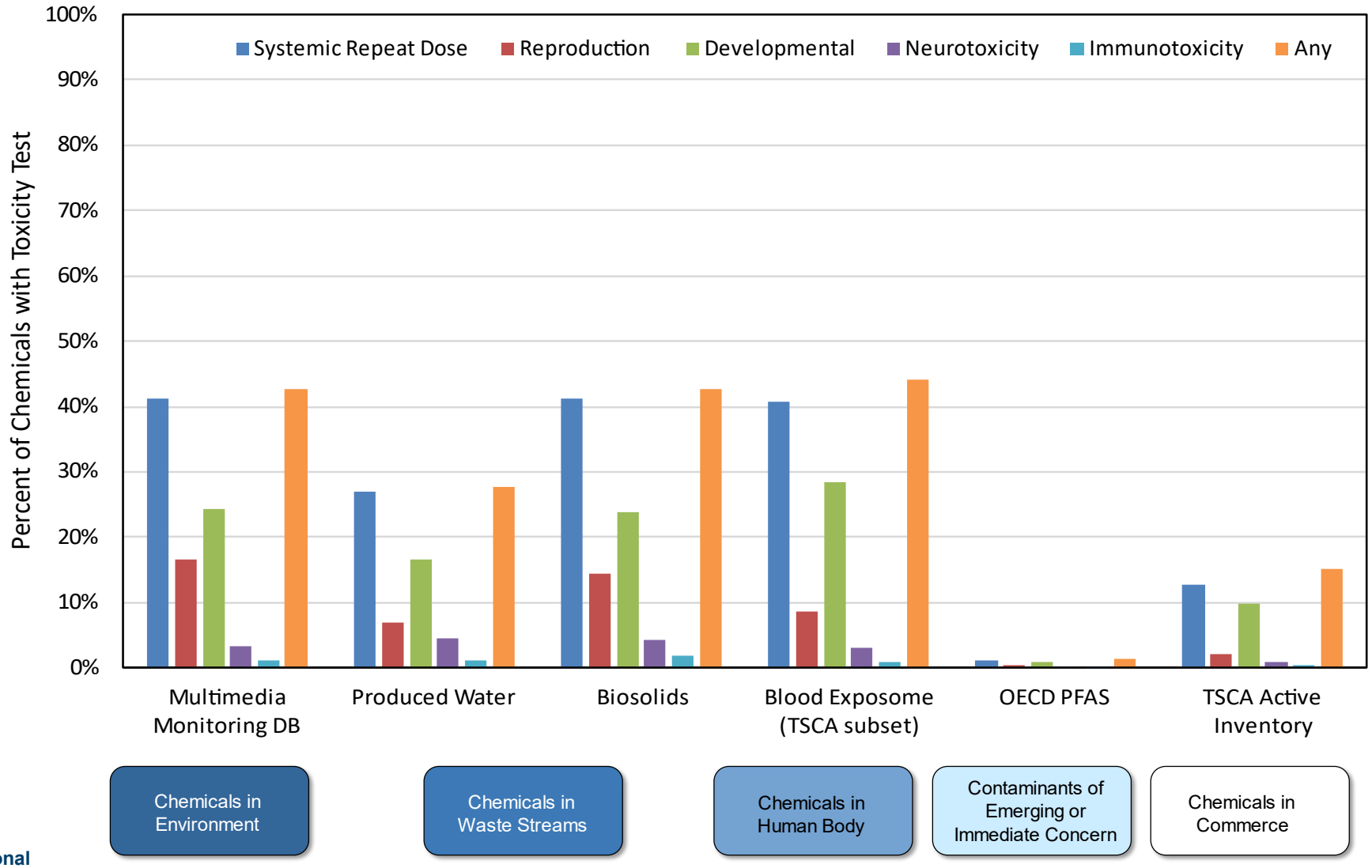
Wang *et al.*, *Env Sci Technol.*, 2020

- A total of 19 inventories surveyed
- 350,000 chemicals and mixtures of chemicals were registered in one or more inventories.
- Total number of substances likely an undercount due to:
  - Thresholds required for registration.
  - Does not include degradation products.
  - Does not include contaminants.

Contextualizing the Domestic and Worldwide Chemical Inventories

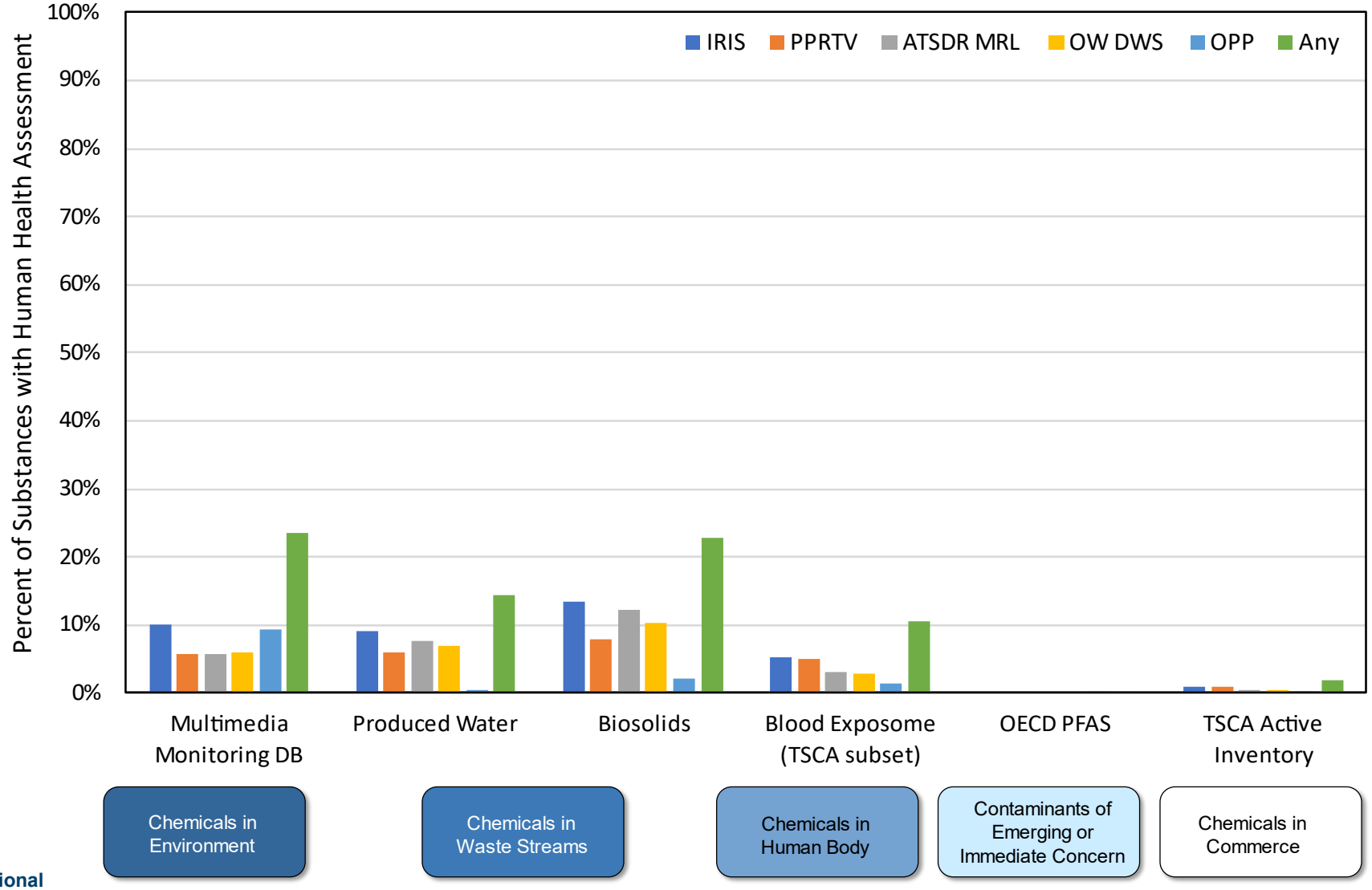


Less Than Half of Chemicals Within the Representative Sets Have Traditional Toxicity Testing Data



*Toxicity testing data obtained from ToxVal v9.4

Even Fewer Chemicals Within the Representative Sets Have Human Health Assessments



IRIS – US EPA Integrated Risk Information System

PPRTV – US EPA Provisional Peer Reviewed Toxicity Values

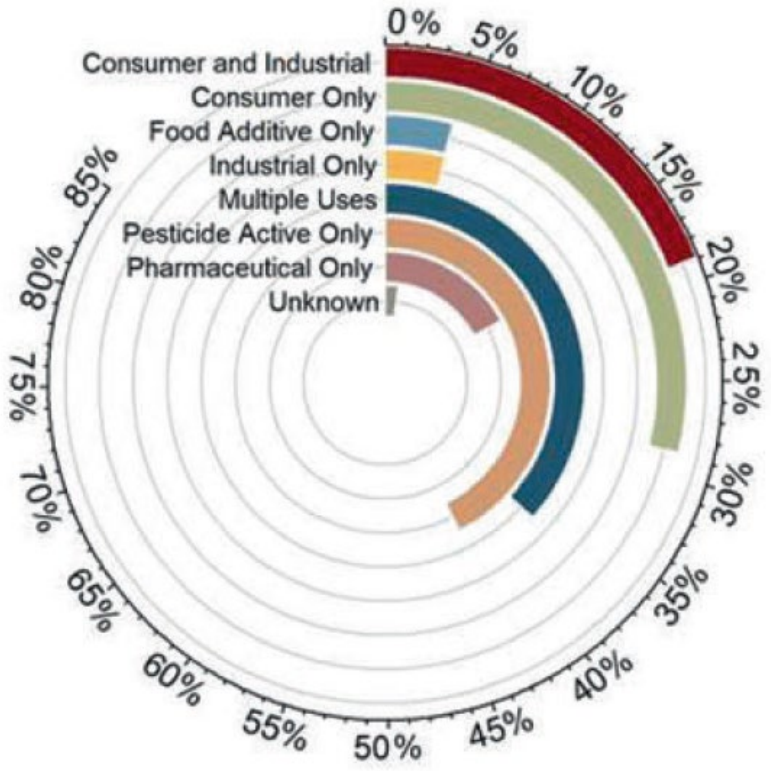
ATSDR MRL – Agency for Toxic Substances and Disease Registry Minimal Risk Levels

OW DWS – US EPA Office of Water Health Advisories

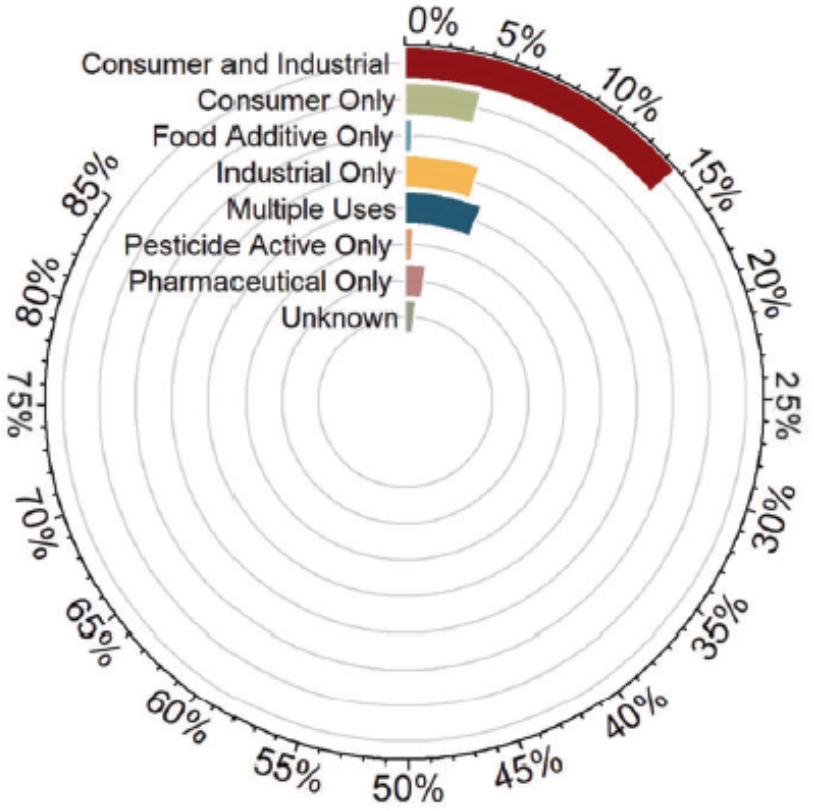
OPP – US EPA Office of Pesticide Programs

Similarly Few Chemicals Have Traditional Exposure Monitoring and Assessments

Percent of Chemicals in Sector with Traditional Monitoring Data



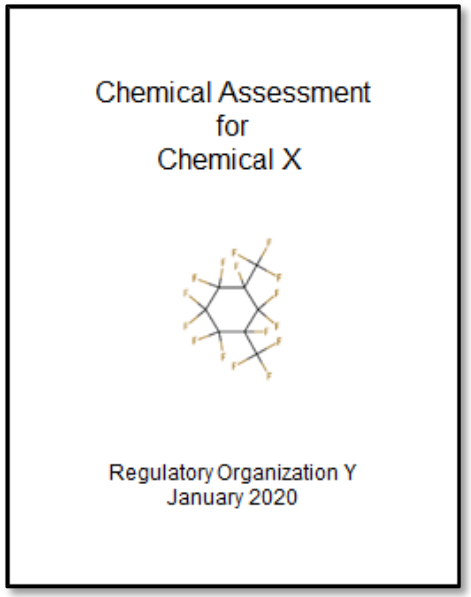
Percent of Chemicals in Sector with Traditional Exposure Assessment



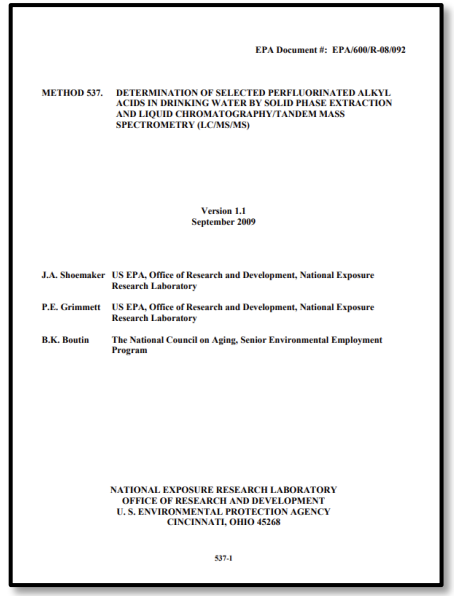
Isaacs *et al*., *J Expo Sci Environ Epidemiol*, 2022

Time From Required to a Understand Human Health Risks Using Traditional Approaches is Significant

Time from chemical identification to finalizing report can range from 2 – 10 years.



- Time to perform a typical human health assessment is 4+ years (Krewski *et al., Arch Toxicol.,* 2020).
- More complex assessments can take substantially longer (NASEM, 2009).



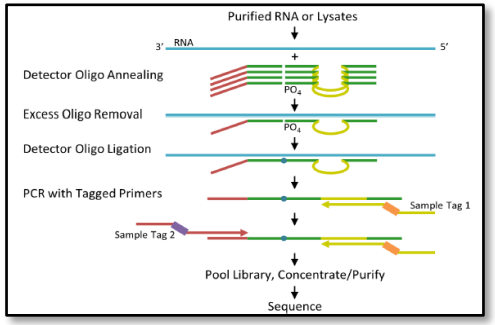
Time to develop an EPA validated analytical method can range from 2 - 5 years.

EPA United States Environmental Protection Agency

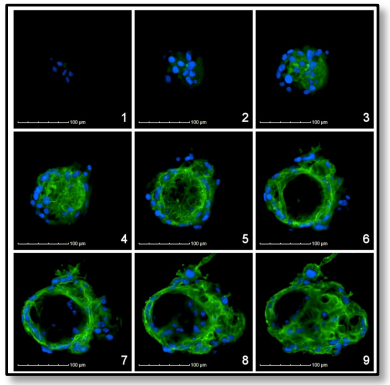
So, Is The Issue A Lack of Data?

Broad Range of Technologies and Methods Available for Generating Alternative Data on Chemical Hazard

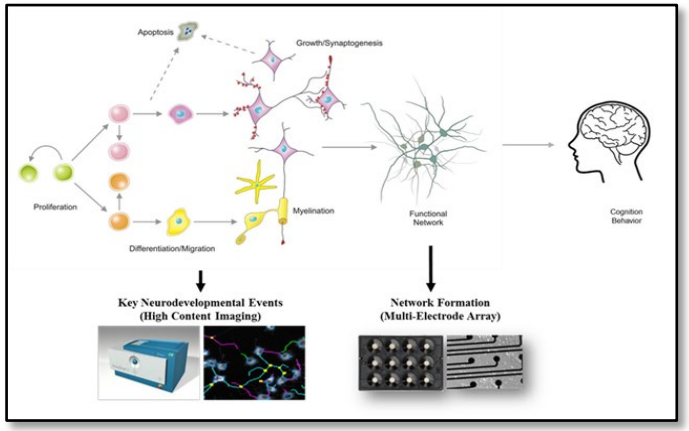
Whole Genome/Reduced Set Transcriptomics



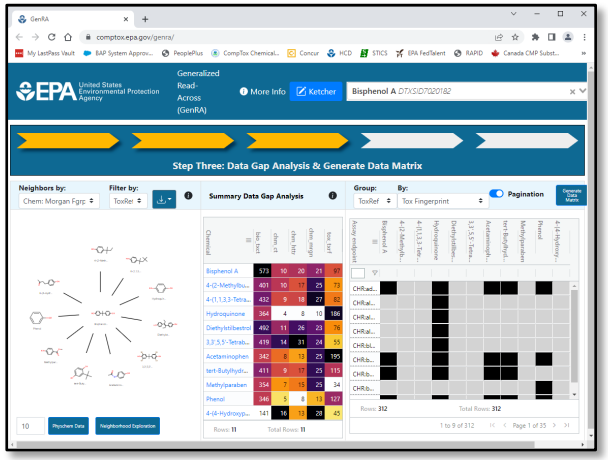
Organotypic Culture Models



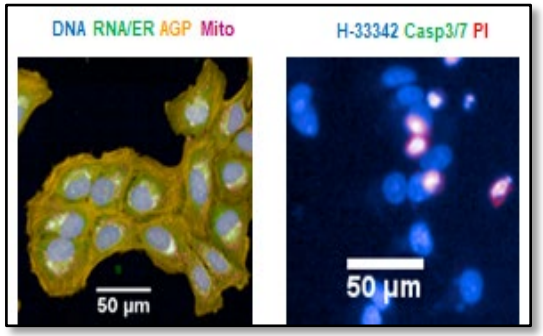
Integrated Approach to Testing and Assessment for DNT



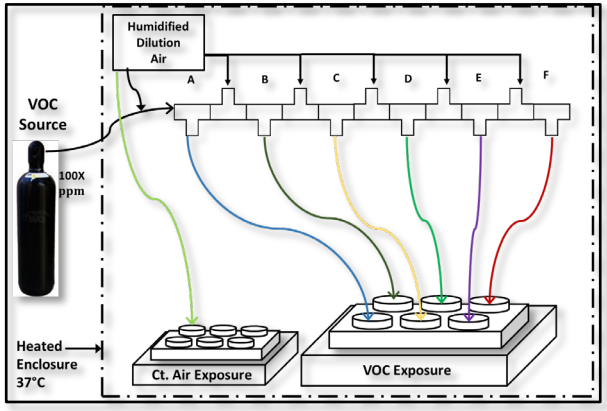
Generalized Read Across Methods and QSAR Modeling



Multi-Parameter Cellular Phenotypic Profiling



Volatile/Aerosol *In Vitro* Exposure Systems



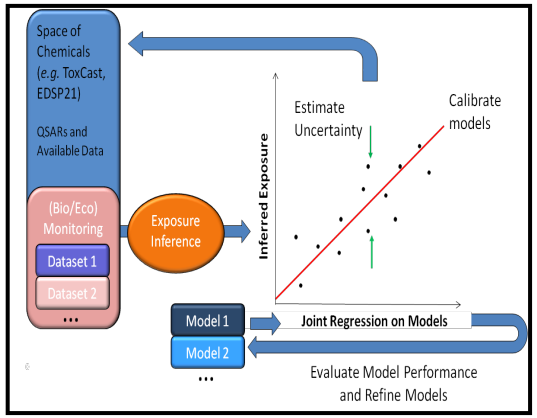
ToxCast High-Throughput *In Vitro* Assay Battery

Transcription Factors	Cholinesterase
Transporter	Phosphatases
Cytokines	Proteases
Kinases	XME metabolism
Nuclear Receptors	GPCRs
CYP450 / ADME	Ion channels

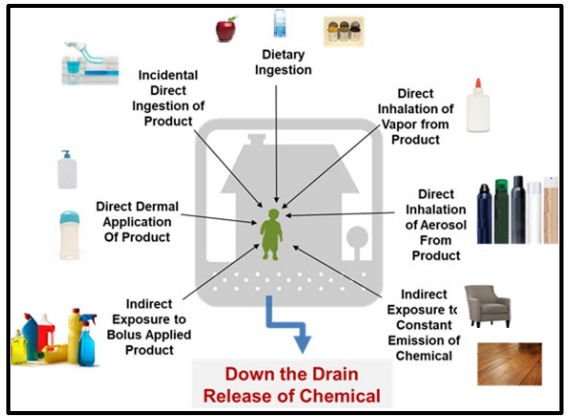
~700 Biochemical/Cellular Assay Endpoints

Similar Range of Technologies and Methods Available for Exposure and Toxicokinetics

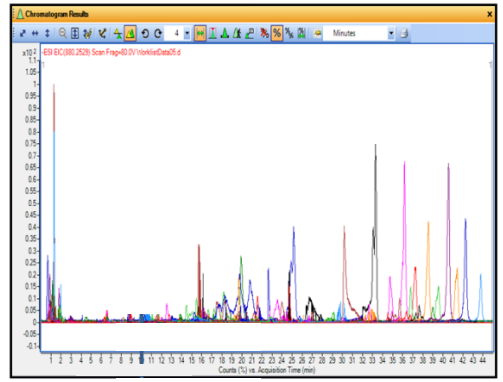
SEEM Consensus Exposure Model



SHEDS-HT Exposure Pathway Model

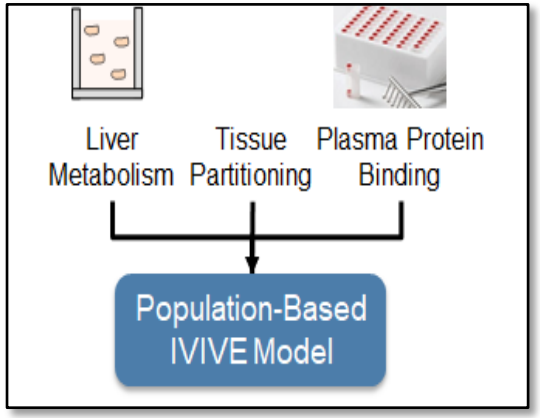


LC and GC Non-Targeted Analysis

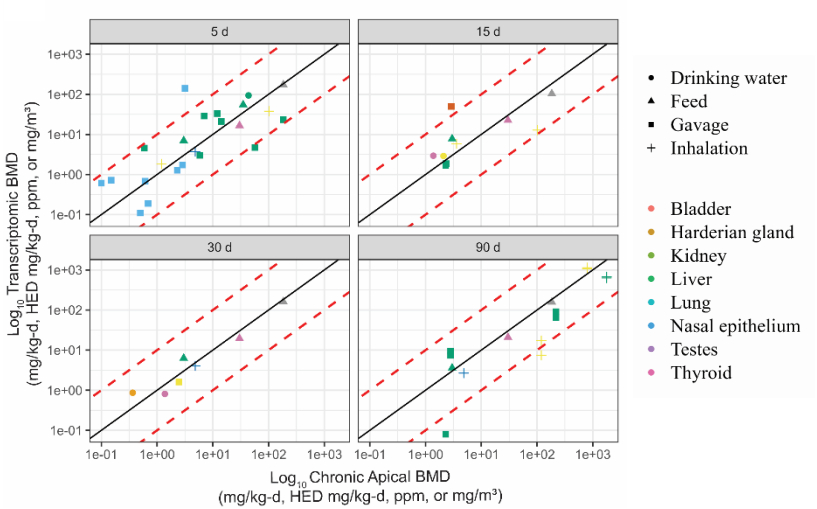


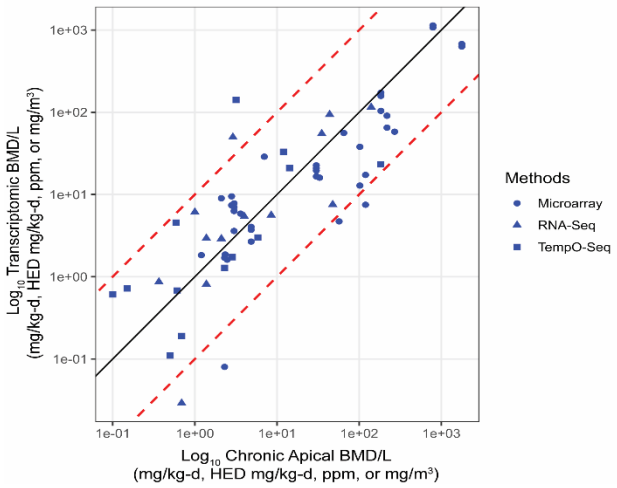
QSUR Functional Use Machine Learning Models

In Vitro Toxicokinetic Assays and Modeling



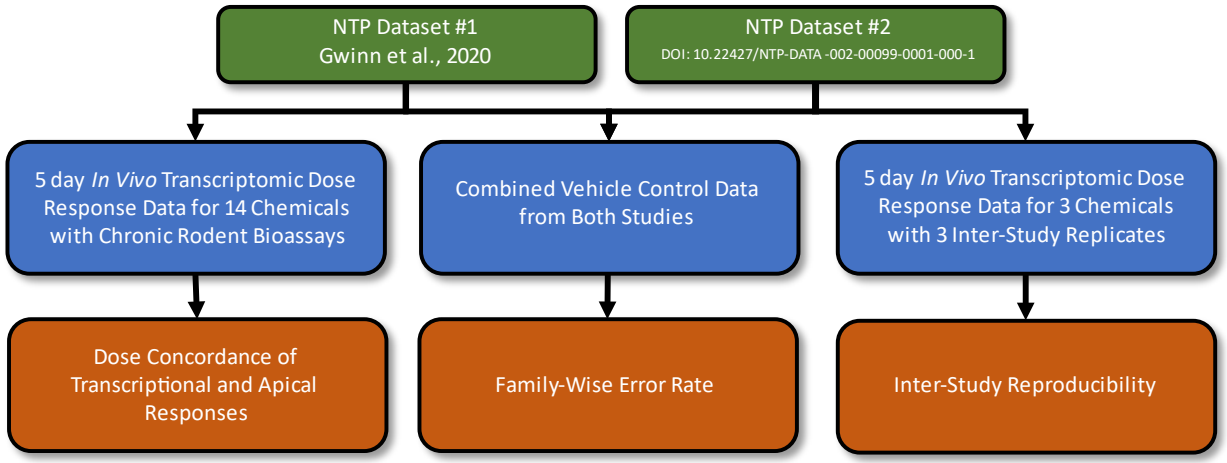
Literature Review Supports Dose Concordance Between Disruption of Gene Activity and Toxicity

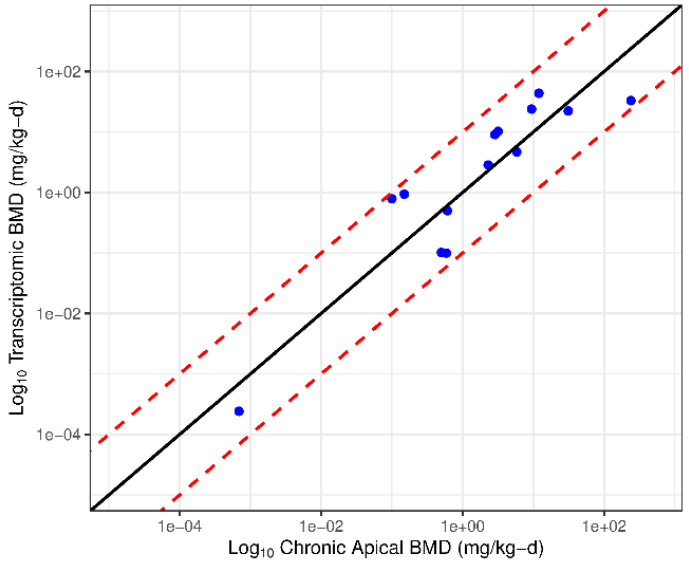




- Literature review identified 140 chemicals in 32 studies.
- Studies covered 4 exposure routes, multiple exposure durations (<1 day to 90 days), 8 tissues, 3 technologies, and broad range of physicochemical properties and toxicokinetic half-lives.
- Across 38 chemicals with chronic bioassays, the Pearson's correlation coefficient for the transcriptomic BMD versus chronic, apical BMD was 0.842 with an RMSD of 0.565 (log_{10} mg/kg-d) and a median absolute ratio of 2.1 ± 0.7 (MAD).
- The RMSD is similar to the range of inter-study standard deviation estimates for the lowest observable adverse effect levels (LOAELs) for systemic toxicity in repeated dose studies (0.45-0.56) (Pham *et al. Comp Toxicol.,* 2020).
- Dose concordance was robust across exposure durations, exposure routes, species, sex, target tissues, physical chemical properties, toxicokinetic half-lives, and technology platforms.

Refining Dose Response Analysis Methods to Derive Transcriptomic Points-of-Departure for ETAP

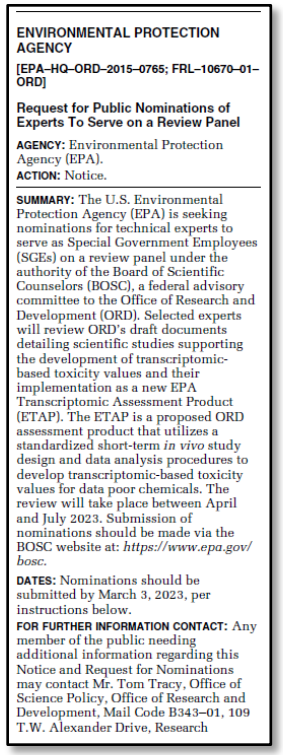




- Standardized study design based on NIEHS DTT/NTP data sets:
  - 5 day, repeat oral dosing in male Sprague Dawley rats.
  - Transcriptomic measurements in the liver and kidney.
  - Reduced gene set targeted RNA-Seq platform (S1500+) (Mav *et al.*, *PLOS One*, 2018).
- Concordance of transcriptional and apical responses
  - Pearson's correlation = 0.910
  - RMSD = 0.567
  - Median absolute ratio = 3.2 $\pm$ 1.9 (MAD)
- Inter-study reproducibility
  - Inter-study $\log_{10}$ BMD SD = 0.24
- False positives
  - Family-Wise Error Rate = 0.006

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.

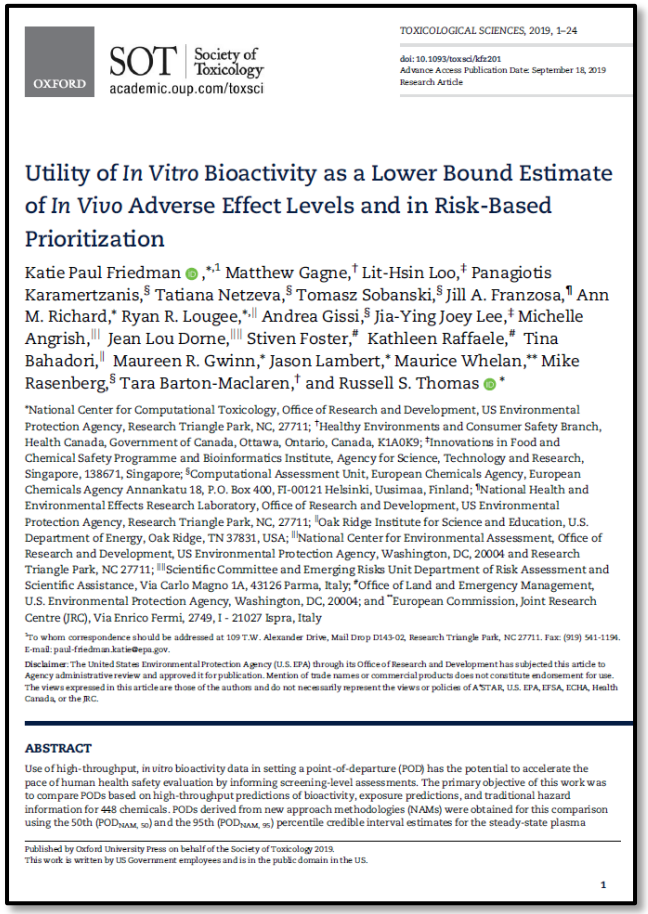
FOR FURTHER INFORMATION CONTACT: Any member of the public needing additional information regarding this Notice and Request for Nominations may contact Mr. Tom Tracy, Office of Science Policy, Office of Research and Development, Mail Code B343–01, 109 T.W. Alexander Drive, Research

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 toxicity values for chronic toxicity; and
- Incorporation of transcriptomic toxicity 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

International Case Study to Demonstrate Application of Alternative Methods To Screening Level Assessments



TOXICOLOGICAL SCIENCES, 2019, 1–24

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

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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[1]To whom correspondence should be addressed at 109 T.W. Alexander Drive, Mail Drop D143-02, Research Triangle Park, NC 27711. Fax: (919) 541-1194. E-mail: paul-friedman.katie@epa.gov.

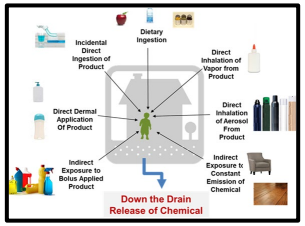
ABSTRACT

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

Published by Oxford University Press on behalf of the Society of Toxicology 2019.

Paul-Friedman et al., 2020

ExpoCast Exposure Estimates

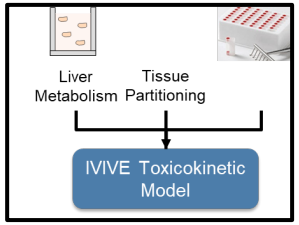


ToxCast Evaluation of Biological Targets

Transcription Factors	Cholinesterase
Transporter	Phosphatases
Cytokines	Proteases
Kinases	XME metabolism
Nuclear Receptors	GPCRs
CYP450 / ADME	Ion channels

~700 Biochemical/Cellular Assay Endpoints

In Vitro Toxicokinetic Assays and Modeling



Bioactivity-exposure ratio

POD_{NAM} 0-5th

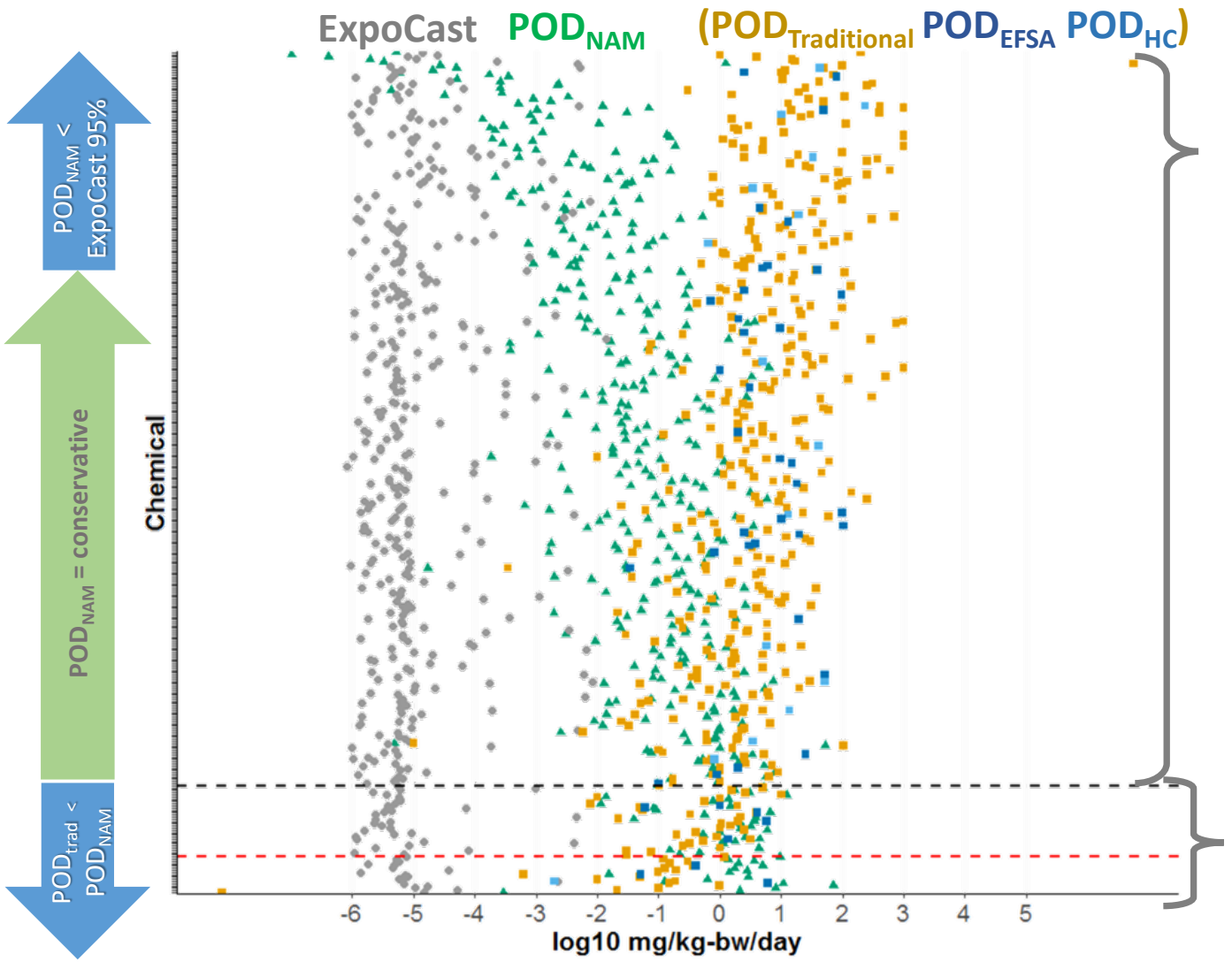
POD_{trad} : POD_{NAM} ratio

ToxVal
EFSA
ECHA

POD_{trad} 5th %

- *NOEL, LOEL, NOAEL, or LOAEL*
- *Oral exposures*
- *Mg/kg-bw/day units*

In Vitro Bioactivity and Toxicokinetics Provided Health Protective Screening Assessments for Most Chemicals

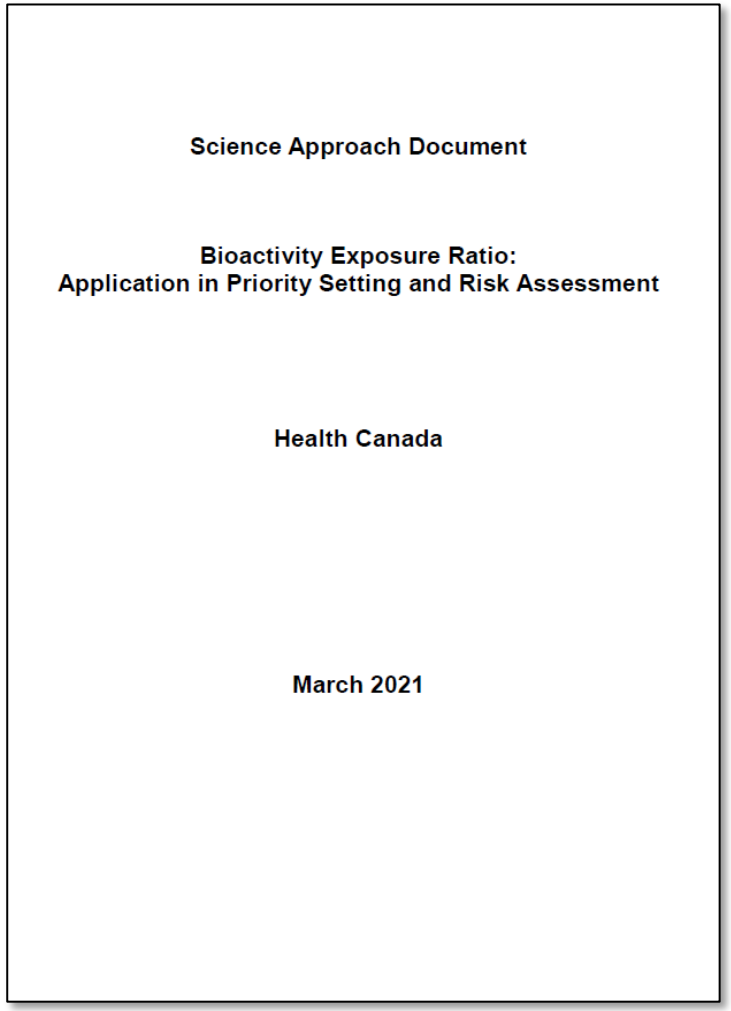


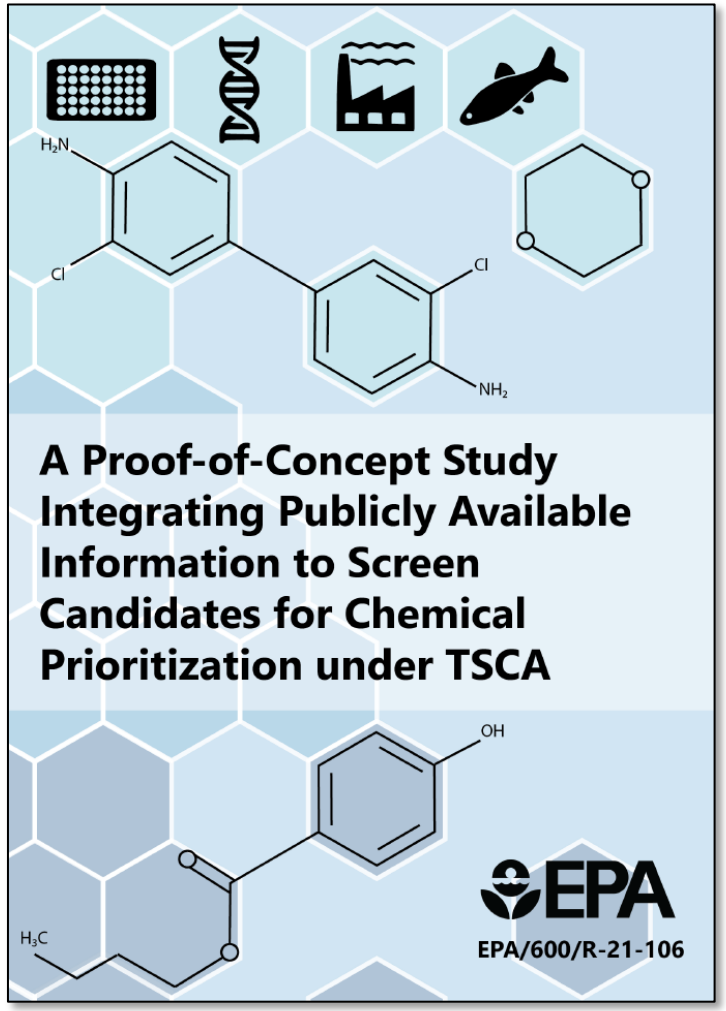
For ~89% of the chemicals, POD$_{NAM}$ was conservative.

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

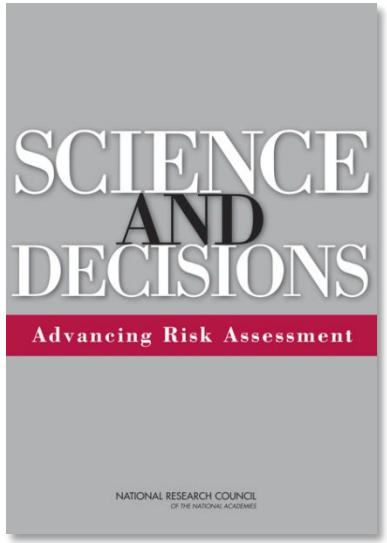
Chemicals where POD$_{NAM}$ was not conservative enriched in OPs/carbamates

Application of the Methods to Regulatory and Commercial Decision Making





Importance of Considering Time as a Factor in Chemical Risk Assessment

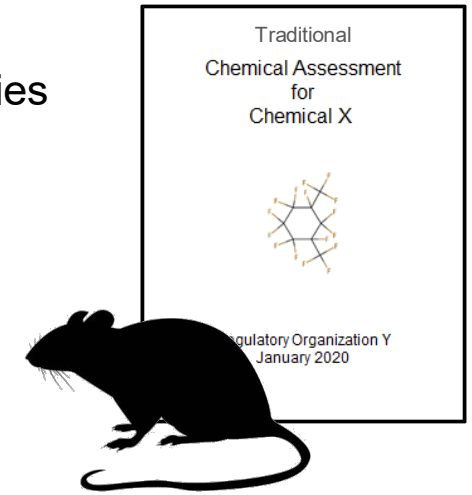


- The NAS committee reflected that **time** is a “major and rarely acknowledged influence in the nature and quality” of a risk assessment.
- Additional studies or improvements in the assessment may reduce uncertainty, but they require additional resources and the delay “can have significant impact on communities who are awaiting risk assessment results.”
- A Value of Information (VOI) analysis listed as a recommendation in the report to provide a more objective decision framework in assessing the trade-offs of time, uncertainty, and cost.
- VOI is a decision analytic method that quantifies the expected value of additional testing/data in reducing decision uncertainty (Tuffaha, 2021).

Difficult Trade-Offs of Uncertainty, Cost, and Timeliness in Toxicity Testing Methods

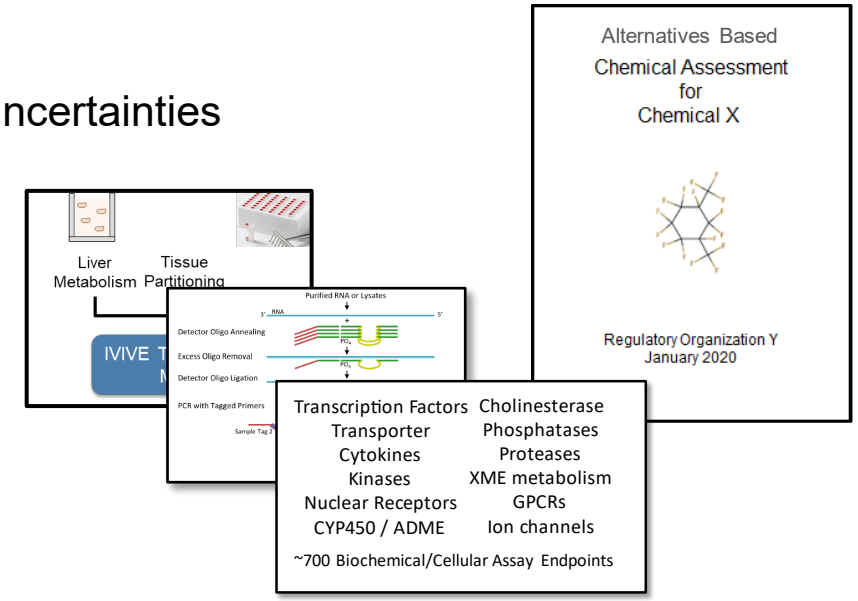
Option 1

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



Option 2

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



What choice would you make?

Incorporating Important Features in Chemical Risk Assessment Into a Value of Information Framework

DOI: 10.1111/risa.13931

ORIGINAL ARTICLE

A value of information framework for assessing the trade-offs associated with uncertainty, duration, and cost of chemical toxicity testing

Shintaro Hagiwara[1,2] | Greg M. Paoli[1] | Paul S. Price[3] | Maureen R. Gwinn[4] | Annette Guiseppi-Elie[3] | Patrick J. Farrell[2] | Bryan J. Hubbell[5] | Daniel Krewski[1,6] | Russell S. Thomas[3]

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[5]Air, Climate, and Energy Research Program, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, North Carolina, USA
[6]McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Canada

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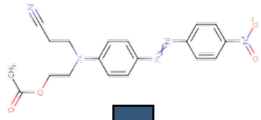
Abstract
A number of investigators have explored the use of value of information (VOI) analysis to evaluate alternative information collection procedures in diverse decision-making contexts. This paper presents an analytic framework for determining the value of toxicity information used in risk-based decision making. The framework is specifically designed to explore the trade-offs between cost, timeliness, and uncertainty reduction associated with different toxicity-testing methodologies. The use of the proposed framework is demonstrated by two illustrative applications which, although based on simplified assumptions, show the insights that can be obtained through the use of VOI analysis. Specifically, these results suggest that timeliness of information collection has a significant impact on estimates of the VOI of chemical toxicity tests, even in the presence of smaller reductions in uncertainty. The framework introduces the concept of the expected value of delayed sample information, as an extension to the usual expected value of sample information, to accommodate the reductions in value resulting from delayed decision making. Our analysis also suggests that lower cost and higher throughput testing also may be beneficial in terms of public health benefits by increasing the number of substances that can be evaluated within a given budget. When the relative value is expressed in terms of return-on-investment per testing strategy, the differences can be substantial.

KEYWORDS
cost of delay, return on investment, risk decision making, social cost, toxicity testing, value of information

1 | INTRODUCTION

Evidence-based risk assessment has become a cornerstone of public and population health risk decision making, integrating evidence on toxicity and exposure from multiple evidence streams. When the available evidence is insufficient to allow a decision to be made with confidence, consideration can be given to gathering additional evidence to strengthen the evidence base. The present paper focuses on the use of value of information (VOI) analysis to evaluate the utility of gathering additional evidence on the toxicity of chemicals. Specifically, we present a VOI analytic framework that builds on previous methodological work in this field, explicitly incorporating the value of additional test data resulting from reductions in the uncertainty in estimates of a chemical's toxicity, the cost of delay in decision making that results



Exposure Level
Population Variability in Exposure
Affected Population Size
Health Effects
Population Variability in Toxicity
Control Costs

Relevant Chemical Characteristics

Uncertainty in Effect Level
Timeliness
Cost

Toxicity Testing Characteristics

Regulatory Decision Context

Timeliness Has Significant Positive Impact on Value of Toxicity Tests

United States Environmental Protection Agency

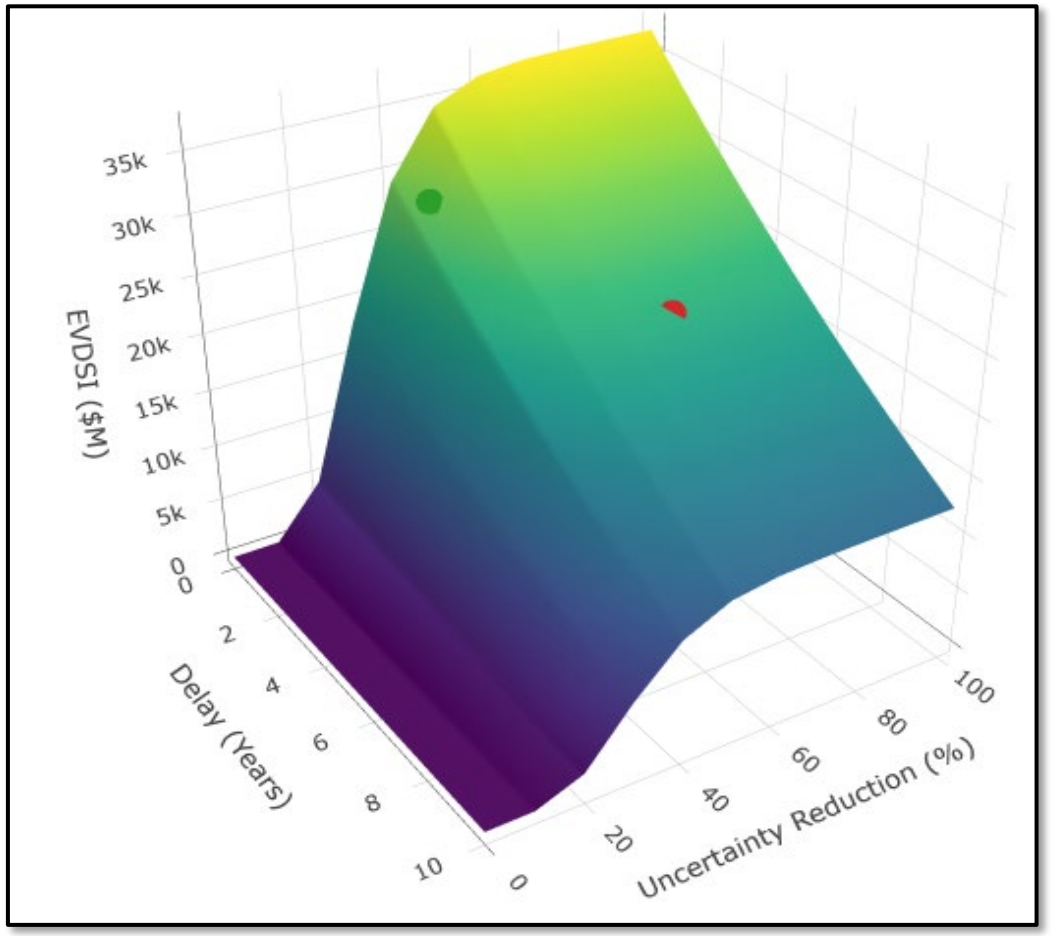
Example Scenarios

- 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
  - 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 higher uncertainty.***
- The positive impact of the shorter tests may be multiplicatively amplified by the ability to test more chemicals.

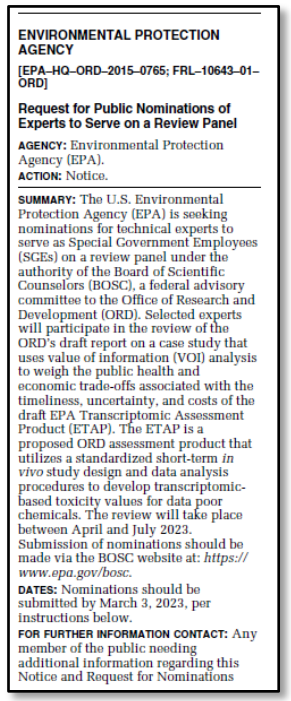
Trade-Offs of Uncertainty and Time of Hypothetical Toxicity Testing Methods
(Target Risk Decision Maker)



Hagiwara et al., Risk Anal., 2022

EPA Announced Case Study on Value of Information Analysis of the EPA Transcriptomic Assessment Product

EPA released public notice for upcoming scientific peer-review and public comment on a case study evaluating the public health and economic trade-offs associated with the timeliness, uncertainty, and costs of the draft EPA Transcriptomics Assessment Product (ETAP). .



ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–ORD–2015–0765; FRL–10643–01–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 participate in the review of the ORD's draft report on a case study that uses value of information (VOI) analysis to weigh the public health and economic trade-offs associated with the timeliness, uncertainty, and costs of the draft 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

ETAP Value of Information Case Study *ad hoc* Board of Scientific Counselors FRN

- Comparison of the ETAP with traditional toxicity testing and human health assessment processes across:
  - Different chemical exposure scenarios
  - Health endpoint valuations
  - Exposure mitigation costs
  - Decision contexts

https://www.federalregister.gov/documents/2023/02/13/2023-03018/request-for-public-nominations-of-experts-to-serve-on-a-review-panel

So… The Question is Do We Lack the Data or Need a Change in Perspective to Use New Approaches?

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- OCSPP

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