Development of a New Transcriptomics-Based Assessment Product for Data Poor Chemicals

NC DEQ

August 3, 2023

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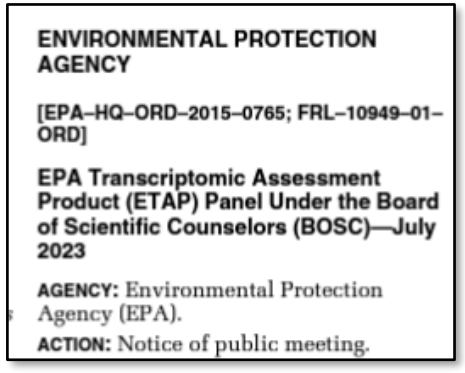
Center for Computational Toxicology and Exposure
U.S. Environmental Protection Agency

EPA is Proposing New Human Health Assessment Product Based on Transcriptomics

EPA is obtaining scientific peer-review and public comment on a new draft ORD human health assessment product for data poor chemicals and a case study evaluating the human health and economic trade-offs of the draft assessment product.



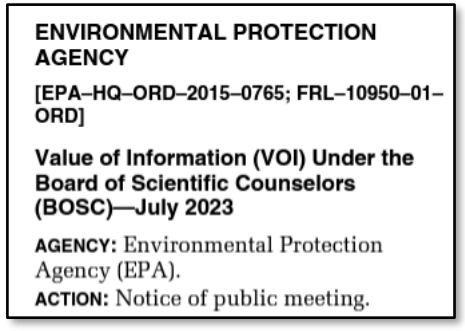
ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–ORD–2015–0765; FRL–10949–01–ORD]

EPA Transcriptomic Assessment Product (ETAP) Panel Under the Board of Scientific Counselors (BOSC)—July 2023

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of public meeting.



ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–ORD–2015–0765; FRL–10950–01–ORD]

Value of Information (VOI) Under the Board of Scientific Counselors (BOSC)—July 2023

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of public meeting.

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

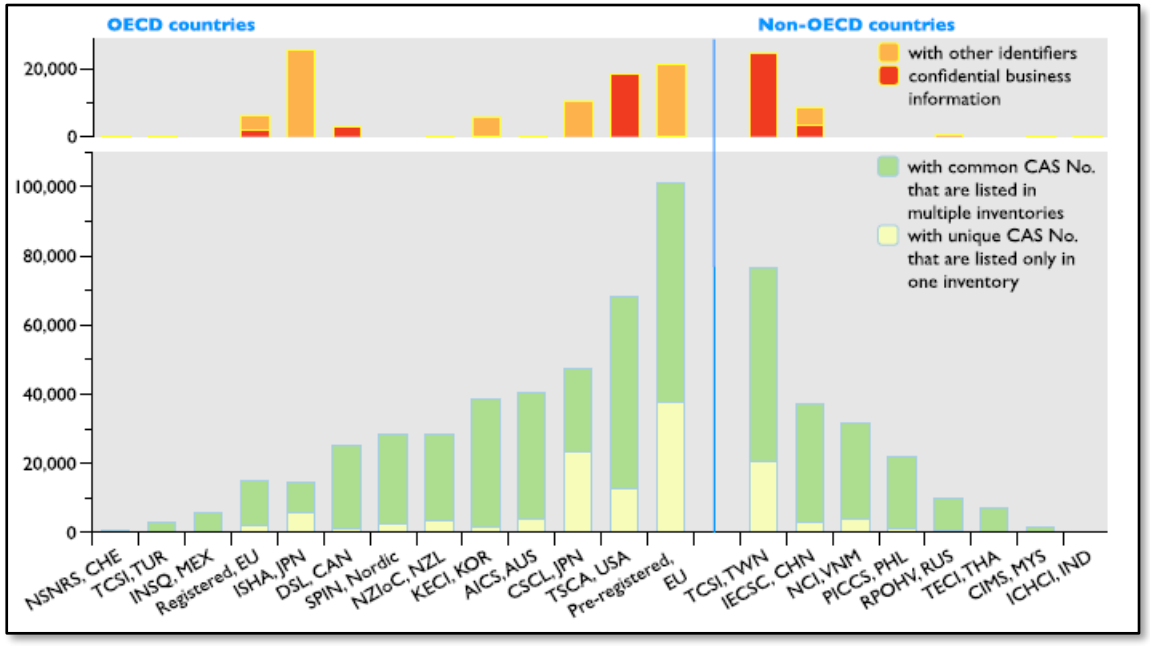
- July 11 – 12, 2023
- Committee details, meeting notice, and scientific reports available at: https://www.epa.gov/bosc/epa-transcriptomic-assessment-products-etap-panel

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

- July 25 – 26, 2023
- Committee details, meeting notice, and scientific reports available at: https://www.epa.gov/bosc/value-information-voi-panel

Thousands of Chemicals are on the Worldwide Inventory and Have Potential for Human Exposure

Survey of Worldwide Chemical Inventories



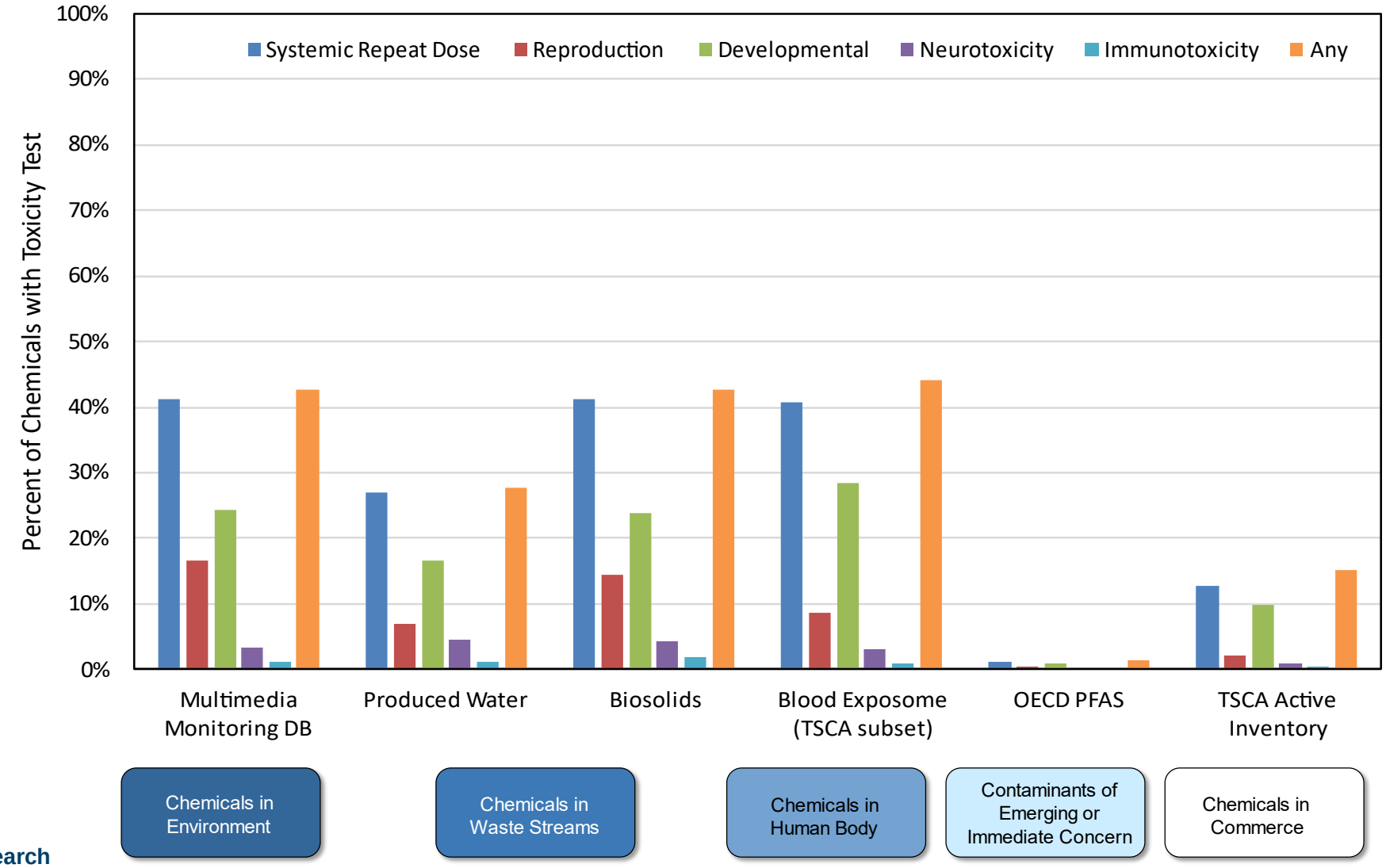
Wang *et al.*, *Env Sci Technol.*, 2020

- 350,000 chemicals and mixtures of chemicals were registered in one or more of the 19 inventories surveyed.
- Likely an undercount due to thresholds required for registration

Contextualizing Chemical Inventories Using Representative Sets

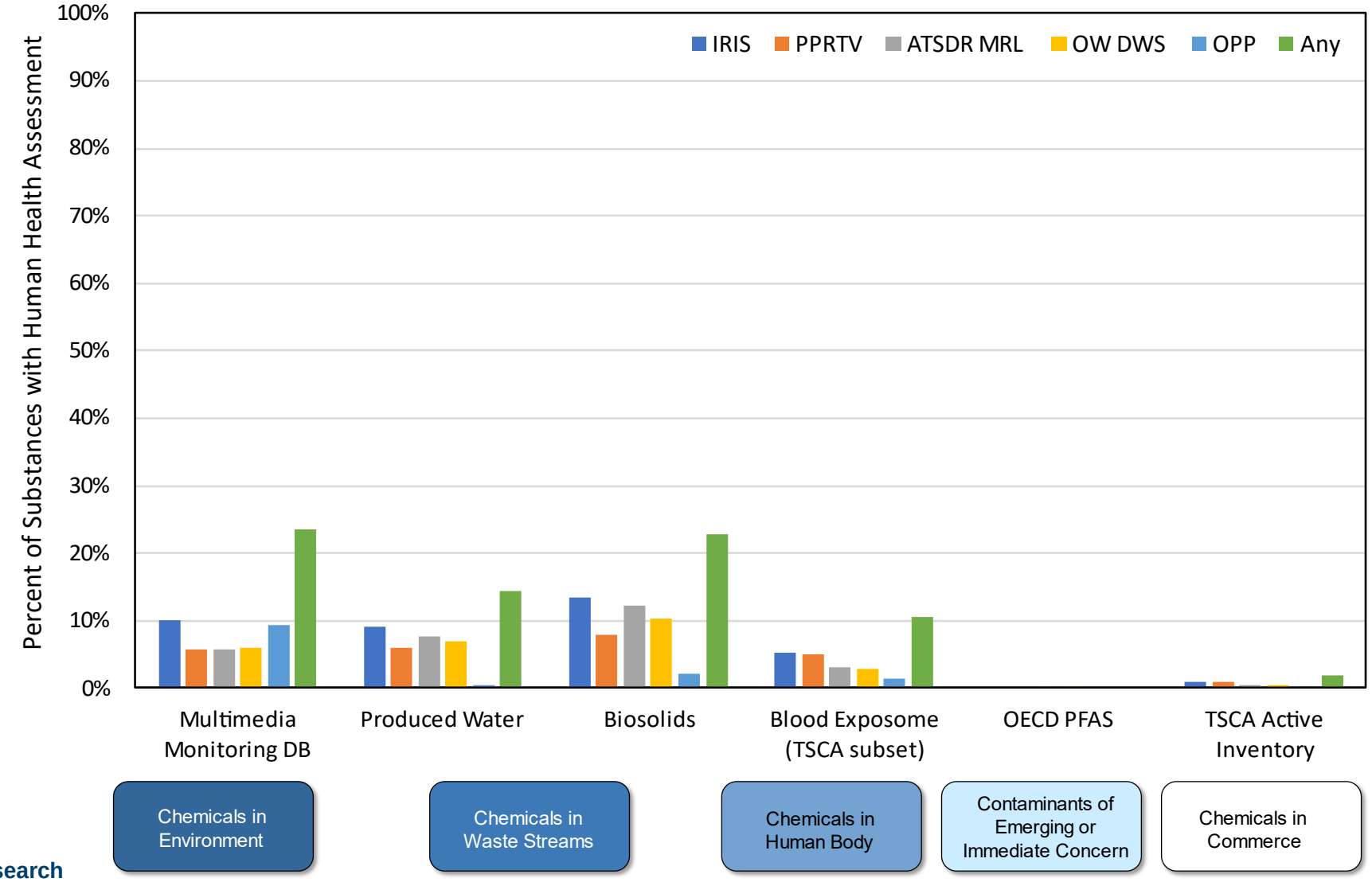
Chemicals in Environment	→	Multimedia Monitoring DB	3,270
Chemicals in Waste Streams	→	Literature Survey of Chemicals in Produced Water	1,197
	→	EPA List of Chemicals Found in Biosolids	739
Chemicals in Human Body	→	Literature Survey of Chemicals in Blood (TSCA Subset)	4,896
Contaminants of Emerging or Immediate Concern	→	OECD PFAS List	4,729
Chemicals in Commerce	→	TSCA Active Inventory	33,856

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 in U.S.



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

Time and Resources From No Data to a Human Health Assessment Using Traditional Approach is Significant

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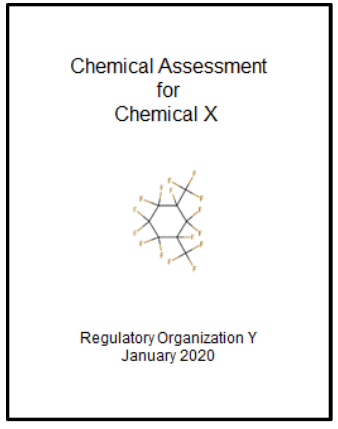


= 6 – 14+ years

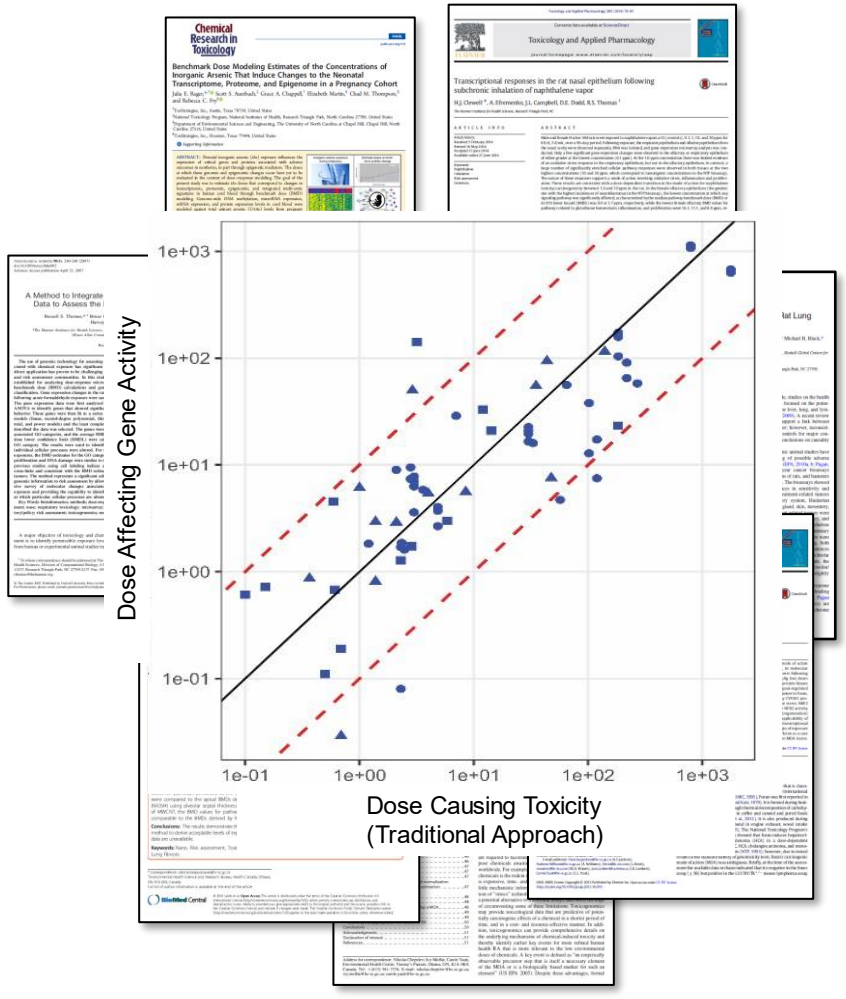
- Time from chemical identification to finalizing report can range from 2 – 10 years

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

Advances in Genome Sequencing Technology and Research Increased Potential for Application to Human Health Assessment

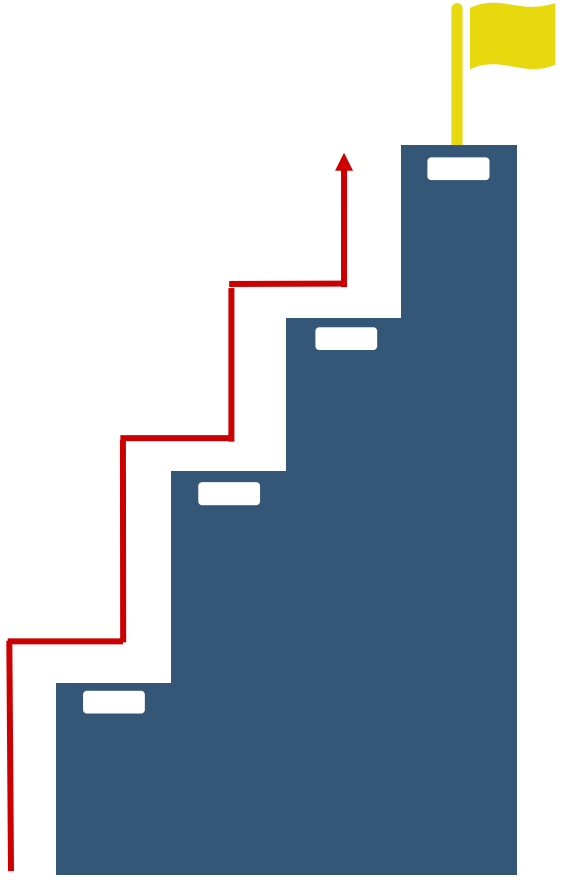
- Throughput
- Acceptance
- Reliability

- Costs



*Note: The scientific discipline involved in large scale measurements of changes in gene activity is called transcriptomics.

Goals and Objectives



Goal: Develop and operationalize a new US EPA human health assessment product for data poor chemicals that can be completed from chemical procurement to publication of the assessment in < 9 months.

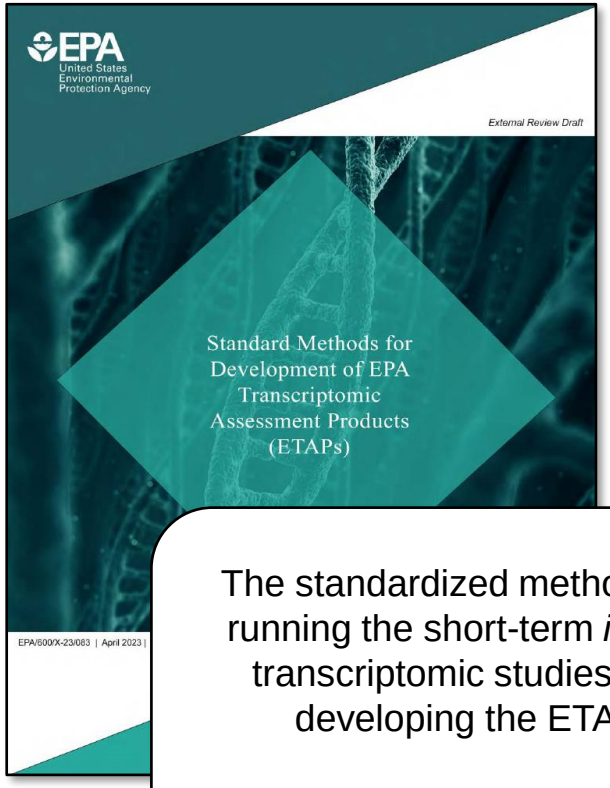
Objectives:

1. Review of relevant literature
2. Refine dose response analysis methods for standardized study design
3. Compare error in concordance with variability in toxicity studies
4. Develop standardized method for the EPA Transcriptomic Assessment Product (ETAP)
5. Compare transcriptomic reference values with traditional RfDs
6. Develop example ETAP for data poor PFAS
7. Conduct socioeconomic case study on the human health and economic value of the ETAP

Goal and Objectives are Addressed in a Complementary Series of Three EPA Reports for Expert Panel Review

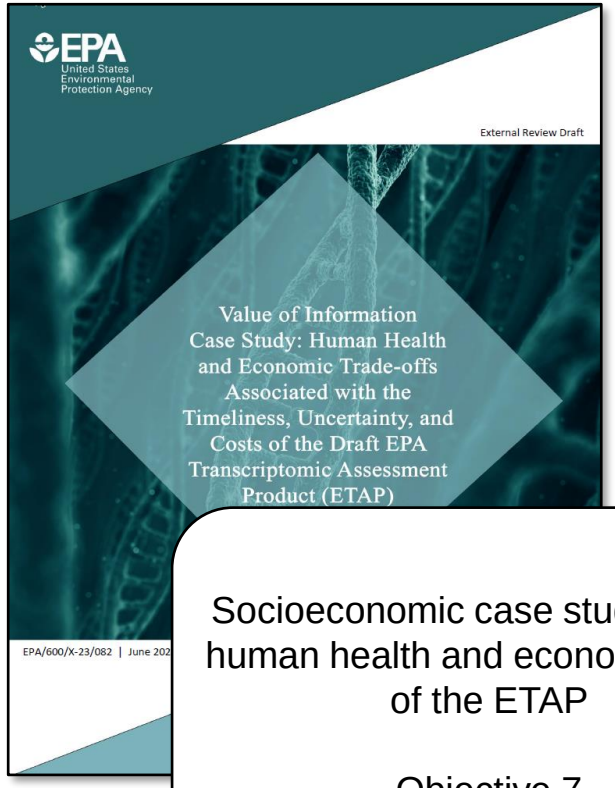
Scientific support for developing and applying transcriptomic points-of-departure

Objectives 1 - 3



The standardized methods for running the short-term *in vivo* transcriptomic studies and developing the ETAP

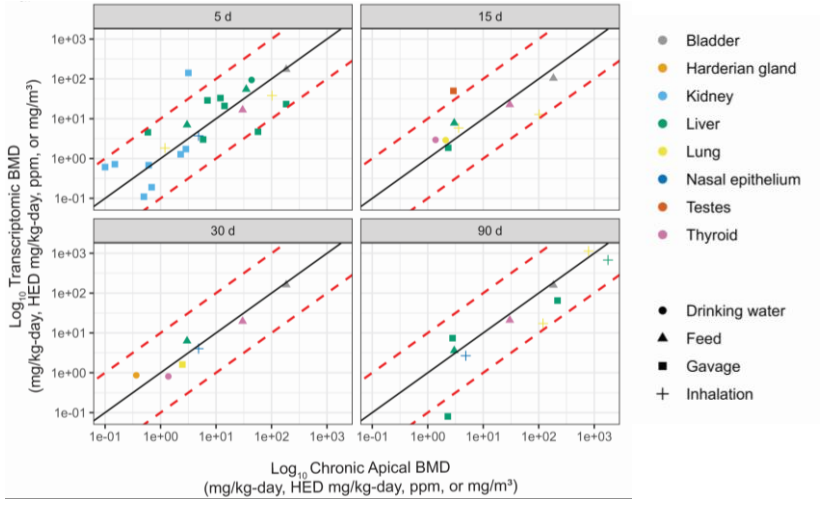
Objectives 4 - 6

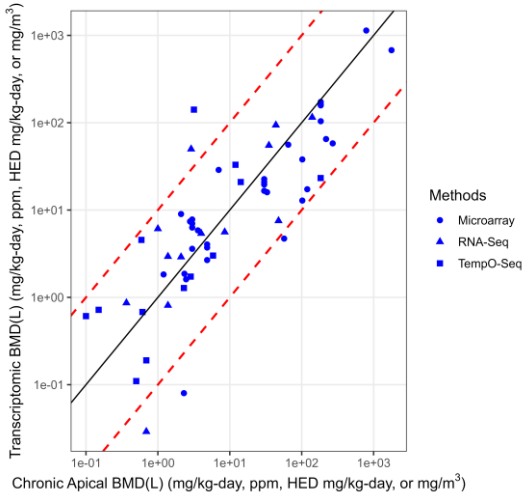


Socioeconomic case study on the human health and economic value of the ETAP

Objective 7

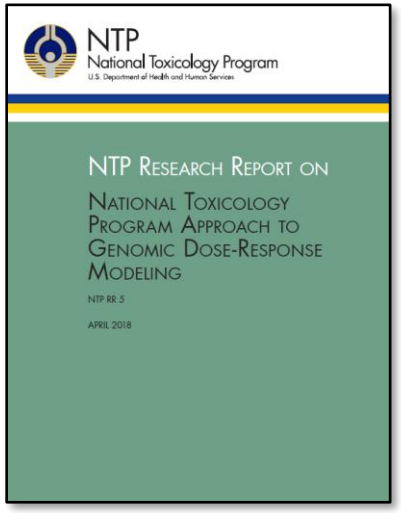
Comprehensive Literature Review Supports Dose Concordance Between Disruption of Gene Activity and Toxicity





- 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 0.825 with an RMSD of 0.561 (log_{10} mg/kg-d) and a median absolute ratio of 1.9 ± 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.

Leverage NTP Report and Data Sets to Standardize Dose Response Analysis Methods for ETAP



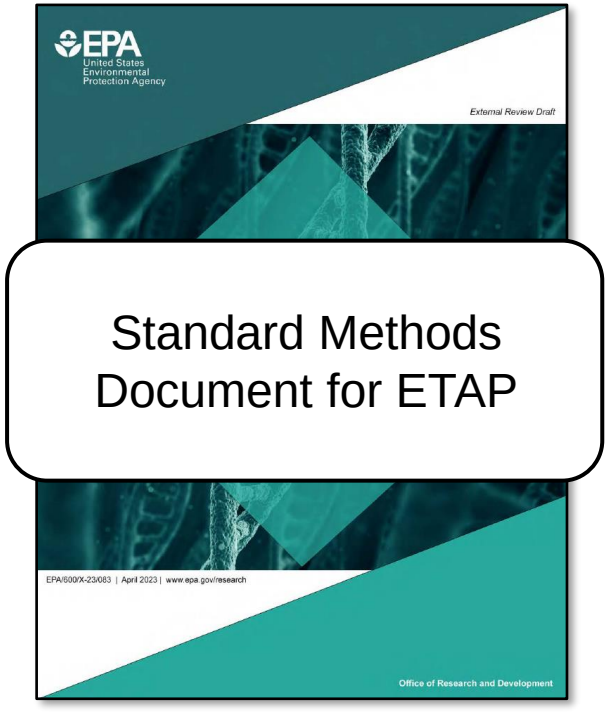
NTP Data Set #1
Gwinn et al., 2020

NTP Data Set #2
Replicate Data

- Dose concordance of transcriptional and apical responses
- Inter-study reproducibility
- Family wise error rate

- Leveraged peer-reviewed NTP Report on Using Genomic Technology for Dose Response Assessment to provide consensus recommendations on transcriptomic dose response analysis process.
- Used existing NTP data sets to refine dose response analysis parameters for ETAP study design:
  - 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).
- Evaluated 48 combinations of dose response analysis parameter choices consistent with NTP consensus recommendations.
- Used median BMD and BMDL for most sensitive biological process gene set for comparison with the most sensitive chronic, apical BMD and BMDL.
- Performance of best dose response analysis parameter combination:
  - Pearson's correlation = 0.910
  - RMSD = 0.567
  - Median absolute ratio = 3.2 $\pm$ 1.9 (MAD)
  - Inter-study $\log_{10}$ BMD SD = 0.242
  - Family-Wise Error Rate = 0.006

Conceptual Approach of the EPA Transcriptomic Assessment Product (ETAP)



Standard Methods Document for ETAP

- More specific than normal guidance
- Method subject to peer-review and public comment
- Focused only on data poor chemicals

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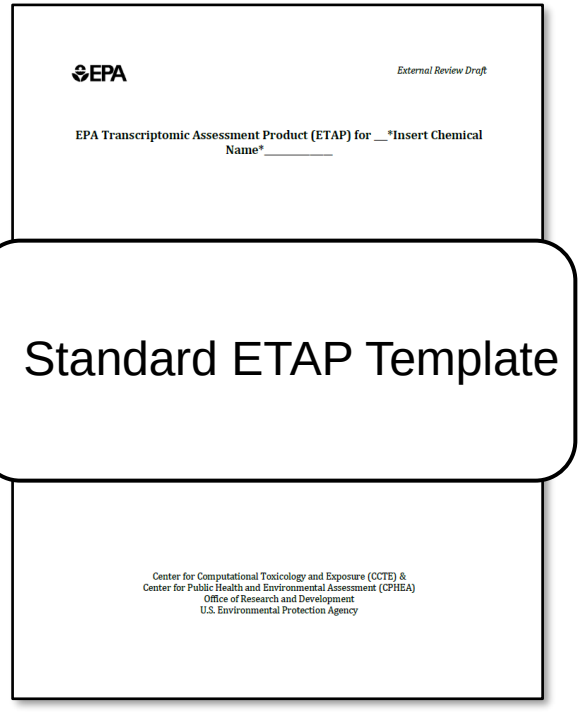

Standard ETAP Template

- Highly standardized assessment template
- Minimal free-form text and no subjective interpretation
- Reviewed for quality and consistency with methods by EPA QA staff
- Internal technical review by ORD scientists

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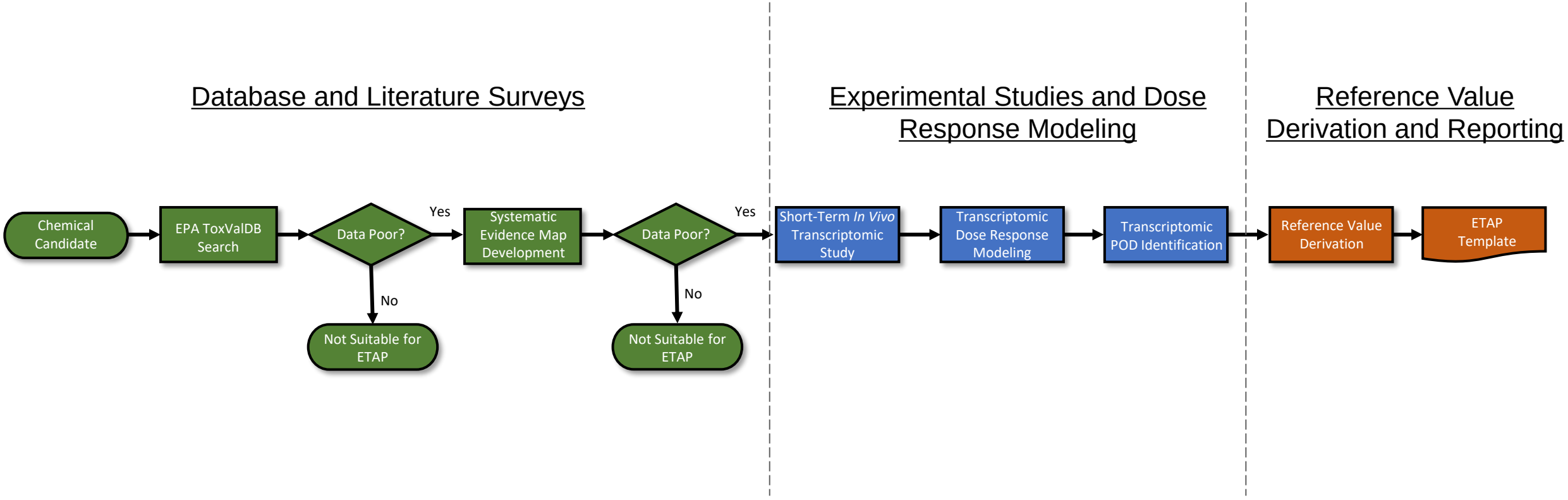
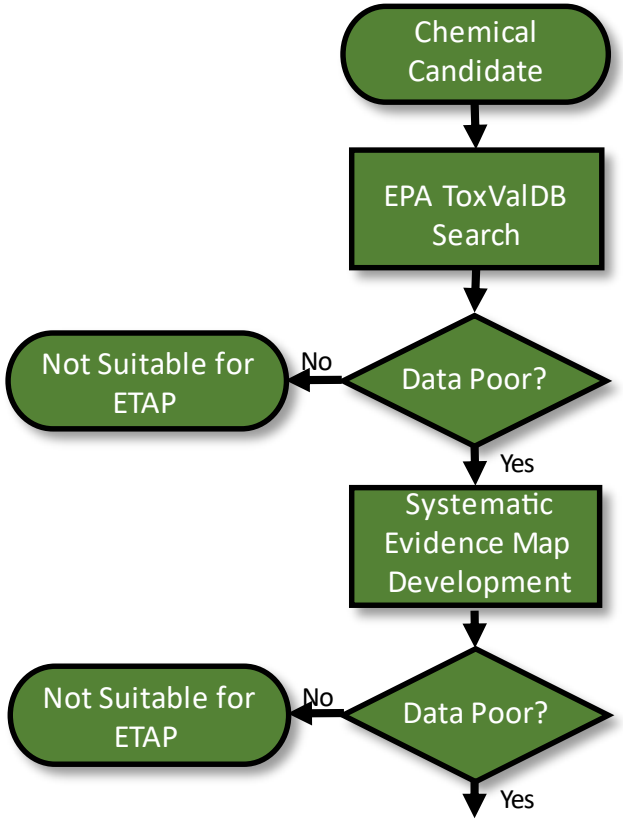
- Rapid experimental execution
- Stream-lined review process
- Target time from initiation to release is < 9 months (vs. 6 – 10 yrs)
- Scalable
- Potential broad application

ETAP Development Includes Three Main Components

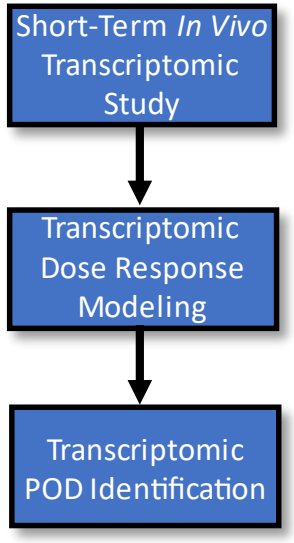


Overview of the Database and Literature Survey Component



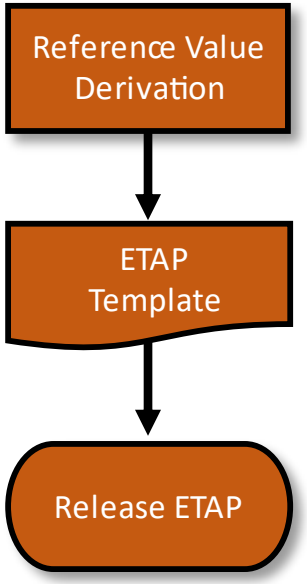
- Initial screening is done using available EPA databases to identify potentially-relevant traditional repeat dose toxicity or human studies.
- If no suitable studies are identified, a Systematic Evidence Map is initiated.
  - Utilize customized Populations, Exposures, Comparators, and Outcome (PECO) criteria to focus search, evaluation, and inclusion/exclusion criteria.
  - Search published and “gray” literature.
- Relevant studies are summarized in DistillerSR.
- Search of CBI data may be incorporated.
- Only chemicals confirmed to have no suitable publicly available mammalian *in vivo* repeat dose toxicity studies or human evidence are eligible to progress.

Overview of Experimental Studies and Dose Response Modeling Component



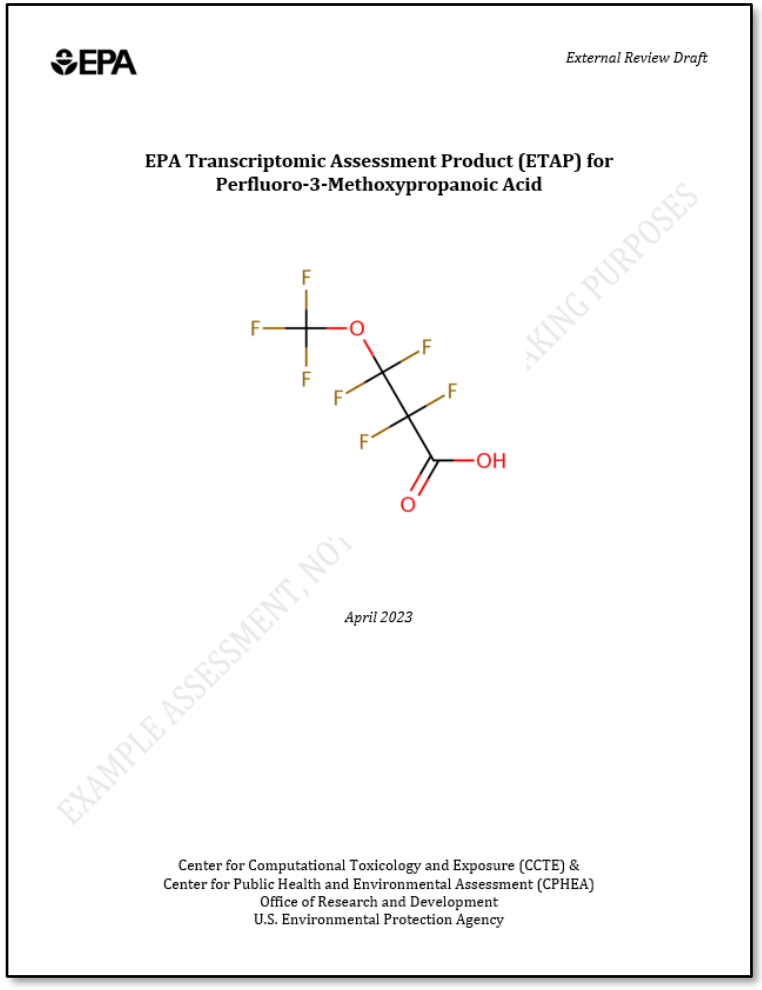
- Analytical QC and dosing solution characterization.
- *In vivo* study:
  - Male and female Sprague Dawley rats.
  - 5-day gavage dosing.
  - Minimum of 5 doses + control (n = 4/dose).
- Gene expression measurements:
  - Minimum tissue battery of kidney, liver, adrenal gland, brain, heart, lung, ovary, spleen, testis, thyroid, thymus, and uterus.
  - Use targeted RNA-seq platform for gene subset (S1500+).
- Benchmark dose analysis of genes grouped by biological process
  - Use median BMDL for the most sensitive biological process gene set as the point-of-departure.
  - **No mechanistic interpretation.**
- **Transcriptomic point-of-departure defined as experimentally determined dose at which there were no coordinated transcriptional changes that would indicate a potential toxicity of concern.**

Overview of Reference Value Derivation and Reporting



- Convert transcriptomic BMDL to human equivalent dose using EPA allometric scaling methods.
- **Apply standard set of uncertainty factor values** to derive Transcriptomics-based Reference Value (TRV):
  - UF_H, Inter-individual Variability = 10
  - UF_A, Animal-to-Human Extrapolation = 3
  - UF_S, Subchronic-to-Chronic = 1
  - UF_L, LOAEL-to-NOAEL = 1
  - UF_D, Incomplete Toxicity Database = 10
  - **Total Composite UF = 300**
- TRV defined as an estimate of a daily oral dose that is likely to be without appreciable risk of adverse effects following chronic exposure.
- Meant to protect both the individual and population from adverse responses that occur via threshold mechanisms.
- Report data in a standardized assessment template with minimal free-form text and **no subjective interpretation**.
- Reviewed for quality and consistency with methods prior to release.

Example ETAP for Perfluoro-3-Methoxypropanoic Acid


EPA

External Review Draft

EPA Transcriptomic Assessment Product (ETAP) for Perfluoro-3-Methoxypropanoic Acid

April 2023

Center for Computational Toxicology and Exposure (CCTE) &
Center for Public Health and Environmental Assessment (CPHEA)
Office of Research and Development
U.S. Environmental Protection Agency

- Nine doses plus control (0.01 – 300 mg/kg-d).
- Tissues evaluated:
  - Male – adrenal gland, brain, heart, kidneys, liver, lung, spleen, testis, thyroid, and thymus.
  - Female – adrenal gland, brain, heart, kidneys, liver, lung, ovary, spleen, thyroid, thymus, and uterus.
- Most sensitive transcriptional response was in female uterus.

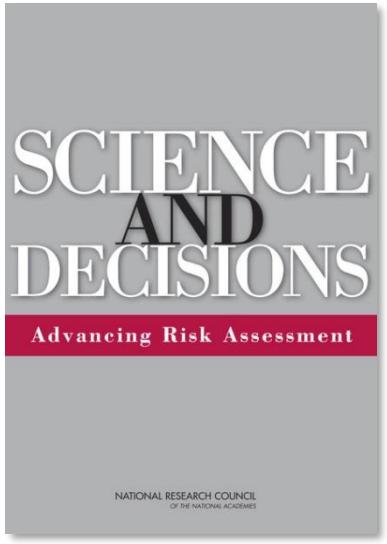
Calculation of the $BMDL_{HED}$ for perfluoro-3-methoxypropanoic acid				
Endpoint	Sex	Organ	BMDL (mg/kg-d)	$BMDL_{HED}$ (mg/kg-d)
Transcriptional changes	Female	Uterus	0.121	0.0279

$$TRV = \frac{0.0279\ mg/kg{-}d}{300} = 0.00009\ mg/kg{-}d$$

*For comparison, the EPA chronic RfD for PFBS is 0.00028 mg/kg-d (~3x higher)

**$BMDL_{HED}$ = BMDL Human Equivalent Dose

Importance of Considering Time, Uncertainty, and Cost in Chemical Risk Assessment



NRC, 2009

- 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 method for quantifying the expected gain in economic terms for reducing uncertainty through the collection of additional data or information.
- VOI has been applied or proposed in toxicology and chemical risk assessment but to date has not considered the impact of time.

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

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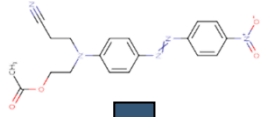
Abstract

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



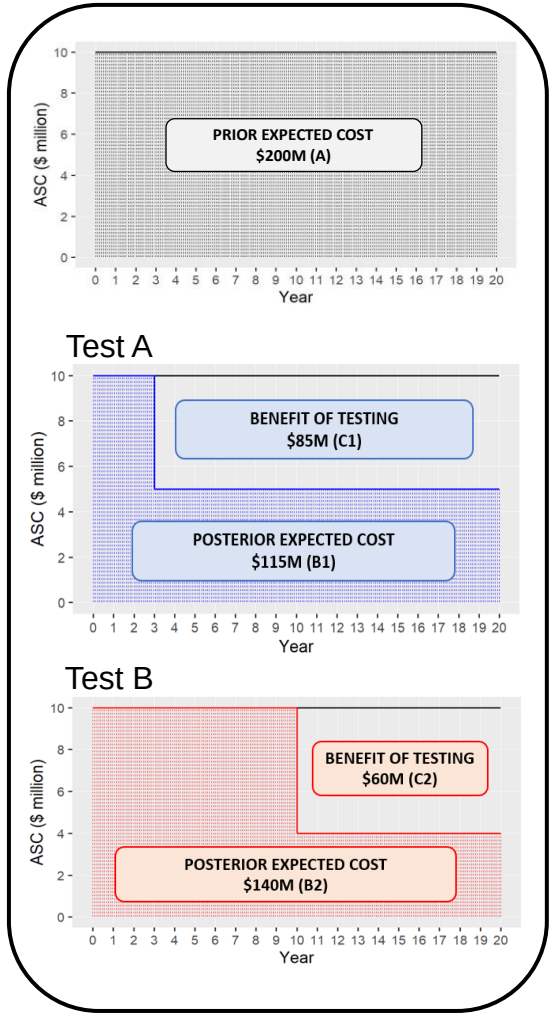
Exposure Level
Population Variability in Exposure
Affected Population Size
Health Effects
Population Variability in Toxicity
Control Costs

Relevant Chemical Characteristics

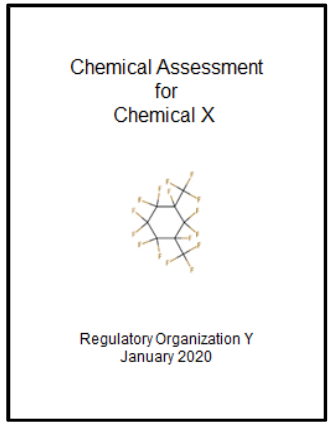
Uncertainty in Effect Level
Timeliness
Cost

Toxicity Testing Characteristics

Regulatory Decision Context → VOI metrics →



Quantifying Trade-Offs of Uncertainty, Cost, and Time Would Allow More Wholistic Evaluation of ETAP

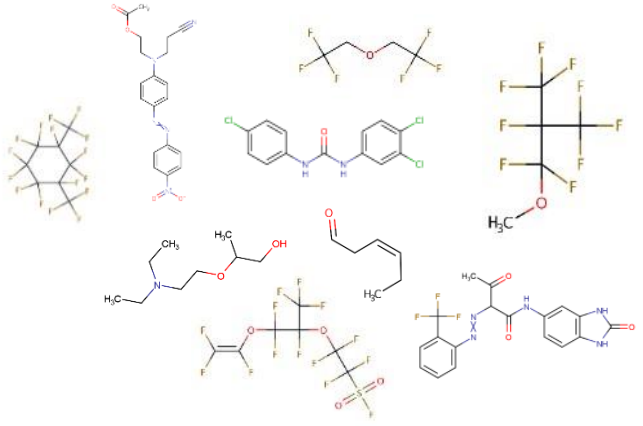


	Short-Term Transcriptomic Study and ETAP	Traditional Toxicity Testing and Human Health Assessment
Time Required	6 months*	8+ years*
Uncertainty	Higher	Lower
Costs	~$200,000	~$4 million

*Does not include 2 yr for implementing regulation.

Adapting Framework to Evaluate Benefits For Application to Diversity of Data Poor Chemicals and Potential Decisions

Diverse Range of Data Poor Chemicals



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

Uncertainty in Effect Level
Timeliness
Cost

Regulatory Decision Context

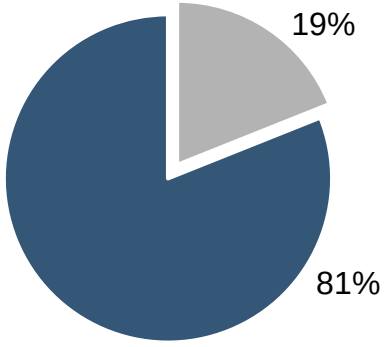
Bounded Range of VOI metrics

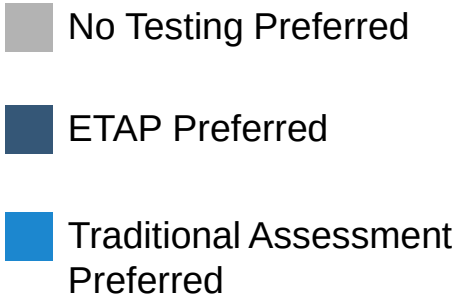
306 Data Driven Scenarios Examined Comparing ETAP vs Traditional HHA Process

- Range of Exposure estimates and population variability
  - SHEDS-HT and TSCA
- Different population sizes
  - US population fractions
- Range of control costs
  - US and REACH data
- Range of health endpoints and associated costs
  - Literature surveys
- Uncertainty assumptions comparing ETAP and chronic bioassay
- Target risk vs benefit risk decision context

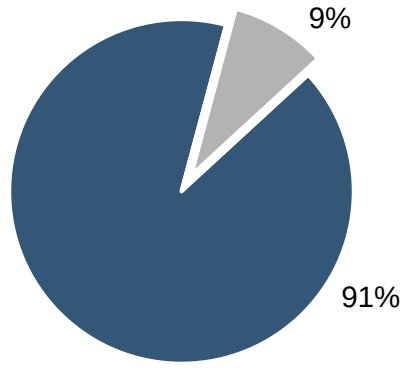
Summary Results Across Chemical Scenarios

Benefit-Risk Decision Context

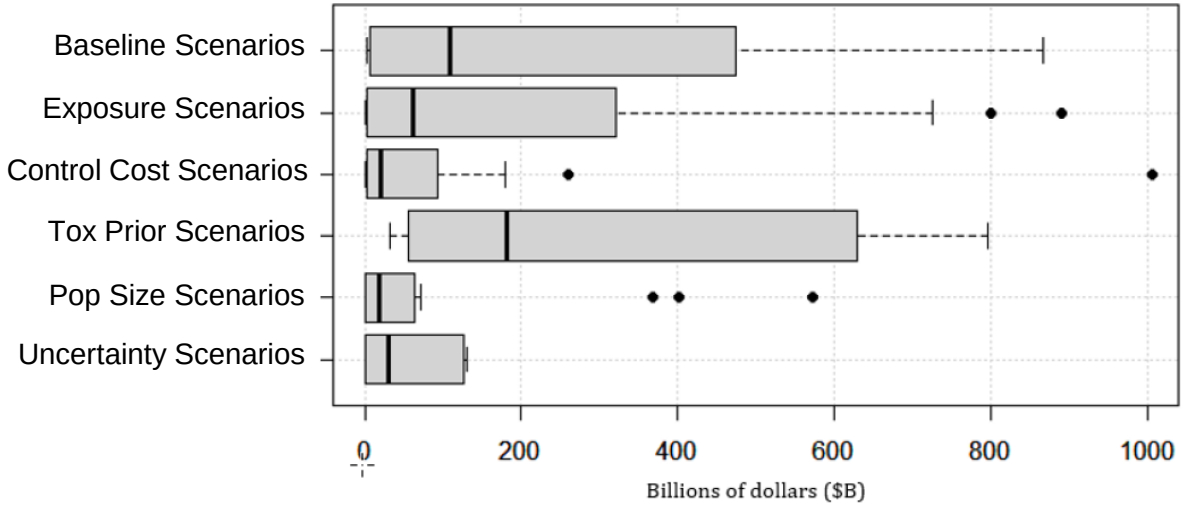




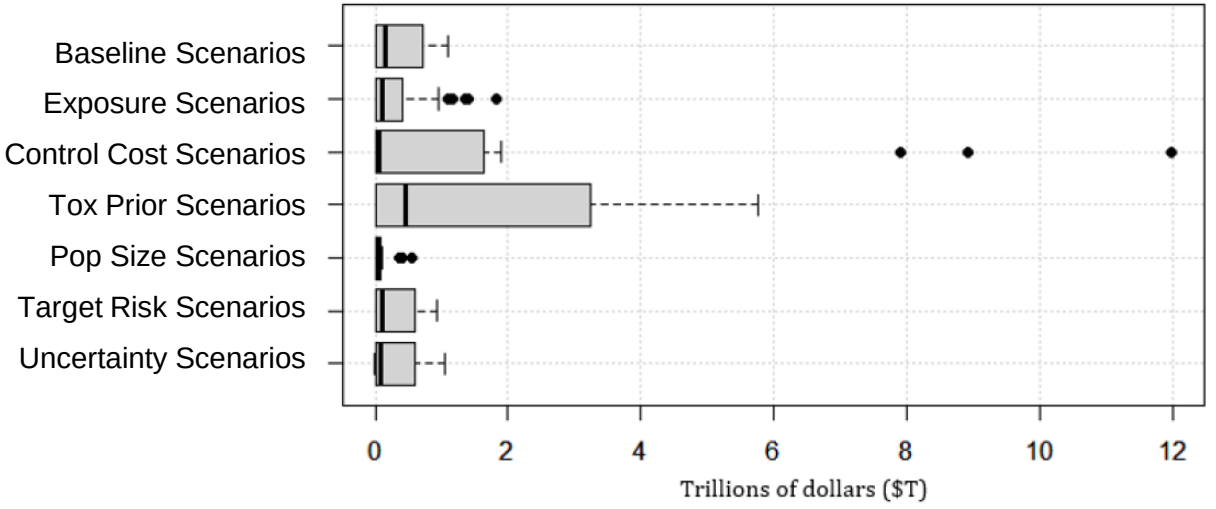
Target-Risk Decision Context



Difference in Expected Net Benefit from Sampling



Difference in Expected Net Benefit from Sampling



Expected Net Benefit from Sampling (Higher is Better) – Reduction in total social costs (includes health and control costs) adjusted for delay and cost of testing. Benefits accrued over a 20-year time horizon.

Summary

- Relatively few chemicals have traditional toxicity testing data or human health assessments.
- A literature review and transcriptomic dose response analysis studies showed high concordance between transcriptomic and apical BMD/L values in traditional animal toxicity studies.
- The error associated with the concordance between the transcriptomic and apical BMD values is approximately equivalent to the combined inter-study variability associated with the transcriptomic study and the two-year rodent bioassay.
- A new draft human health assessment was developed based transcriptomic points-of-departure defined as the dose with no coordinated transcriptional changes that would indicate a potential toxicity of concern, but not linked to a specific hazard.
- Transcriptomic reference values are derived using a standardized set of uncertainty factors due to the carefully prescribed design of the animal studies and data analysis procedures.
- Comparison of transcriptomic toxicity values with traditional reference doses demonstrated similar levels of protection across a broad range of chemicals and effects.
- Socioeconomic analysis favored ETAP over traditional toxicity testing and human health assessment approaches for the majority of data poor scenarios evaluated.

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Questions?