Computational Toxicology and Exposure Communities of Practice

Sharing research and promoting collaboration

Thursday, August 22, 11 AM-12 PM ET

Agenda:

- **Introduction: Sammy Hanf**
  Communications Specialist, ORD Center for Computational Toxicology and Exposure
- **Presenter: Alison Harrill**
  Associate Director for Toxicology in the Center for Computational Toxicology and Exposure (CCTE)
- **Q&A**
- **Closing remarks: Sammy Hanf**

For more information on the CompTox CoP, visit:
epa.gov/chemical-research/computational-toxicology-communities-practice

The Scientific Underpinnings of the EPA Transcriptomic Assessment Product (ETAP) and Value of Information (VOI) Case Study

Alison Harrill,
Associate Director
for Toxicology, CCTE

Upcoming Webinars

EPA hosts webinar series dedicated to delivering the latest information and training on our cutting-edge research addressing environmental and public health issues.

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Small Drinking Water Systems

August 27: *Consolidation, Restructuring, Partnerships, and Regionalization*

Registration and Additional Information

Healthy and Resilient Communities Research

September 10: *Brownfields, Gentrification, and Environmental Justice Research: Learning from Past Experiences*

Registration and Additional Information

Emergency Response Research

September 11: *Premise Plumbing and Wildfires*

Registration and Additional Information

Computational Toxicology and Exposure Communities of Practice

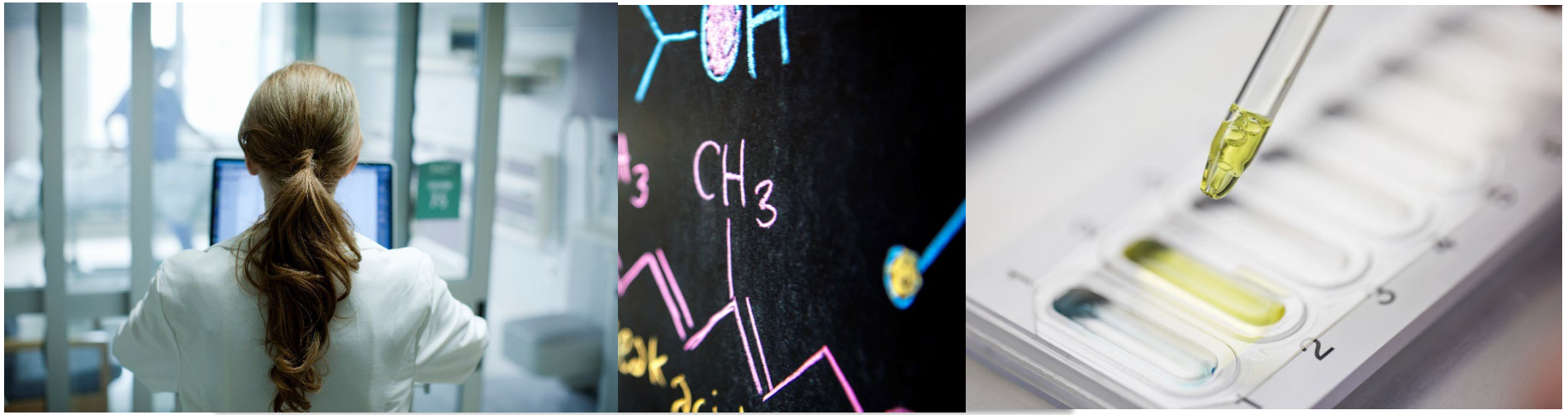
September 26: *Using Environmental RNA to Understand the Effects of Pollution on Aquatic Ecosystems*

Registration and Additional Information

Innovations in Health Assessments: New Approach Methods and EPA's Transcriptomics Assessment Product

Alison Harrill, PhD

Associate Director for Toxicology, EPA Office of Research and Development (CCTE)

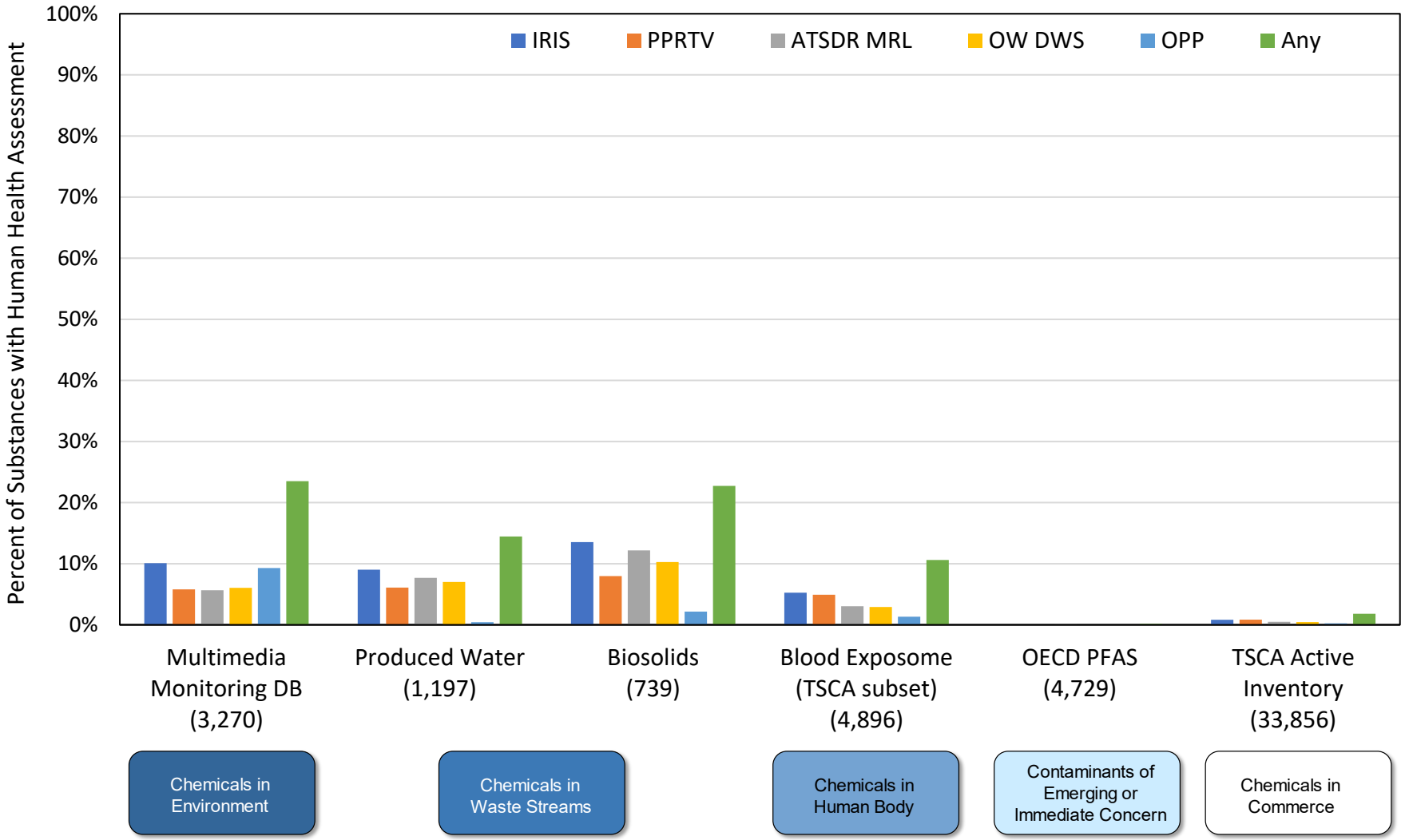


The views expressed in this presentation are those of the presenter and do not represent the views or policies of the U.S. EPA

Chemical landscape is large and growing

- >95% of manufactured goods and articles are estimated to be reliant upon an industrial chemical process
- >350,000 chemicals or mixtures registered in one or more inventories among 19 countries and regions
- In US, TSCA inventory contains >86,000 chemicals, with 42,000 commercially active
- These numbers are a snapshot in time, trends in chemical production continue to rise

Relatively few chemicals in different exposure or regulatory contexts have human health assessments



IRIS – US EPA Integrated Risk Information System

PPRTV – US EPA Provisional Peer Reviewed Toxicity Values

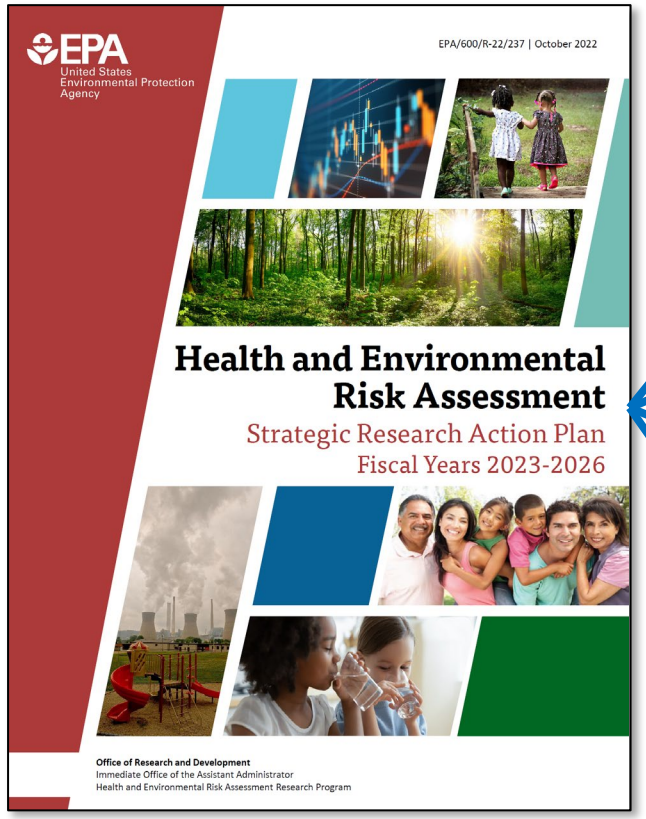
ATSDR MRL – Agency for Toxic Substances and Disease Registry Minimal Risk Levels

OW DWS – US EPA Office of Water Health Advisories

OPP – US EPA Office of Pesticide Programs

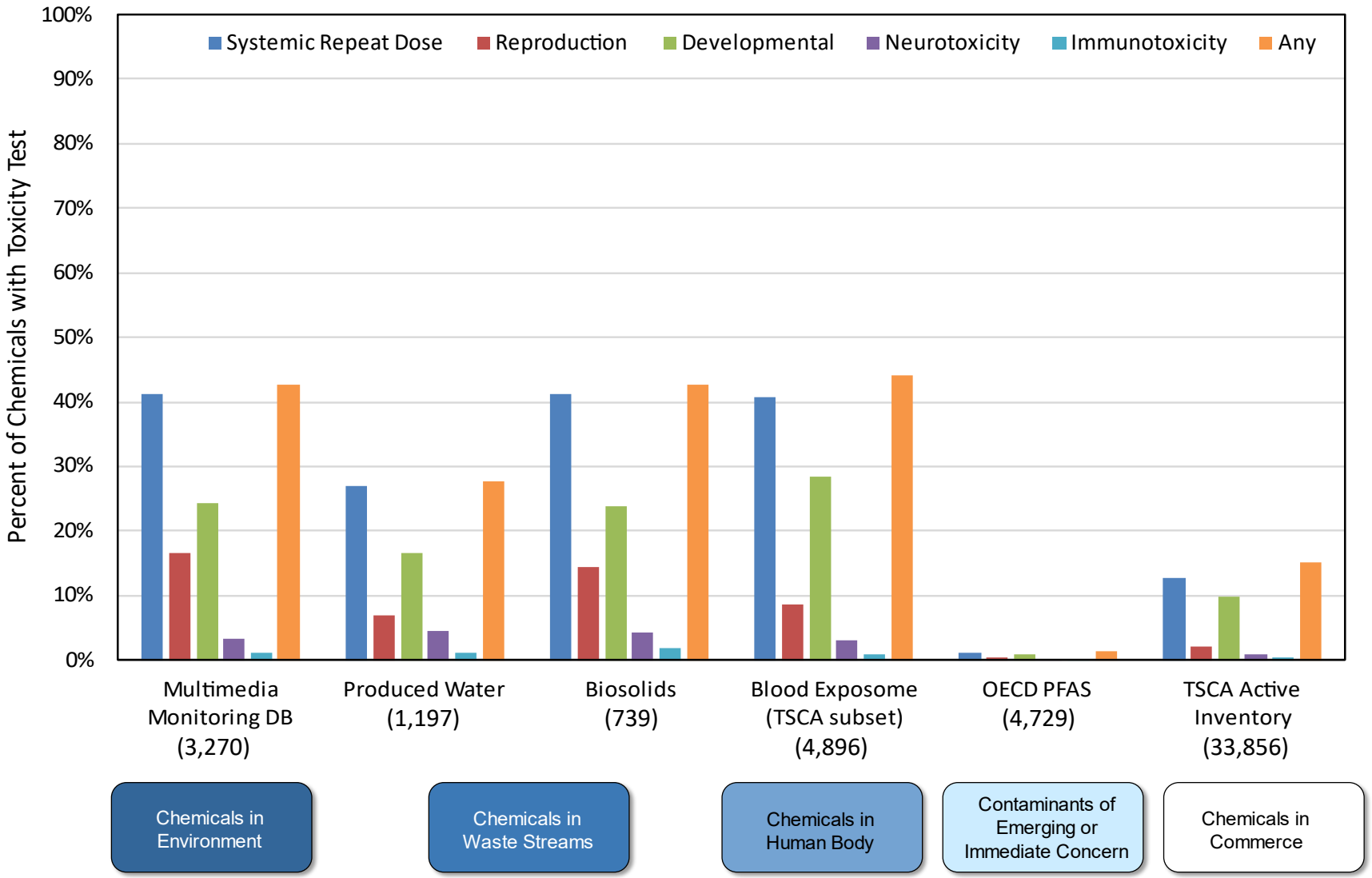
Science Assessment Development

ORD is focused on producing **high quality**, **transparent**, **consistent**, and **scientifically defensible** assessment products to meet EPA's diverse statutory and policy needs.



- Integrated Science Assessments (ISAs) → National Ambient Air Quality Standards (NAAQS)
- Integrated Risk Information System (IRIS) → National and site-specific decisions
- Provisional Peer-Reviewed Toxicity Values (PPRTVs) → Superfund risk assessments
- Human Health Toxicity Value (HHTV) Assessments → Site-specific risk assessments

Fewer than half of chemicals within representative sets have traditional toxicity testing data



*Toxicity testing data obtained from ToxVal v9.4

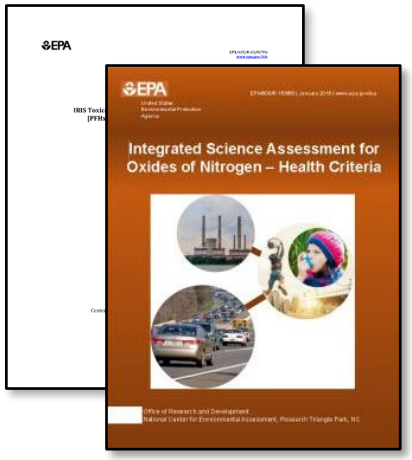
Innovating ORD's portfolio of assessment products

ORD is incorporating fit-for-purpose considerations and innovations in assessments and developing new assessment products, including for 'data-poor' chemicals.

Data-Rich

Relative Data Availability

Data-Poor

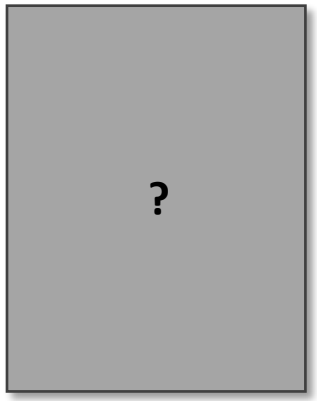


ISAs, IRIS

PPRTVs

Human Health Toxicity Assessments

Fit-for-purpose



Longer

Shorter

Relative Development Time

Traditional approach requires significant time and resources for toxicity assessment

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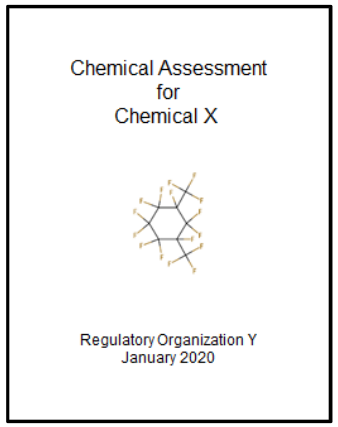

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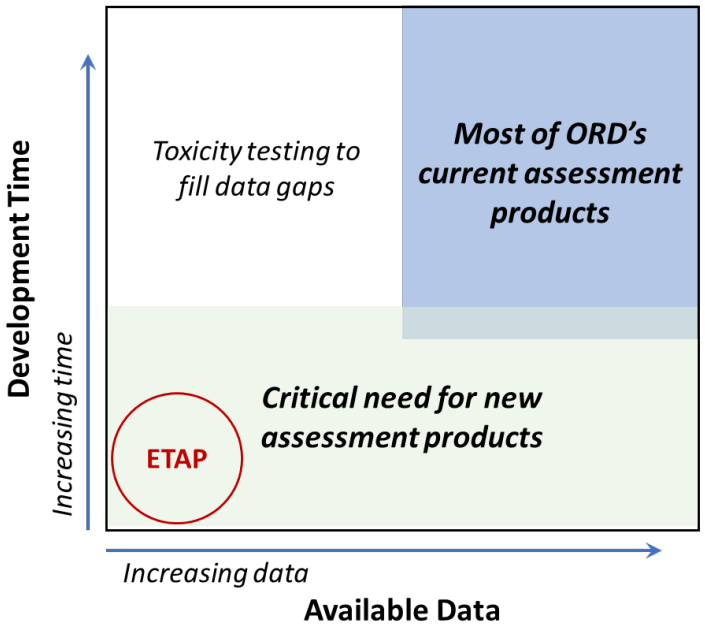
6 – 14+ years

- 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)

Methods-based development projects may help fill the testing & assessment gap



Systemic

Bioactivity-based point of departure

Short-term rodent study

EPA Transcriptomic Assessment Product (ETAP)*

**Formal assessment product 2024*
Target release < 1 year

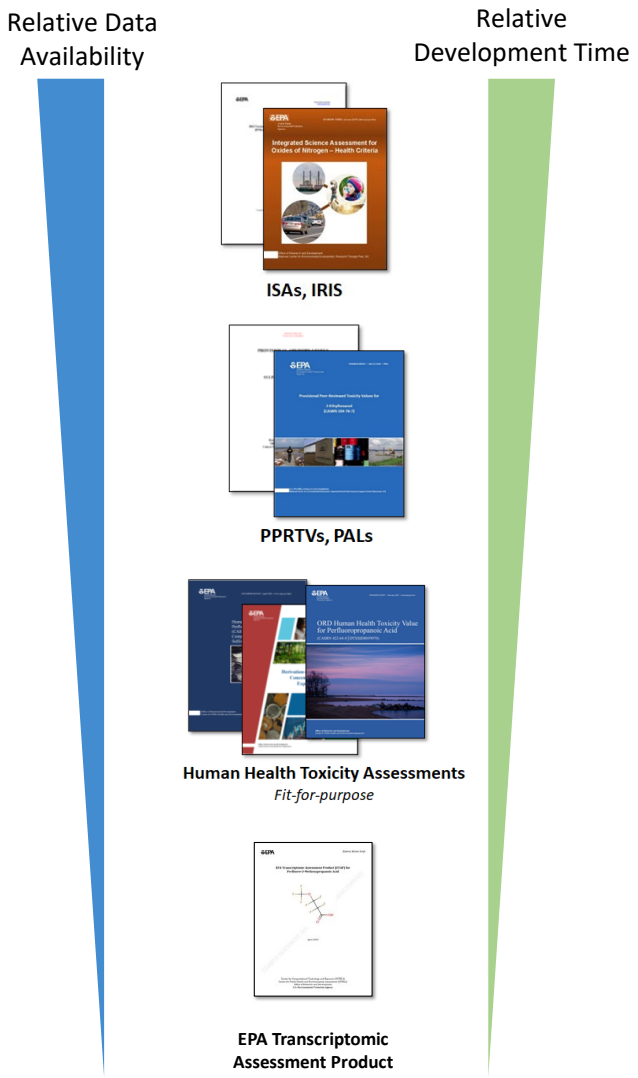
Advances in genetic sequencing technology and research Increased potential for application to human health assessment

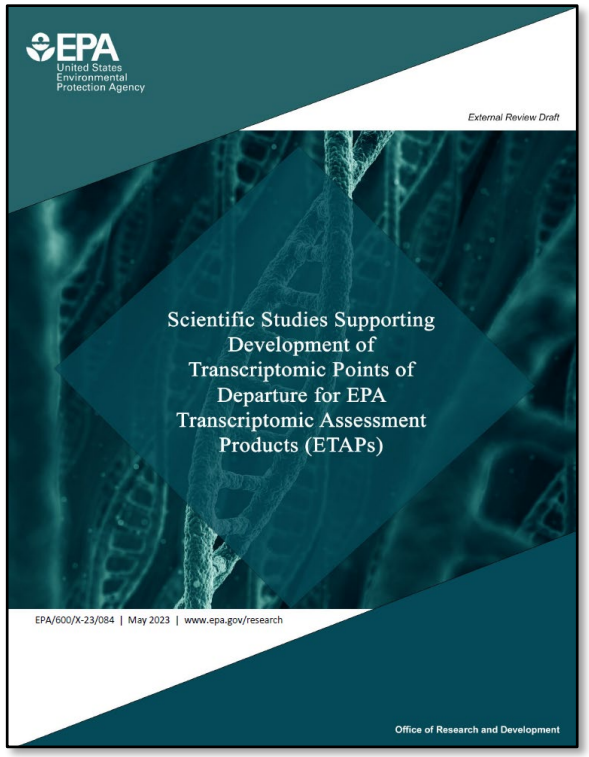
- Throughput
- Acceptance
- Reliability

- Costs

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

EPA completed peer review on a new human health assessment product based on transcriptomics

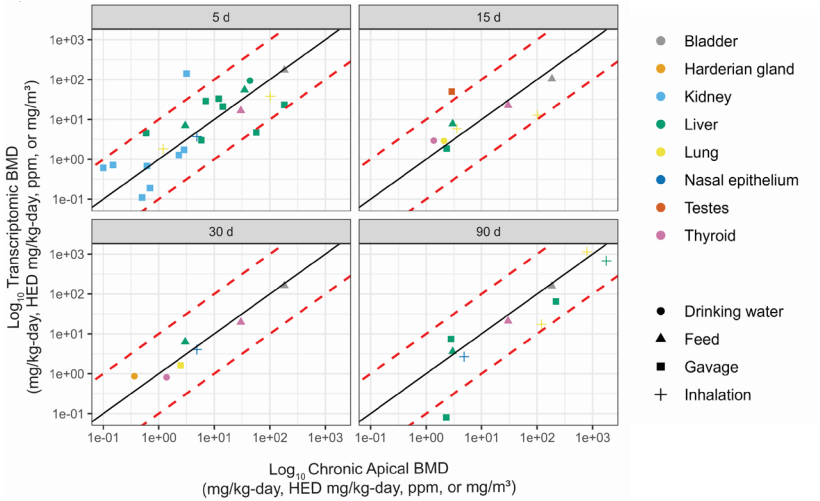


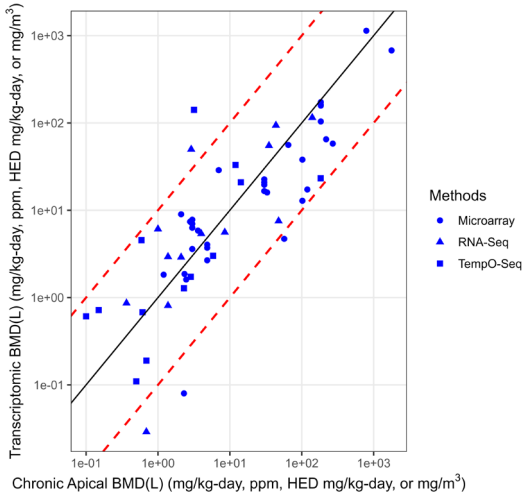


EPA Transcriptomic Assessment Product (ETAP) Board of Scientific Counselors Review

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

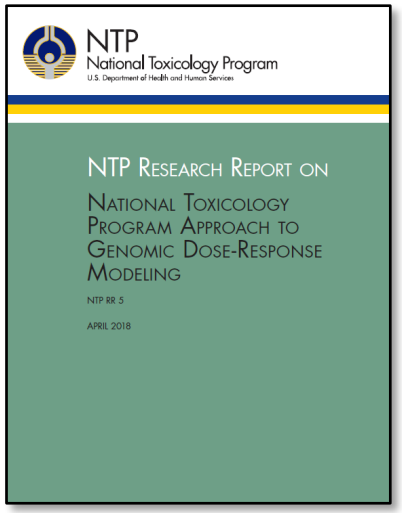
Comprehensive literature review supports dose concordance between disruption of gene activity and toxicity

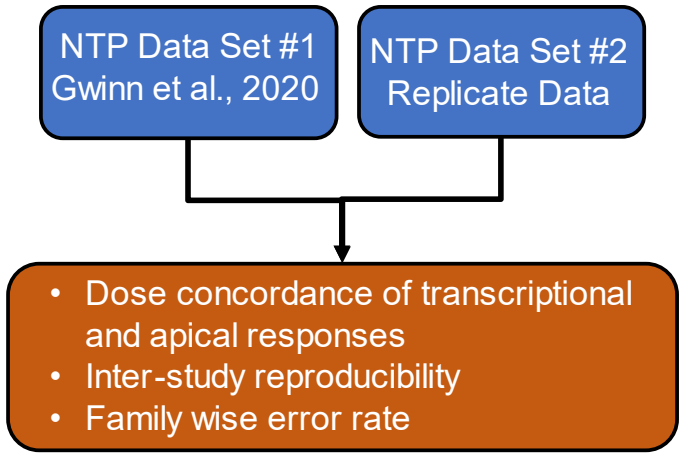




- Literature review identified 140 chemicals in 32 studies
- Studies covered 4 exposure routes, multiple exposure durations (<1 day to 90 days), 8 tissues, 3 technologies, and broad range of physicochemical properties and toxicokinetic half-lives
- Among chemicals with chronic bioassays, the transcriptomic BMD was highly correlated with the chronic, apical BMD (r = 0.825)
- The concordance RMSD (0.561) 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 (Pham *et al. Comp Toxicol.*, 2020)
- The concordance was robust across exposure durations, exposure routes, species, sex, target tissues, physical chemical properties, toxicokinetic half-lives, and technology platforms

Transcriptomic dose response analysis methods showed robust performance

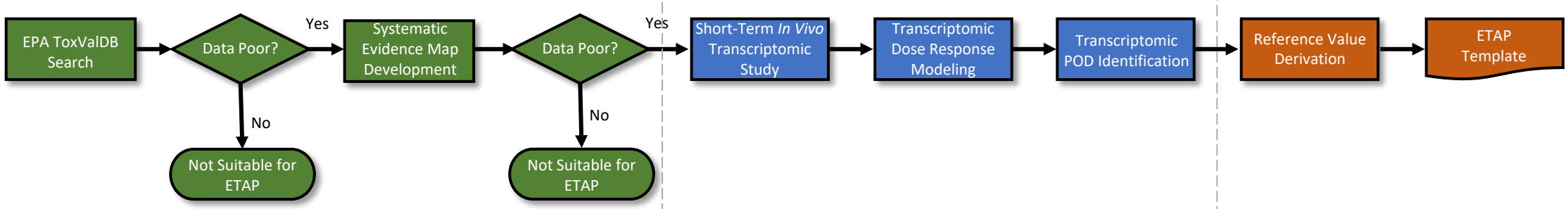




- Leveraged peer-reviewed NTP Approach to Genomic Dose Response Modeling as framework for transcriptomic dose response analysis process
- Performed dose response analysis optimization using existing NTP data sets:
  - Chemicals with both 5-day transcriptomic studies and chronic rodent bioassays
  - Replicate studies on a subset of chemicals
- Correlation of transcriptional and apical BMD(L) values was 0.910 with an RMSD = 0.567
- The error in concordance was approximately equivalent to the combined inter-study variability associated with the transcriptomic and traditional chronic toxicity studies
- The family-wise error rate was < 1%

ETAP development includes three main components

Database and Literature Surveys



- Initial screening is done using available EPA databases
- If no suitable studies are identified, a Systematic Evidence Map is initiated
- Only chemicals confirmed to have no publicly available mammalian *in vivo* repeat dose toxicity studies or suitable human evidence are eligible to progress

Experimental Studies and Dose Response Modeling

- Five day, repeat dose study in male and female Sprague Dawley rats
- Perform gene expression measurements in 12 tissues
- Benchmark dose analysis of genes grouped by biological process
- Transcriptomic point-of-departure defined as the dose at which there were no coordinated transcriptional changes that would indicate a potential toxicity of concern

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 chronic Transcriptomics-based Reference Value (TRV)
- TRV defined as an estimate of a daily oral dose that is likely to be without appreciable risk of adverse non-cancer health effects over a lifetime
- Report data in a standardized assessment template

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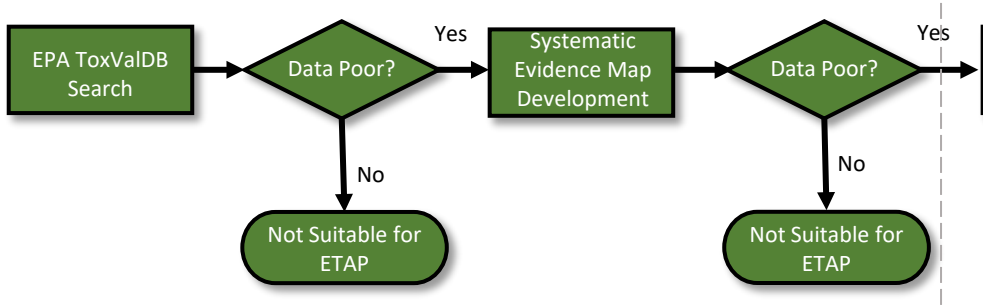

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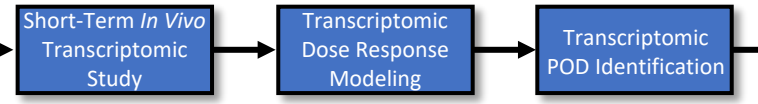

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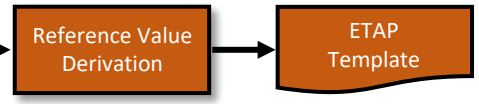

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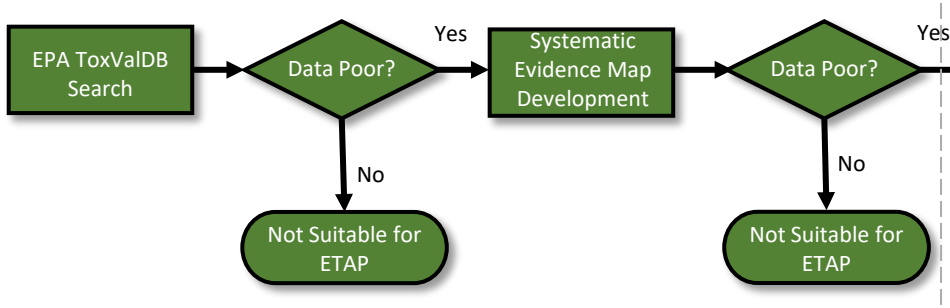

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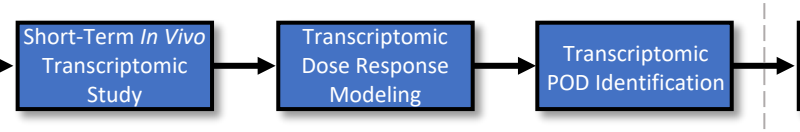

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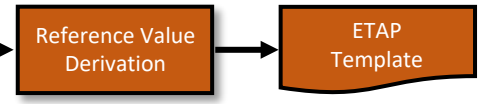

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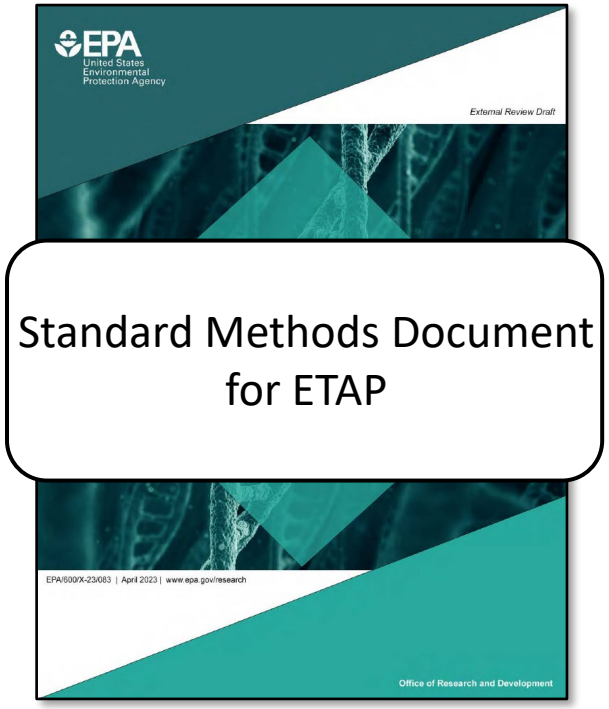
Comparison of ETAP with other EPA reference values for chemicals identified in the literature review

Chemical	TRV (mg/kg-day or mg/m³)	Exposure Duration (d)	Sex, Species, Tissue	Reference	RfD or RfC (mg/kg-day or mg/m³)	Source, Sex, Species, Study Type	TRV-to-RfD Ratio
Acrylamide	2.4E-03	31	Male Rats, Testis	(Recio et al. 2017)	2.0E-03	IRIS 2010, Male Rats, Chronic	1.20
Allyl alcohol	1.8E-03	8	Male Rats, Liver	(Johnson et al. 2020)	5.0E-03	IRIS 1987, Male Rats, Subchronic	0.37
Benzo[a]pyrene	9.4E-05	3	Male Mice, Liver	(Moffat et al. 2015)	3.0E-04	IRIS 2017, Rats, Developmental	0.31
Bromobenzene	3.4E-03	8	Male Rats, Liver	(Johnson et al. 2020)	8.0E-03	IRIS 2009, Male Mice, Subchronic	0.43
Chloroprene[a]	1.4E-02	5	Female Mice, Lung	(Thomas et al. 2013a)	2.0E-02	IRIS 2010, Male and Female Rats, Female Mice, Chronic	0.68
Dichloroacetic acid	3.5E-02	6	Male Mice, Liver	(Cannizzo et al. 2022)	4.0E-03	IRIS 2003, Male and Female Dogs, Subchronic	8.67
…	…	…	…	…	…	…	…
A total of 20 chemicals (47 chemical x tissue x time point combinations) had IRIS/PPRV assessments.							

Overall Median Absolute Ratio = 2.3 ± 1.1 (MAD)
Median Absolute Ratio (Non-Matched Species) = 3.2 ± 1.3 (MAD)
Median Absolute Ratio (Matched Species) = 1.5 ± 1.1 (MAD)

IRIS, EPA Integrated Risk Information System; PPRTV, EPA Provisional Peer Reviewed Toxicity Values; MAD, median absolute deviation

Reporting, review, and release of the ETAP is different than other EPA assessments



Standard Methods Document for ETAP

- More specific than normal guidance
- Method subject to peer-review and public comment

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Standard ETAP Template

- Minimal free-form text and no subjective interpretation
- Reviewed for quality and consistency with methods

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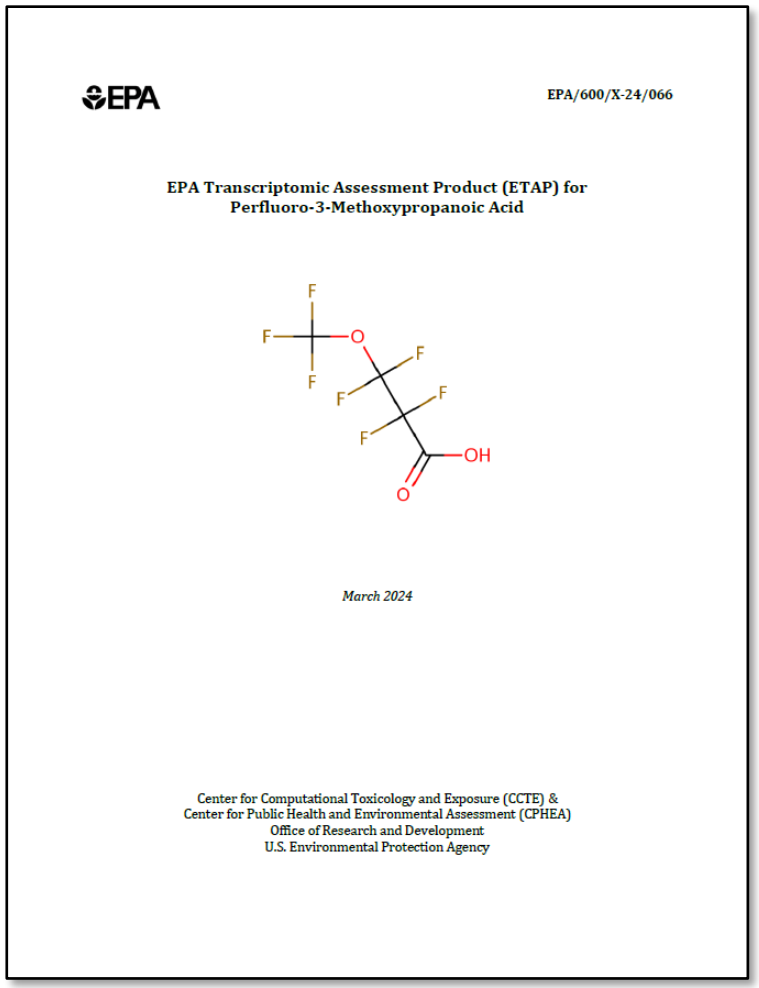
- Rapid experimental execution
- Stream-lined review process
- Target time from initiation to release is < 9 months
- Scalable

ETAP for Perfluoro-3-Methoxypropanoic Acid (MOPA)


EPA

EPA/600/X-24/066

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

March 2024

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, kidney, liver, lung, spleen, testis, thyroid, and thymus
  - Female – adrenal gland, brain, heart, kidney, liver, lung, ovary, spleen, thyroid, thymus, and uterus
- Most sensitive transcriptional response was in female uterus

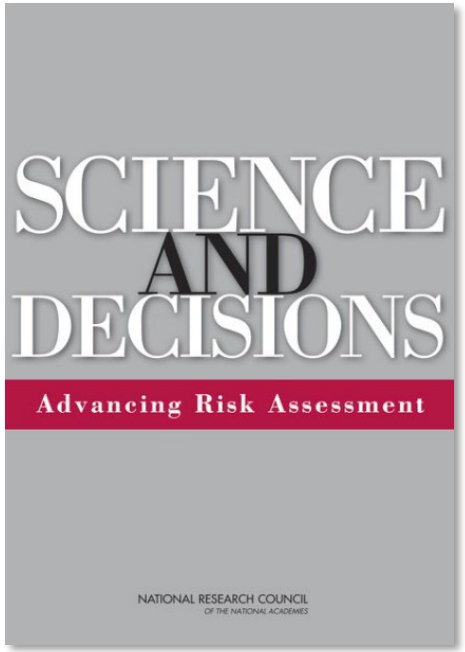
Calculation of the $BMDL_{HED}$ for perfluoro-3-methoxypropanoic acid				
Endpoint	Sex	Organ	BMDL (mg/kg-d)	$BMDL_{HED}$ (mg/kg-d)
Transcriptional changes	Female	Uterus	0.121	0.0279

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

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

**For comparison, the TRV for perfluoro-3-methoxypropanoic acid is
~5X lower to the chronic RfD for PFPrA (0.0005 mg/kg-day)
~3X lower than the EPA chronic RfD for PFBS (0.0003 mg/kg-day)
~30X higher than the chronic RfD for GenX (0.000003 mg/kg-day)

VOI: Charting a path forward for testing



- The National Research Council 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 was 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 measures describe expected loss reductions (or benefit gains) from collecting further information – how $ much should one spend to obtain perfect information (more certainty)?

Value of Information: EPA-developed 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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[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

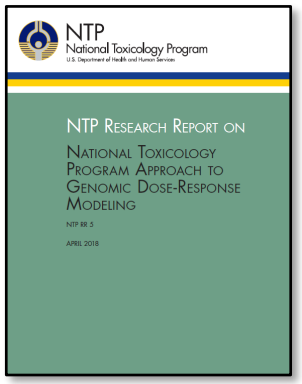
Evidence-based risk assessment has become a cornerstone of public and population health risk decision making, integrating evidence on toxicity and exposure from multiple evidence streams. When the available evidence is insufficient to allow a decision to be made with confidence, consideration can be 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

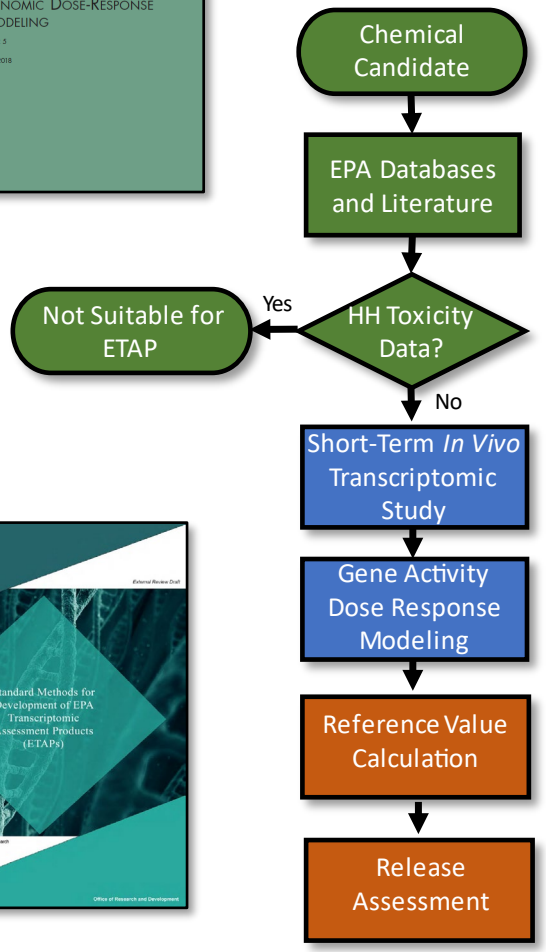
Utilize the EPA-developed VOI framework that is ground-breaking because it explicitly considers the impact of delay in decision-making.

The framework takes into account:

- Amount of **uncertainty** reduced
- **Cost** of additional toxicity testing
- **Delay** in obtaining and evaluating toxicity testing data

Case study: Value of Information associated with ETAP





The VOI analysis in this study aimed to answer the following question: ***given that additional toxicity testing data may be beneficial, which toxicity testing methodology and assessment process provides the most value?***

Case study compared chronic 2-year rodent toxicity test & assessment to ETAP

	Transcriptomics Study and Human Health Assessment	Traditional Toxicity Testing and Human Health Assessment
Time Required	<1 year	8 years
Quantitative uncertainty	Modestly greater	Modestly less
Costs	~$200,000	~$4 million

The effects of delay – economic considerations

- **NOT testing a chemical may also have a cost** borne by the public in terms of healthcare costs arising from exposure to a chemical
  - Economists think in terms of annualized health costs for a variety of outcomes, in terms of healthcare costs, lost productivity, and direct non-medical costs such as education or transportation
  - Annual economic values for a variety of conditions have been estimated
    - Ex: autism spectrum disorder ($69,530/year), asthma ($36,500/yr), pervasive developmental disorders ($10,538/yr)
    - EPA estimates fatality at $110,000/yr, considering a value of statistical life (VSL) of $8.8 mil and an 80-year life span

- **Delay has a cost –** Annualized healthcare costs accumulate over time if the exposure is not mitigated and are multiplicative based on the size of the affected population
  - 100,000 people exposed for 5 years prior to mitigation with a $10k annual healthcare cost (total health cost is $5 billion)
    - Mitigating exposure after 2 years saves the public $3 billion
  - 30 million people exposed for 10 years prior to mitigation with a $10k annual healthcare cost (total health cost is $3 trillion)
  - For VOI, we consider a time horizon over which benefits of a particular testing strategy may be realized, economists typically use a 20-year time horizon

What does exposure mitigation cost? – economic considerations

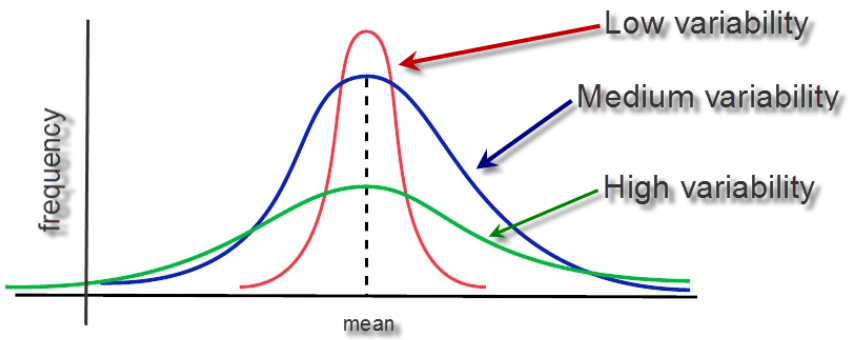
- **There's another cost to be considered once a regulatory action is finalized –** cost of control
  - Variety of actions that can be taken – ex. reducing emissions, incorporating water treatment/purification modalities, excavating and moving soil, substituting one chemical in a product formulation for an alternative
  - Under REACH (2021), annualized control costs had a mean of $50.6M and a median of $5.7M

Choice of test method – cost & time considerations

- Testing chemicals has a cost (*e.g.* chemistry + assay + analysis)
- Estimates of the cost of a 2-year chronic rodent toxicity test ranges $1-4 million
- Different test methods may be less expensive, may be equivalent, or may be more expensive
- Different methods will require different lengths of time to collect & analyze the data, and report the findings

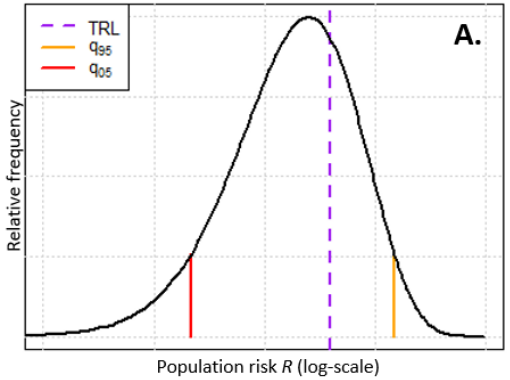
Choice of test method – uncertainty considerations

- Newer test method options may also have greater *quantitative uncertainty* around a point-of-departure estimate, for a number of reasons -
  - Has been established more recently and thus run fewer times than established method, so the available database to assess variability around a POD is much smaller
  - Greater variability may be more inherent to the method or endpoint measured
  - Difference in sample sizes between methods can impact variance measurements
  - VOI can help contextualize trade-offs in quantitative uncertainty in terms of public benefit

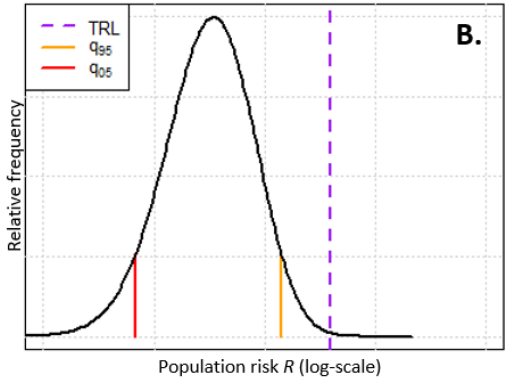


Two idealized decision makers in case study

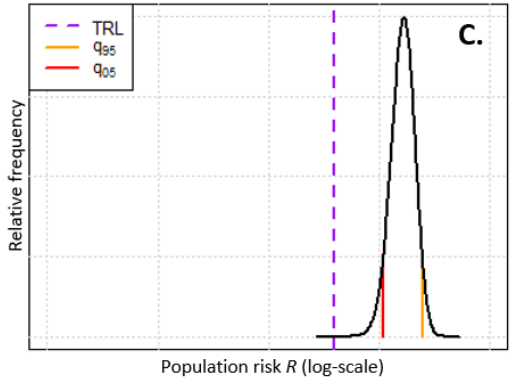
- Benefit-Risk Decision Maker (BRDM): Chooses to regulate a chemical if the reduction in health cost (or increased health benefit) outweighs the associated cost of control
- Target-Risk Decision Maker (TRDM): Chooses to regulate a chemical if the (lower quantile of) risk exceeds the pre-specified target risk level



TRDM would need additional evidence to make a decision



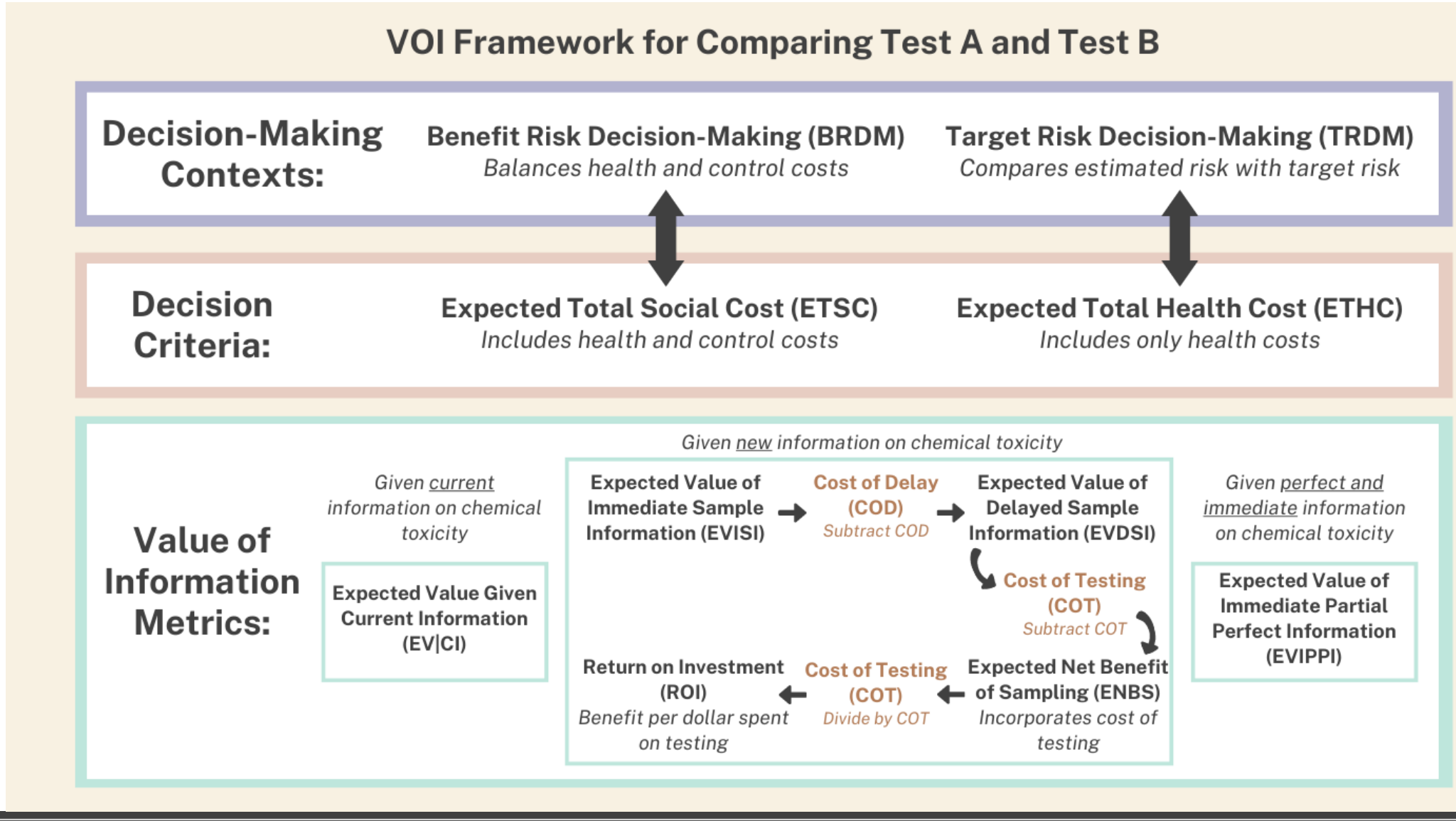
Target risk level is greater than the uncertainty distribution, no regulatory action required



Target risk level is below the 5th percentile of uncertainty distribution, regulatory action is required

TRL: Prespecified Target Risk Level

Using socioeconomic analysis to evaluate trade-offs in choosing one test method over another



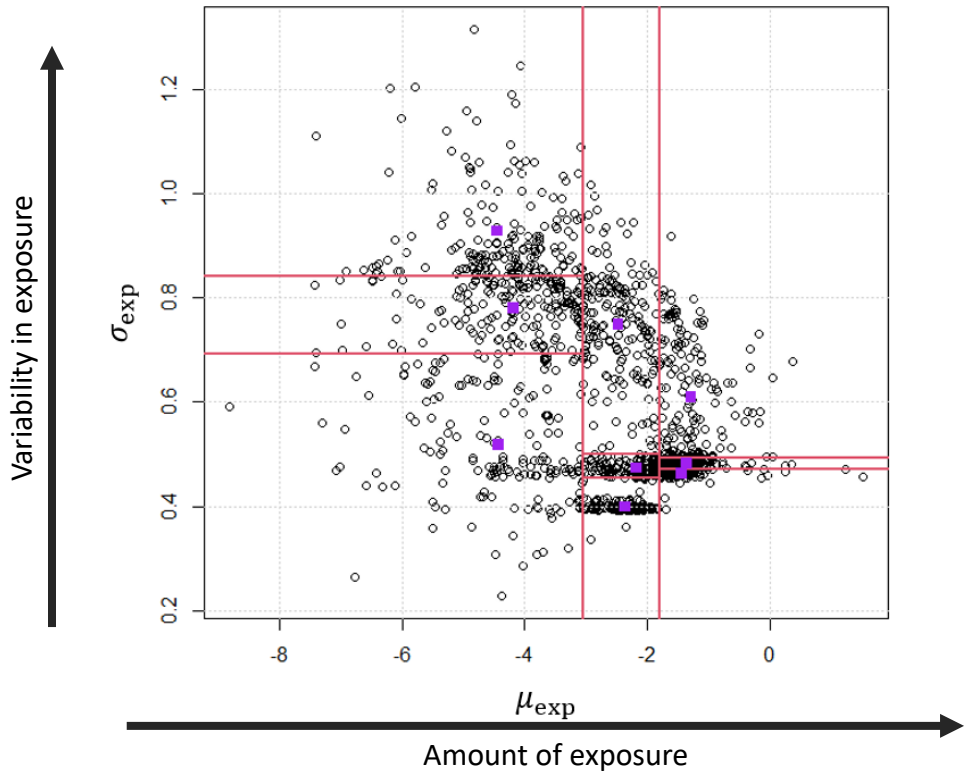
VOI framework established: Hagiwara et al. *Risk Analysis* 2022

Data-informed exposure scenarios

In the VOI framework, the decision maker considers the exposure level (dose) and variability around exposure to the chemical in assessing value of making a risk determination and pursuing a regulatory action

The case study did not focus on any one particular chemical, instead considering the potential range of potencies that could be encountered for chemicals of interest to regulators

Data from SHEDS-HT on exposure to 1,578 chemicals on the TSCA Active Inventory informed exposure estimates

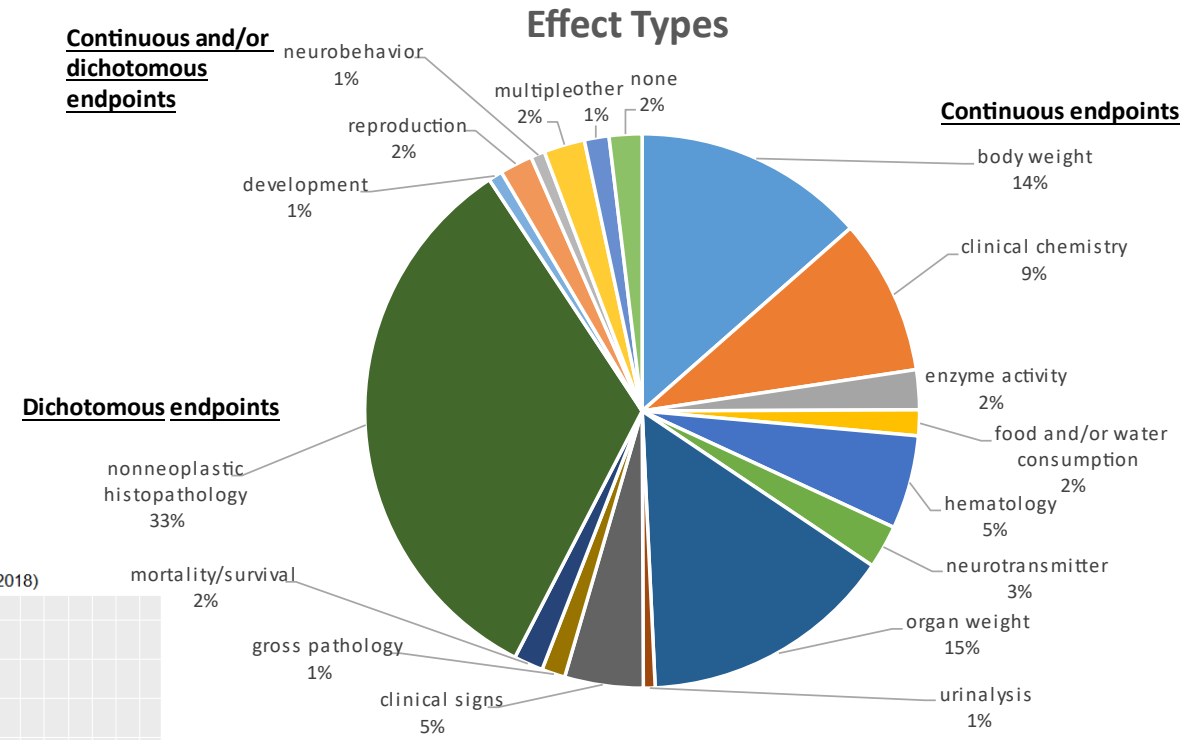


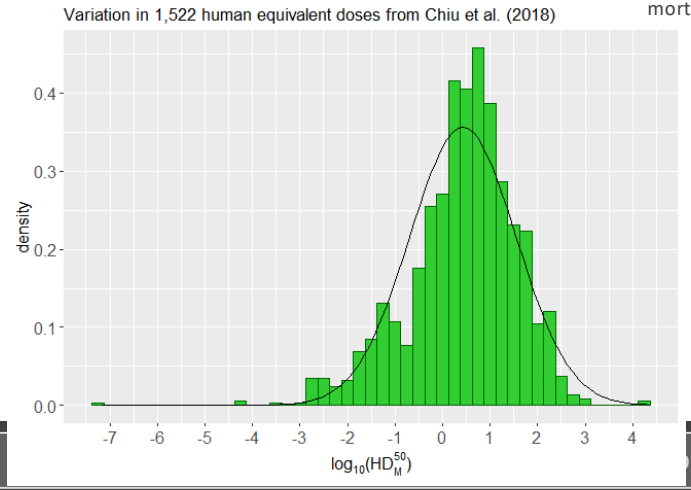
SHEDS-HT: EPA's High-Throughput Stochastic Human Exposure and Dose Simulation Model
With thanks to Kristin Issacs

Data-informed chemical potency ranges

Range of potencies can be estimated from 1,522 chemicals cataloged by Chiu et al. (*EHP* 2018), for non-cancer critical effects representing a range of subchronic and chronic effects

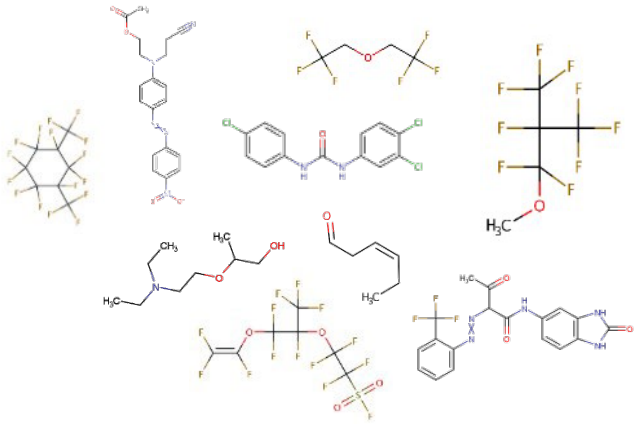
These data were used to establish a prior distribution of uncertainty in chemical toxicity in the absence of any specific knowledge about the toxicity of the chemical to be tested





Inputs for evaluation of VOI associated with ETAP or THHA

Diverse Range of 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

360 Data Driven Scenarios Examined Comparing ETAP vs Traditional HHA Process

- SHEDS-HT exposure tertiles
- Population sizes (US)
  - 33, 165, **330 million** (10, 50, **100%**)
- Time horizons
  - **20**, 40, 75 years
- Testing costs
  - THHA $1M or **$4M** (M=million)
  - ETAP **$200K** or $250K (K=thousand)
- Time from testing start to assessment finish
  - THHA 6, **8**, 14 years
  - ETAP **0.5**, 1, 2 years
- Control costs
  - $50M or **$23.1B** for 25% reduction
- Annualized health costs
  - $1K, **$10K**, $110K
- Discount rate: 3, **5**, 7%
- Uncertainty around the point-of-departure
  - SD about the mean for each assay from empirical measurements
  - Additional uncertainty added to ETAP

VOI metrics subset – 9 exposure scenarios

VOI for the Benefit – Risk Decision Maker, who seeks to balance population health costs and control (societal costs of risk reduction)

A. VOI analysis results under benefit-risk decision-making

μ_{exp}	Low						Medium						High					
σ_{exp}	Low		Medium		High		Low		Medium		High		Low		Medium		High	
Scenario	1		2		3		4		5		6		7		8		9	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
CoD ($M)	186	4,570	573	11,882	311	7,087	5,410	85,092	11,271	168,585	11,555	171,653	63,538	876,092	69,122	951,815	98,749	1,342,144
ENBS ($M)	4,175	3,423	12,868	8,906	6,988	5,310	77,908	20,184	100,873	-25,911	94,374	-36,497	-4,740	-775,121	-9,824	-848,864	-71,576	-1,283,473
ROI	20,875	856	64,342	2,226	34,941	1,327	389,540	5,046	504,365	-6,478	471,870	-9,124	-23,700	-193,780	-49,121	-212,216	-357,880	-320,868

VOI for the Target – Risk Decision Maker, who seeks to reduce potential risks when the risk is anticipated to exceed a specified target risk level

B. VOI analysis results under target-risk decision-making

μ_{exp}	Low						Medium						High					
σ_{exp}	Low		Medium		High		Low		Medium		High		Low		Medium		High	
Scenario	1		2		3		4		5		6		7		8		9	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
CoD ($M)	<0.1	25	34	4,280	99	6,620	3,635	92,335	9,665	179,665	13,076	193,751	53,590	814,446	62,467	891,921	85,817	1,187,474
ENBS ($M)	-0.01	15	765	3,205	2,214	4,960	81,658	69,231	217,121	134,712	293,743	145,275	1,203,840	610,685	1,403,232	668,778	1,927,771	890,390
ROI	-0.2	4	3,826	801	11,068	1,240	408,291	17,308	1,085,604	33,678	1,468,713	36,319	6,019,198	152,671	7,016,162	167,194	9,638,857	222,597

Expected Net Benefit from Sampling (ENBS; Larger is better) – Reduction in total social costs (includes health and control costs) adjusted for delay and cost of testing with benefits accrued over 20-year time horizon

Cost of Delay (COD, Smaller is better) - The loss in value solely due to the delay component

Return on investment (ROI, Larger is better) - The ratio between ENBS and cost of testing, reflects the economic benefits per dollar spent in testing

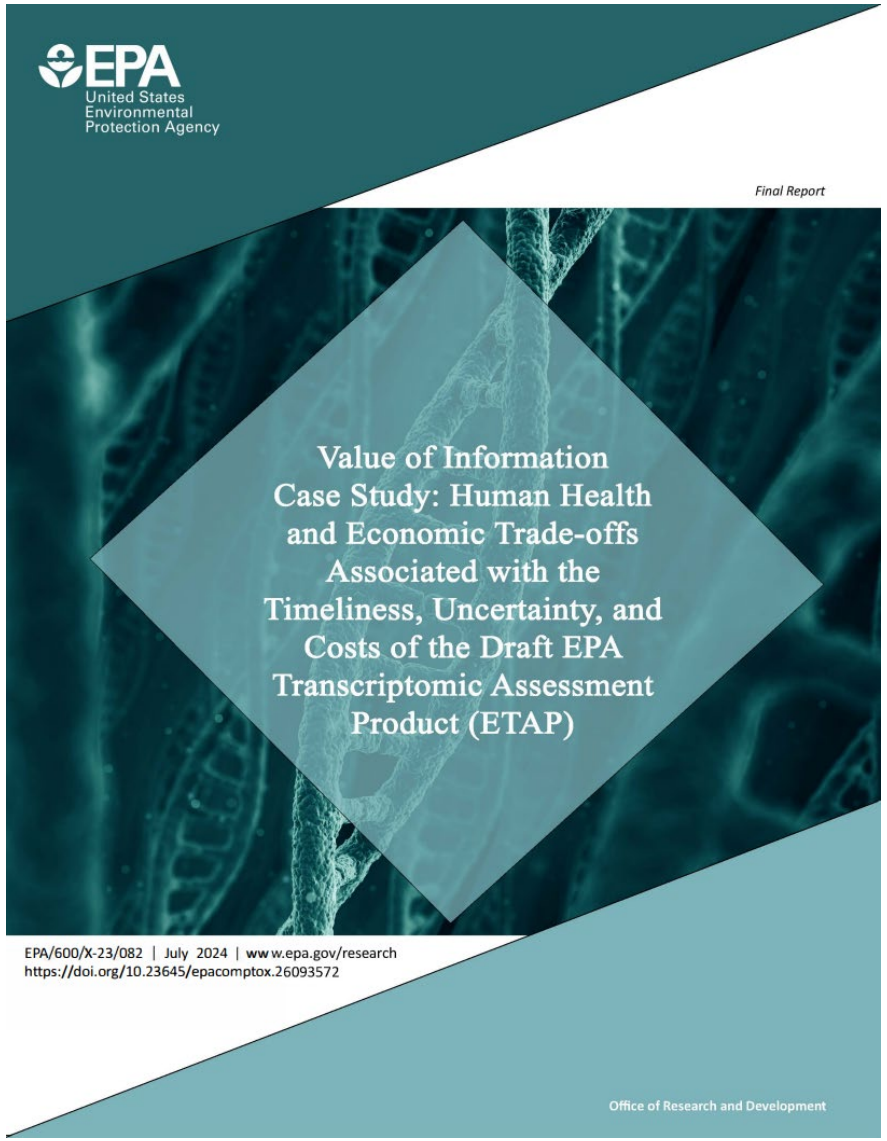
ETAP was preferred over THHA in most scenarios , time was a major factor

- The VOI Case study evaluated 360 scenarios
  - For each decision context, 9 baseline and 171 sensitivity scenarios

- Benefit-Risk Decision Maker (180 scenarios)
  - In 82% of scenarios, ETAP was preferred with favorable ROI & ENBS
  - 18% - no testing preferred
  - Average benefit was $44 billion for BRDM
- Target-Risk Decision Maker (180 scenarios)
  - ETAP was preferred in 89% of scenarios (ENBS) and 99% of scenarios (ROI)
  - 7.2% - no testing preferred
  - Average benefit was $81 billion for TRDM

VOI case study published

- In the scenarios considered, ETAP was most often the preferred method in terms of socioeconomic cost and public health benefit
- This conclusion is remarkably robust in that VOI metrics favor ETAP over the THHA across a wide range of exposure scenarios reflecting a broad range of conditions, and across sensitivity analyses for multiple parameter options
- VOI analysis could be leveraged to understand relative benefits of testing strategies, enabling contextualization of relative uncertainties in economic terms

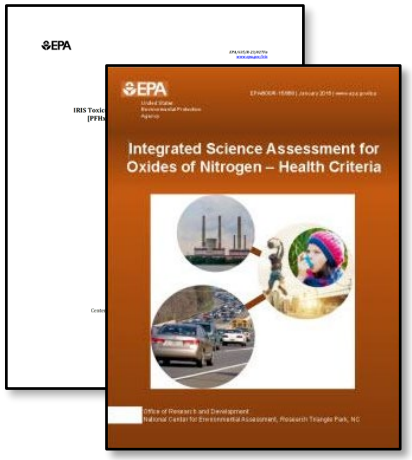


Link to VOI case study white paper - https://www.epa.gov/etap/value-information-voi-case-study-etap

ETAP joins ORD's portfolio of human health assessments

ETAP was formally adopted in March 2024. More at www.epa.gov/etap

Data-Rich **Relative Data Availability** Data-Poor



ISAs, IRIS

PPRTVs

Human Health Toxicity Assessments

Fit-for-purpose

ETAP

Longer **Relative Development Time** Shorter

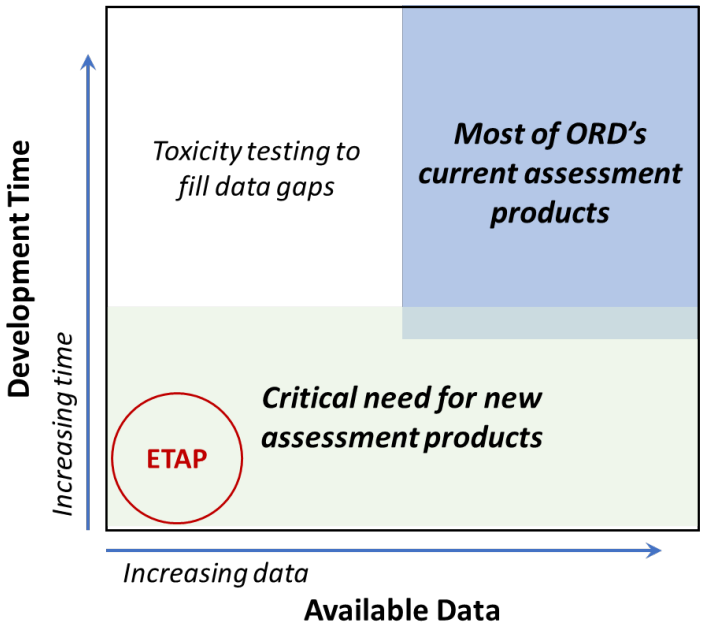
ETAP nomination process early implementation

- Nomination panel will include representatives of:
  - EPA Program Offices
  - EPA Regions
  - Environmental Council of the States (ECOS)
  - Environmental Research Institute of States (ERIS)
  - Association of State and Territorial Health Officials (ASTHO)
  - Tribal Science Council
  - National Institute of Environmental Health Sciences Division of Translational Toxicology

- Representatives will nominate chemicals for ETAP, providing rationale for selecting the chemical
- 2 meetings a year: nominations kickoff (~Nov 2024) and mid-year progress report
- ORD aims to release 3-5 ETAPs annually

Methods-based development projects may help fill the testing & assessment gap

International collaborations



Systemic

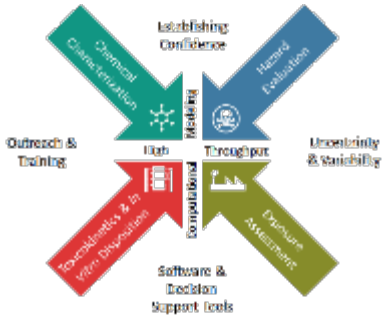
Bioactivity-based point of departure

Short-term rodent study

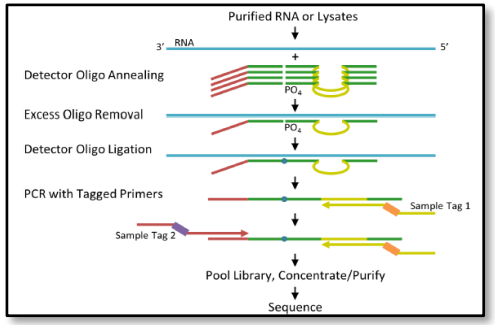
ETAP*

**Formal assessment product 2024*
Target release < 1 year

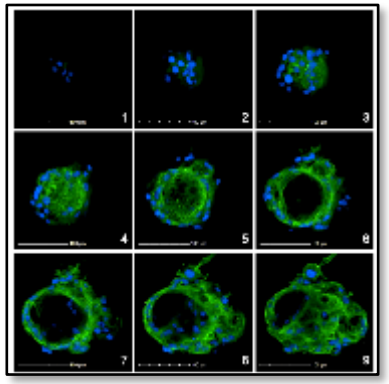
Variety of new approach methods under development at EPA



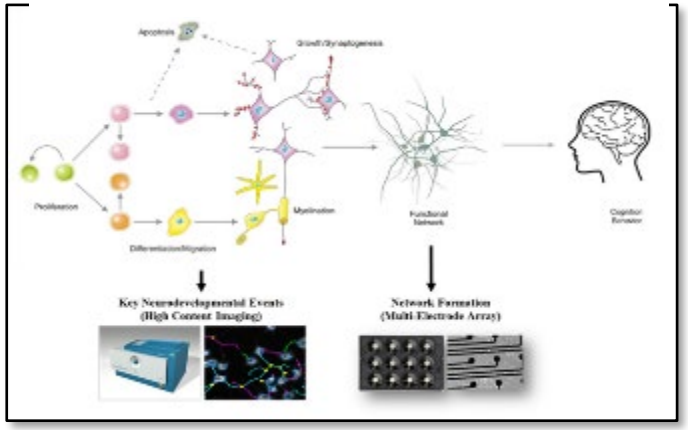
Comprehensive Transcriptomics



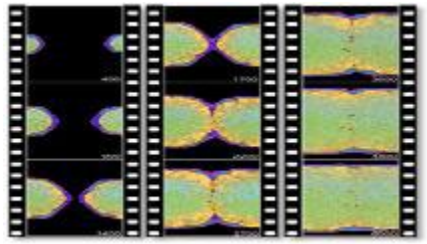
Organotypic Culture Models



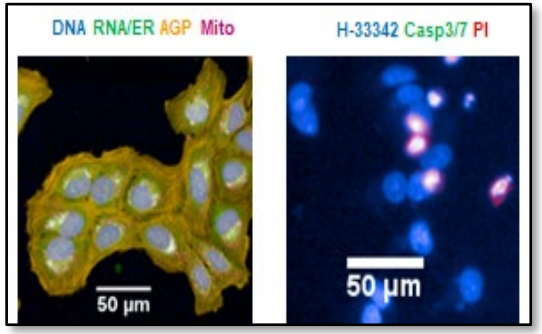
OECD Initial recommendations on evaluation of data from the DNT IVB



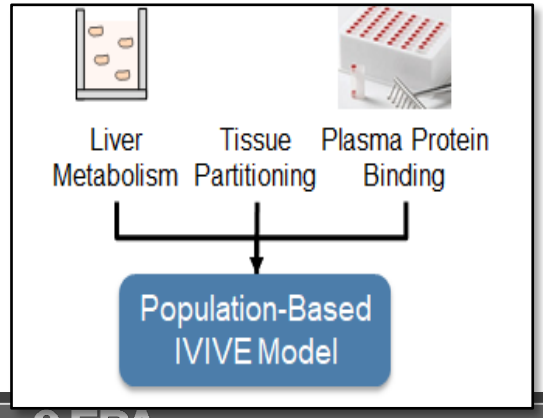
Virtual Tissue Models



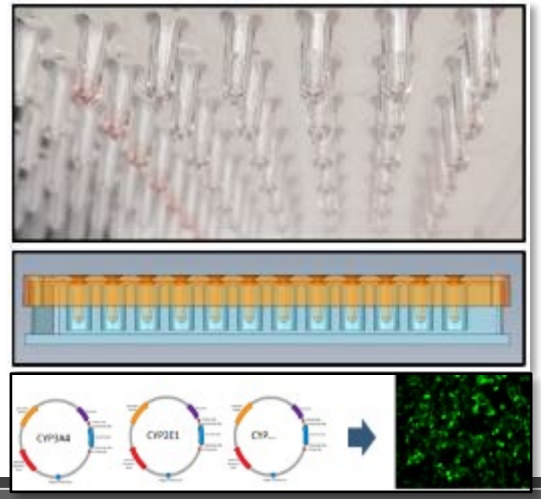
Multi-Parameter Cellular Phenotypic Profiling



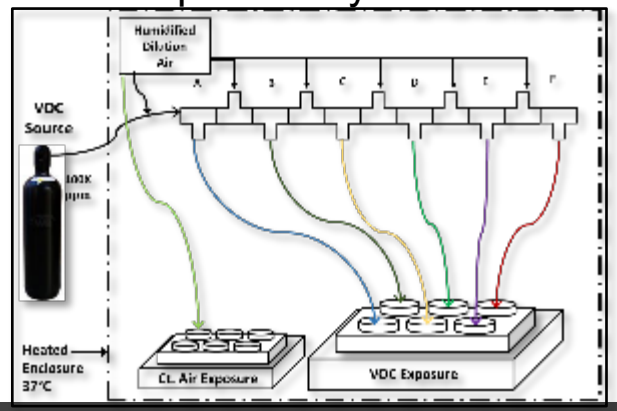
Toxicokinetic Measurements and Modeling



Metabolic Retrofitting



Volatile/Aerosol *In Vitro* Exposure Systems

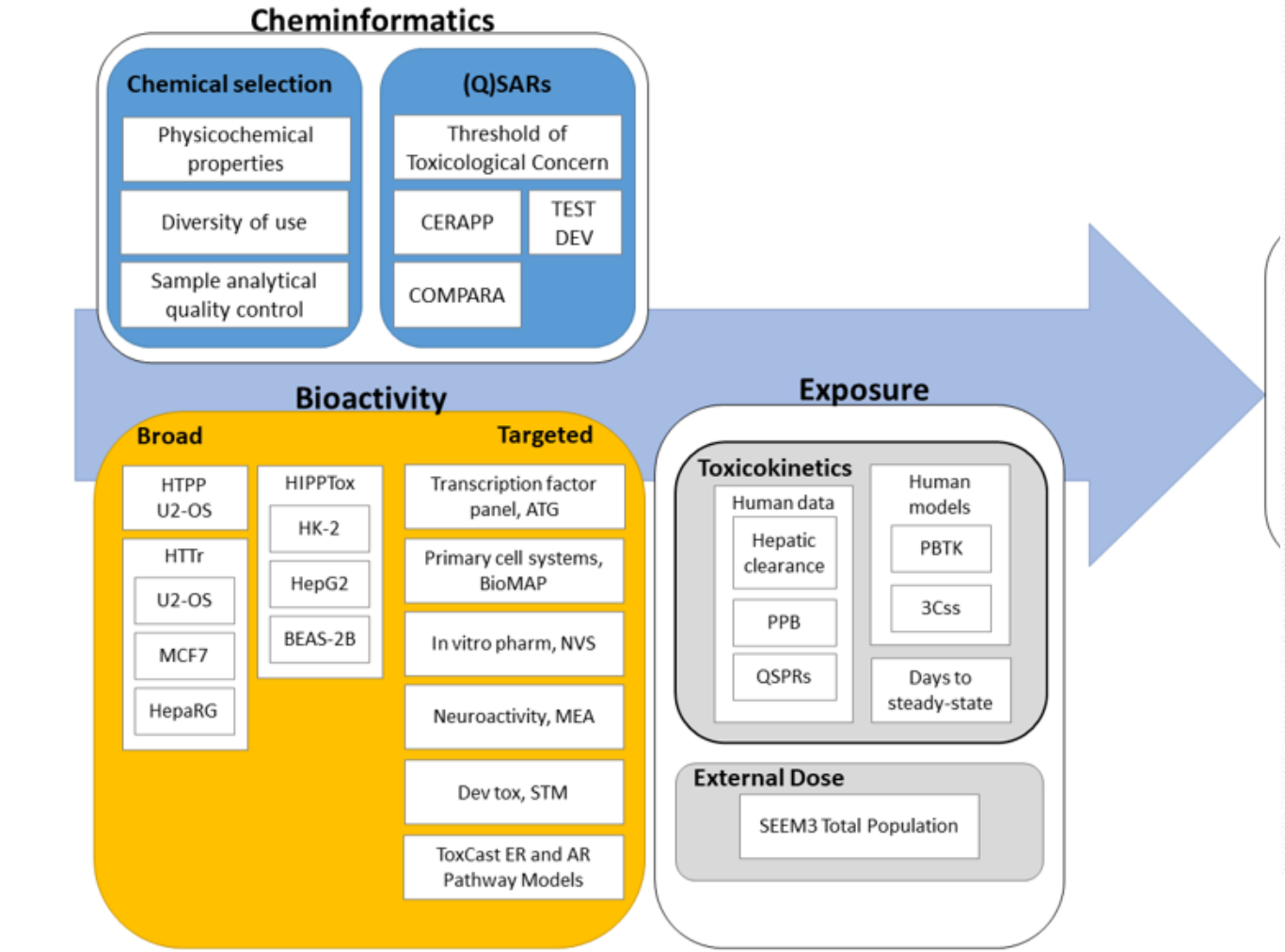


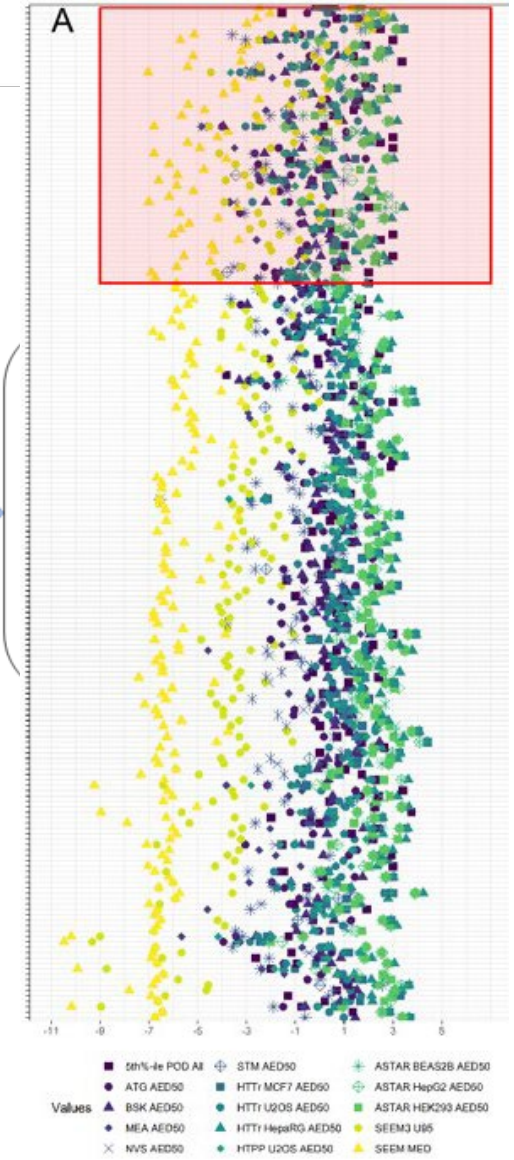
Sequence Alignment to Predict Across Species Susceptibility

APCRA: EPA-led Prospective Case Study on NAMs Integration

- 200 chemicals in ToxCast library
- Generate data
- Derive POD_{NAM}
- Estimate bioactivity:exposure ratio (BER)
- Evaluate hazard flags

Collaboration between EPA, ECHA, JRC, Health Canada





APCRA: Accelerating the Pace of Chemical Risk Assessment

Katie Paul Friedman et al, *in prep.*

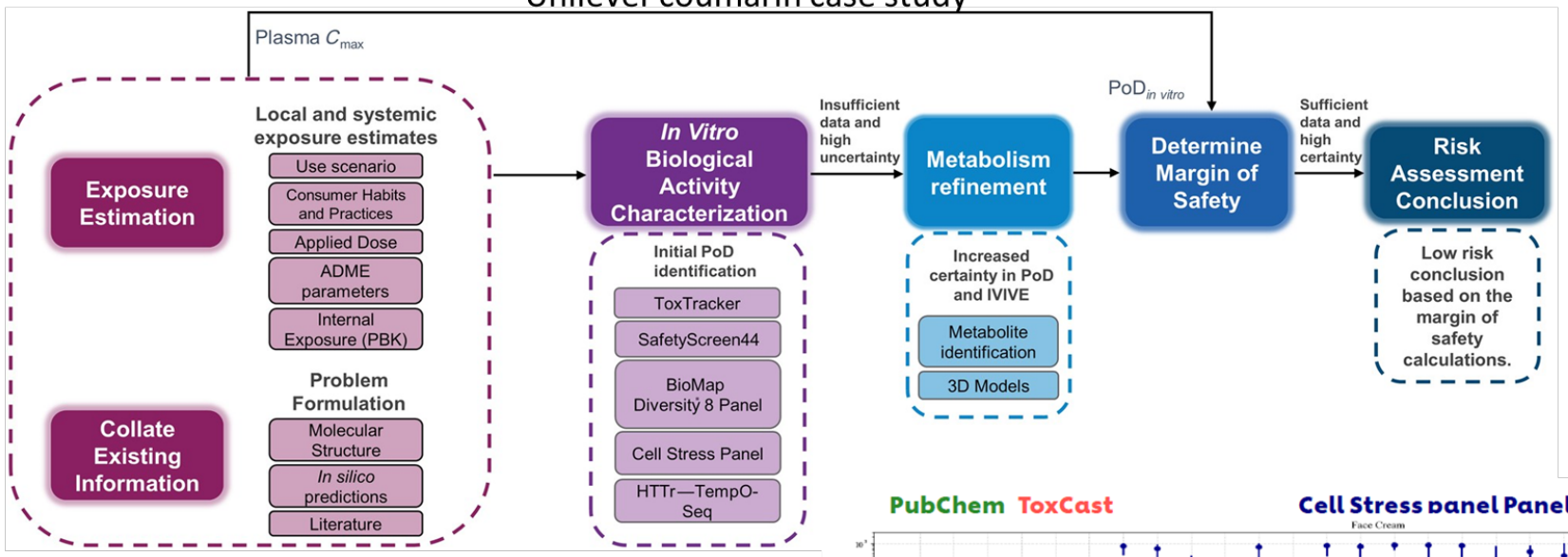
Linking testing modalities to evaluate systemic toxicity toolbox

- Recent advances in methods lend to development of:
  - Hazard-based toxicity testing products
  - Bioactivity and exposure-based screening methods

OECD NAMs & systemic tox expert group formed 2024

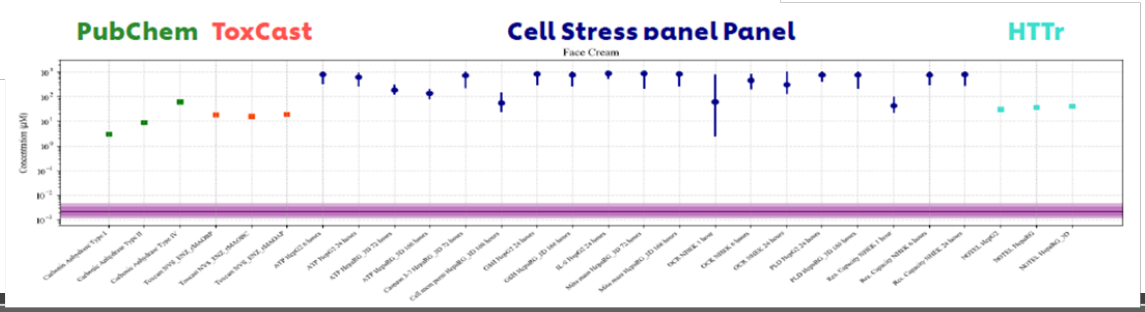
CRADA project collaboration between EPA and Unilever

Unilever coumarin case study



CRADA project:
Cell line selection
Metabolism
In vitro disposition
Cross-species eval
Httr & HTPP

For coumarin, a safety assessment based on non-animal approaches was at least as protective as the risk assessment based on traditional approaches



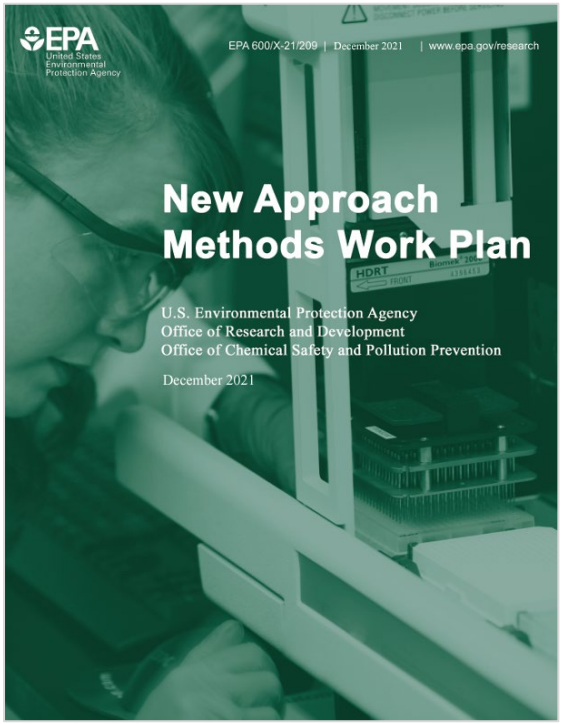
Baltazar et al. *Tox Sci*, Volume 176, Issue 1, July 2020

Building confidence in new approaches requires frameworks at multiple scales

Efforts with EPA partnership and leadership

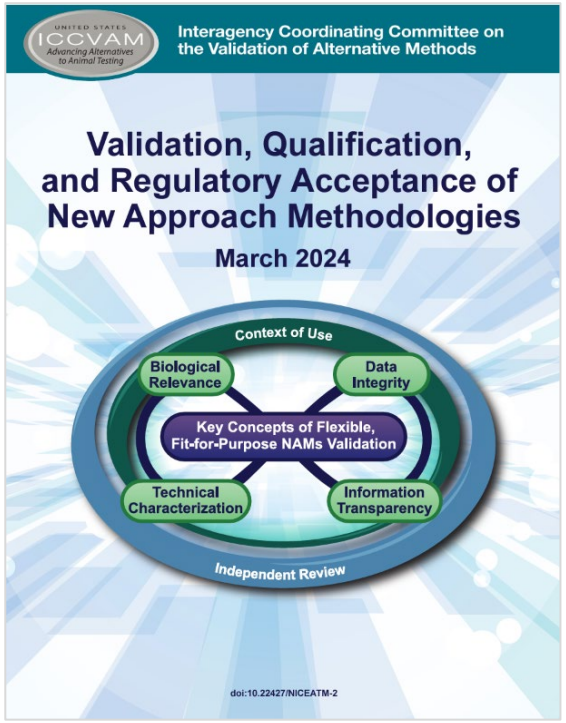
US EPA NAM Workplan

Confidence framework coming soon



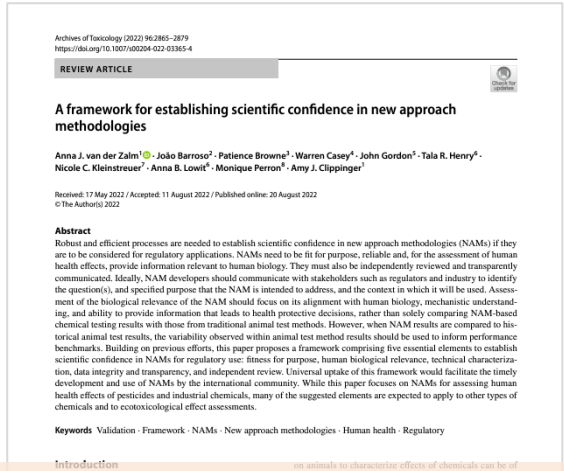
https://www.epa.gov/chemical-research/new-approach-methods-work-plan

US Interagency framework



https://ntp.niehs.nih.gov/sites/default/files/2024-03/VWG_Report_27Feb2024_FD_508.pdf

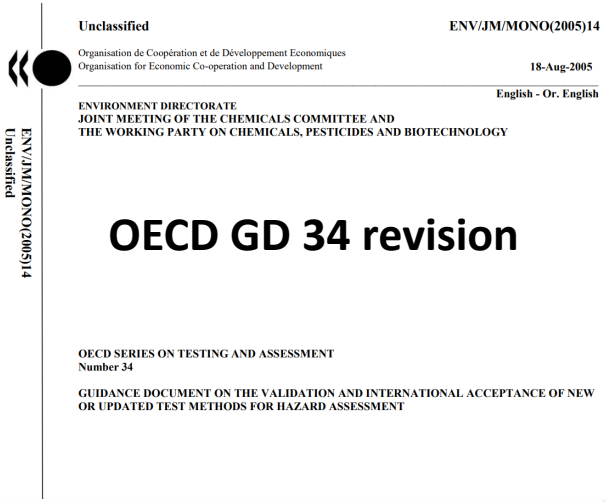
International scientific principles



PETA Science Consortium International
European Commission, Joint Research Centre
Organisation for Economic Co-Operation and Development (OECD)
National Institutes of Health
US Consumer Product Safety Commission
US Environmental Protection Agency
Interagency Center for the Evaluation of Alternative Toxicological Methods (ICCVAM)

https://pubmed.ncbi.nlm.nih.gov/35987941/

International OECD framework



US, JRC, Netherlands co-leading project to **modernize** OECD guidance (GD 34) on validation and international acceptance of new and updated test methods for hazard assessment.

Conclusions

- ETAP joins ORD's portfolio of human health assessment products
- The VOI analysis framework developed by EPA suggests socioeconomic benefits to the public of using ETAP under a wide variety of data-informed scenarios
- EPA ORD continues to pursue innovative technologies in developing NAMs and advancing their use in decision making as a key component of the science-to-action mission

https://www.epa.gov/etap/

Thank you

CCTE and CPHEA collaborators on the ETAP & VOI Teams, contractor Risk Sciences International, CSS & HERA National Program Directorates, ORD IOAA, and collaborators at the NIEHS/DTT

Have questions about ETAP? Contact me at harrill.alison@epa.gov

Upcoming Webinars

EPA hosts webinar series dedicated to delivering the latest information and training on our cutting-edge research addressing environmental and public health issues.

If you are interested in upcoming webinars, stay up-to-date with email notifications:

Webinar dates and topics are subject to change.

Small Drinking Water Systems

August 27: *Consolidation, Restructuring, Partnerships, and Regionalization*

Registration and Additional Information

Healthy and Resilient Communities Research

September 10: *Brownfields, Gentrification, and Environmental Justice Research: Learning from Past Experiences*

Registration and Additional Information

Emergency Response Research

September 11: *Premise Plumbing and Wildfires*

Registration and Additional Information

Computational Toxicology and Exposure Communities of Practice

September 26: *Using Environmental RNA to Understand the Effects of Pollution on Aquatic Ecosystems*

Registration and Additional Information