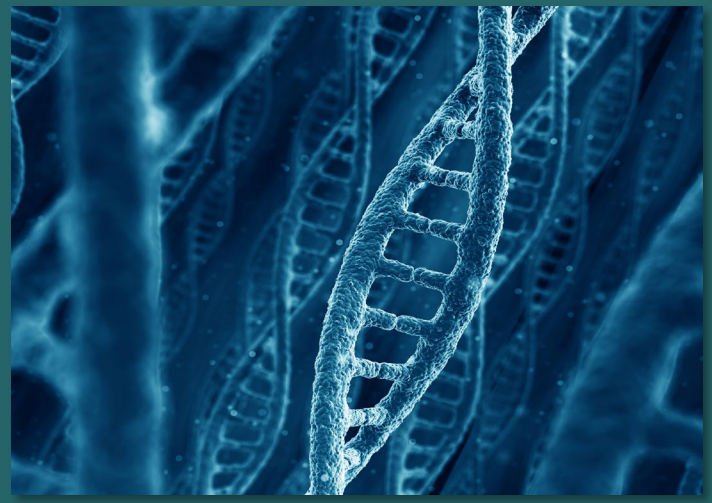
ETAP Day 1 Agenda and Charge Questions

Rusty Thomas
Director, Center for Computational Toxicology and Exposure



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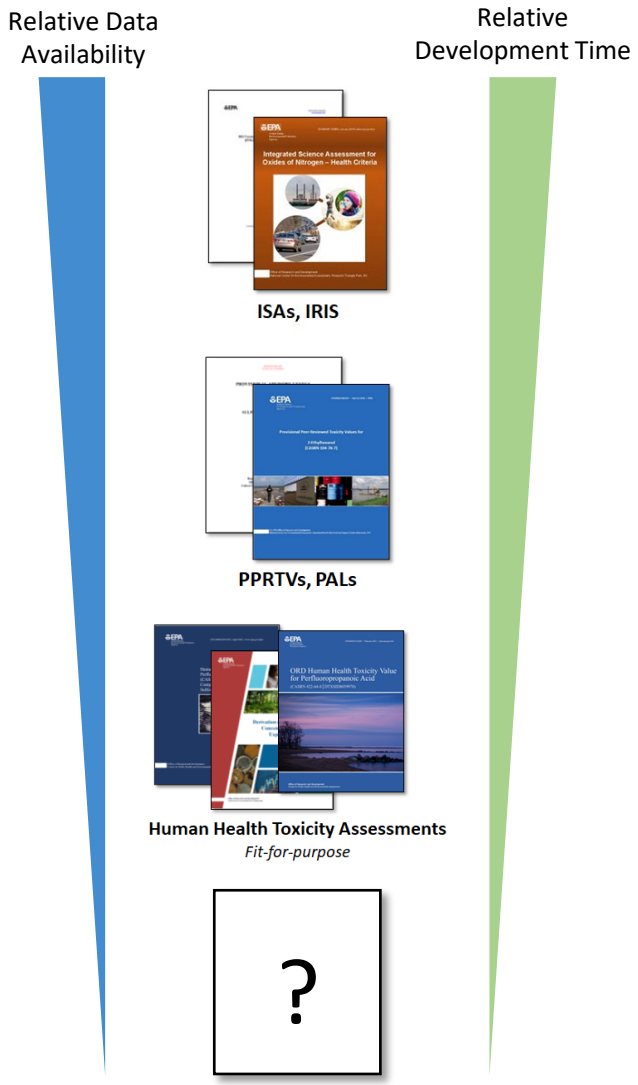
ETAP Goals and Objectives

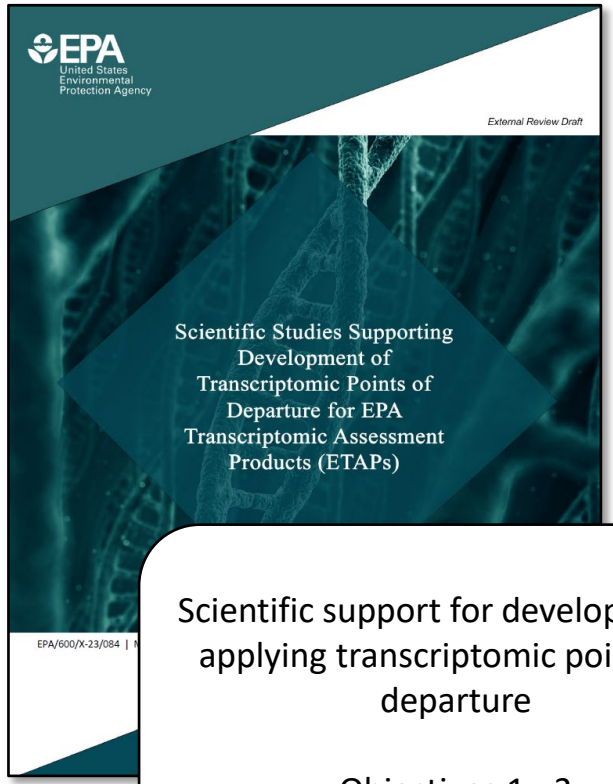


Goal: Develop and operationalize a new US EPA human health assessment product for data poor chemicals that can be completed from chemical procurement to publication of the assessment in < 9 months

Objectives:

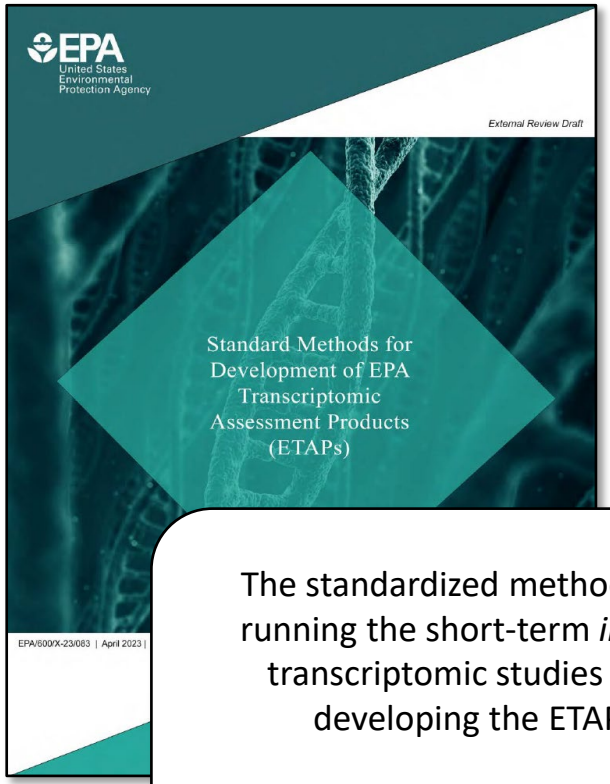
1. Review of relevant literature
2. Refine dose response analysis methods for standardized study design
3. Compare error in concordance with variability in toxicity studies
4. Develop standardized method for the EPA Transcriptomic Assessment Product (ETAP)
5. Compare transcriptomic reference values with 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 Series of Three EPA Reports



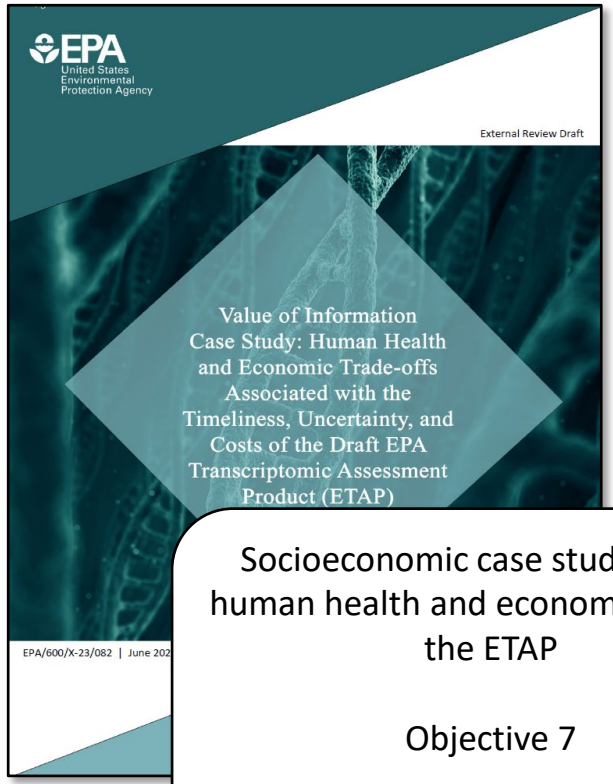
Scientific support for developing and applying transcriptomic points-of-departure

Objectives 1 - 3



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

Objectives 4 - 6

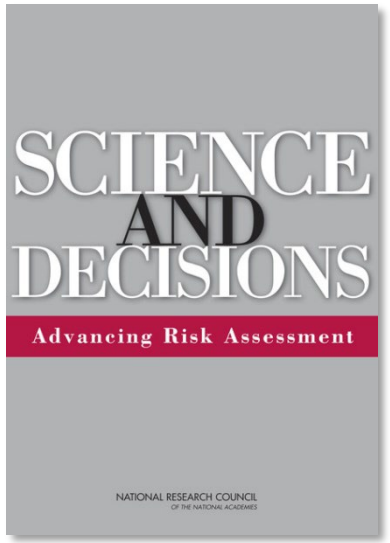


Socioeconomic case study on the human health and economic value of the ETAP

Objective 7

(Not part of this BOSC Review)

Background on the Socio-Economic Case Study



NASEM, 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 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 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 of 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

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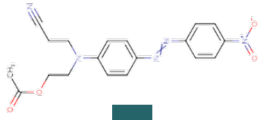
Hagiwara *et al., Risk Anal*, 2022



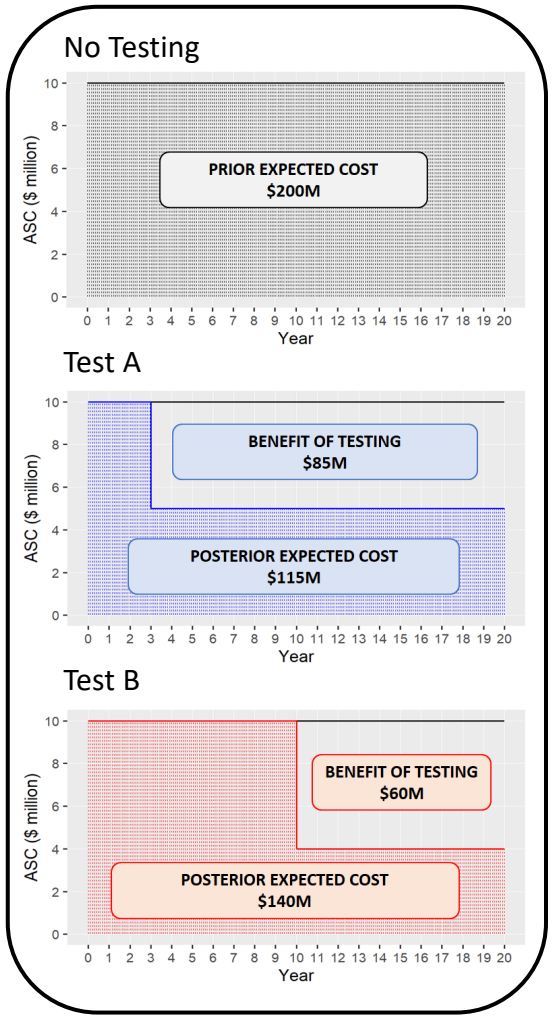
Exposure Level
Population Variability in Exposure
Affected Population Size
Health Effects
Population Variability in Toxicity
Control Costs

Relevant Chemical Characteristics

Uncertainty in Effect Level
Timeliness
Cost

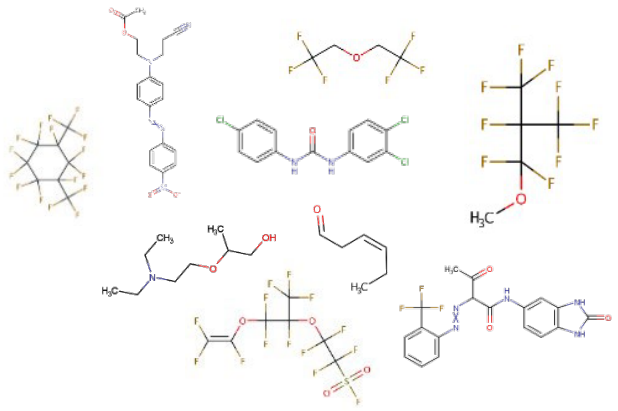
Toxicity Testing Characteristics

Regulatory Decision Context → VOI metrics →



Adapting Framework to Evaluate Range of Benefits For Data Poor Chemicals

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

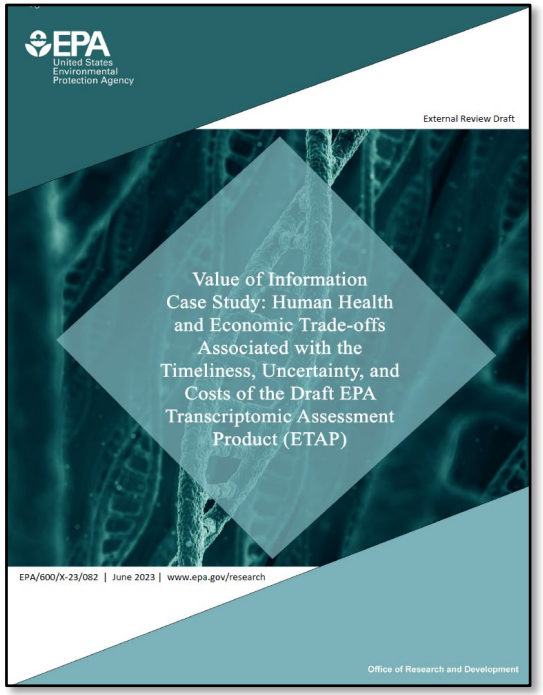
Regulatory Decision Context

Bounded Range of VOI Metrics

306 Data Driven Scenarios Examined Comparing ETAP vs Traditional Testing and Assessment 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

Brief Results Summary of the Socio-Economic Case Study

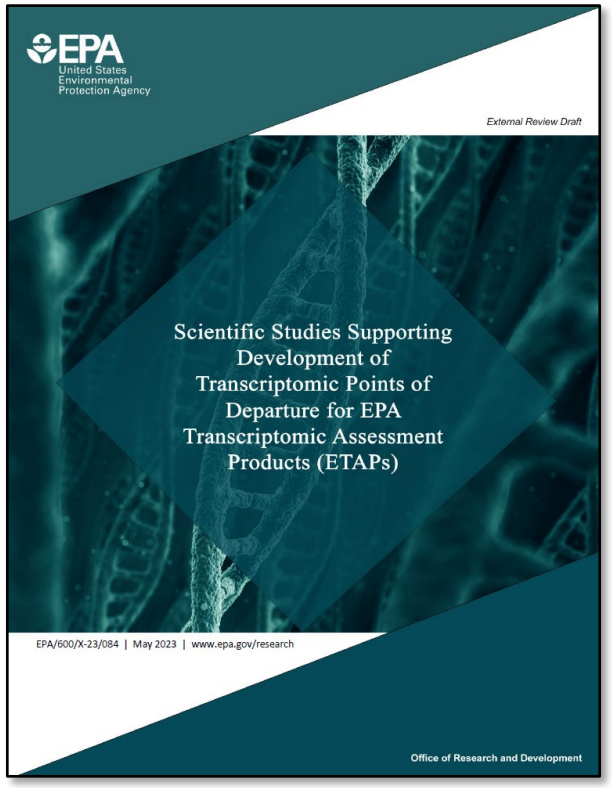


https://www.epa.gov/bosc/voi-july-25-26-2023-meeting

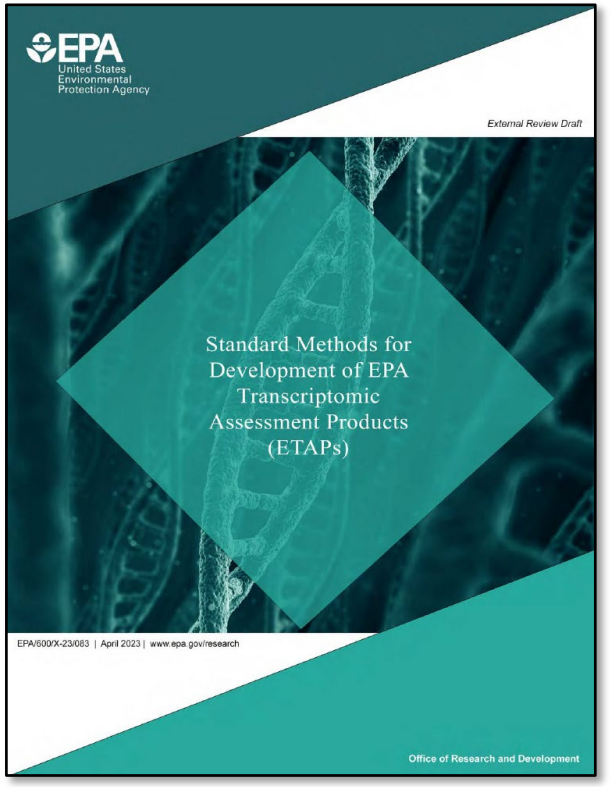
- A socio-economic analysis of the trade-offs in the timeliness, uncertainties, and costs showed that the ETAP was favored over the traditional toxicity testing and human health assessment process in most of the scenarios examined
- For benefit-risk decisions, the ETAP was favored 81% of the time, while the remaining 19% favored neither ETAP or traditional process
- For target-risk decisions, the ETAP was favored between 89 – 99% of the time, while 9% favored neither ETAP or traditional process
- Across all scenarios evaluated, the median difference between ETAP and the traditional process in one VOI metric, the Expected Net Benefit of Sampling (ENBS), was $47B for benefit-risk decisions and $81B for target-risk decisions
- Negative values for ENBS were more frequently observed for the traditional process in the benefit-risk decision context, suggesting that the delay and costs associated with testing and decision-making were greater than the eventual benefit in some scenarios

BOSC Agenda Divided Based on Topics in the Two ETAP Reports

Day 1



Day 2



ETAP BOSC Review Agenda – Day 1

Time	Duration	Topic	Speaker
9:00-9:10 am	10 minutes	Welcome	Maureen Gwinn
9:10-9:20 am	10 minutes	Introduction to the Panel	Tom Tracy
9:20-9:45 am	25 minutes	EPA ORD Portfolio Approach and Where ETAP Fits	Samantha Jones
9:45-10:00 am	15 minutes	Day 1 Agenda, Introduction of ETAP Team, and Charge to the Panel (Review Charge Qs)	Rusty Thomas
10:00-10:30 am	30 minutes	Break	
10:30-11:00 am	30 minutes	Science Support Introduction/Background	Alison Harrill
11:00-11:30 am	30 minutes	Literature Review	Leah Wehmas
11:30-12:00 pm	30 minutes	NTP Genomics Report Overview	Scott Auerbach
12:00- 1:00 pm	60 minutes	Working Lunch 12:00-12:30 pm Break 12:30-1:00 pm Discussion of Panel Roles and Responsibilities	
1:00-1:30 pm	30 minutes	Dose Response Methods and Parameter Refinement	Logan Everett
1:30-2:00 pm	30 minutes	Concordance Analysis with Inter-study Variability	Kelsey Vitense
2:00-2:10 pm	10 minutes	Summary	Alison Harrill
2:10-2:30 pm	20 minutes	Break	
2:30-3:30 pm	60 minutes	Facilitated Panel Q/A	Co-Chairs: Craig and Katherine
3:30– 4:30 pm	60 minutes	Public Comment Period	Facilitator: Tom Tracy
4:30 – 4:45 pm	15 minutes	Wrap Up	Annette Guiseppi-Elie
4:45 – 5:45 pm	60 minutes	Break up into Charge Question groups 1-4 and Initial Discussions (closed session)	Co-Chairs: Craig and Katherine

ETAP Team Introductions


Rusty Thomas
(EPA CCTE)


Leah Wehmas
(EPA CCTE)


Alison Harrill
(EPA CCTE)


Sarah Davidson-Fitz
(EPA CCTE)


Logan Everett
(EPA CCTE)


Michael Hughes
(EPA CCTE)


Grace Patlewicz
(EPA CCTE)


Susan Hester
(retired)


Jason Lambert
(EPA CCTE)


Kelsey Vitense
(EPA CCTE)

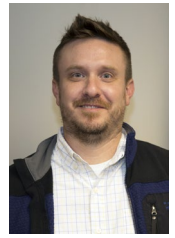

Mike Devito
(EPA CCTE)

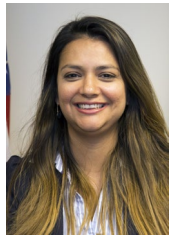

John Cowden
(EPA CCTE)


Kris Thayer
(EPA CPHEA)


Scott Auerbach
(NIEHS DTT)


Warren Casey
(NIEHS DTT)


Jeffrey Dean
(EPA CPHEA)


Lucina Lizarraga
(EPA CPHEA)


Roman Mezencev
(EPA CPHEA)


Avanti Shrike
(EPA CPHEA)


Dan Chang
(EPA CCTE)

Individuals in blue will be presenting to the committee

Structure for Responses to Charge Questions

- Response categories
  - **Tier 1: Recommendations** – Responses necessary to adequately support scientific basis of the ETAP and implementation as a new ORD assessment product or to improve clarity of the presentation.
  - **Tier 2: Suggestions** – Responses for EPA to consider to strengthen the scientific basis of the ETAP and implementation as a new ORD assessment product or to improve clarity of the presentation.
  - **Tier 3: Future Considerations** – Advice you may have for scientific exploration or research to inform future work.

Review of Charge Questions

1. Given the literature review and the data analysis presented in the documents, please comment on whether the approach outlined for transcriptomic benchmark dose analysis and gene set summarization following a 5-day *in vivo* exposure are clearly described and provide a scientifically supportable estimate of the point-of-departure for chronic toxicity for data poor chemicals. (Topic primarily covered in Day 1)
2. EPA has proposed standard uncertainty factors to account for intraspecies variability (UF_H), interspecies differences (UF_A), database limitations (UF_D), duration (UF_S), and LOAEL-to-NOAEL extrapolation (UF_L) in the standard methods document. Are the uncertainties in the derivation of the reference values clearly described, and are the uncertainty factors scientifically justified? (Topic primarily covered in Day 2)

Review of Charge Questions

3. To facilitate timely development and release of ETAPs, EPA is proposing to have the standard methods document undergo peer-review. Individual ETAP reports based on these peer-reviewed methods would undergo internal technical and quality control review but not need to be individually peer-reviewed externally. Please comment on this proposed approach. (Topic primarily covered in Day 2)
4. To facilitate rapid development and review of each ETAP, the results from the systematic evidence mapping, 5-day transcriptomic study, and TRV derivation are compiled and reported in a standardized ETAP reporting template with minimal free-form text. The ETAP template and an example ETAP using empirical data are provided for your review. Please comment on the extent to which the content and format of the reporting template and the example ETAP provide the important quantitative human health assessment information for a data poor chemical, with suggestions for improvement if warranted. (Topic primarily covered in Day 2)