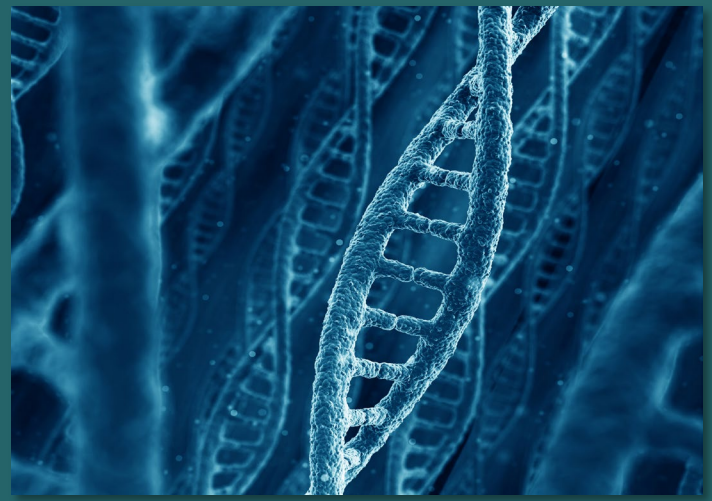
Design of the VOI Case Study

Alison Harrill, Ph.D. – Associate Director for Toxicology



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

Objectives

- Discuss features of the two-year bioassay and traditional human health assessment process
- Summarize the proposed EPA Transcriptomic Assessment Product
- Provide an overview of the VOI case study

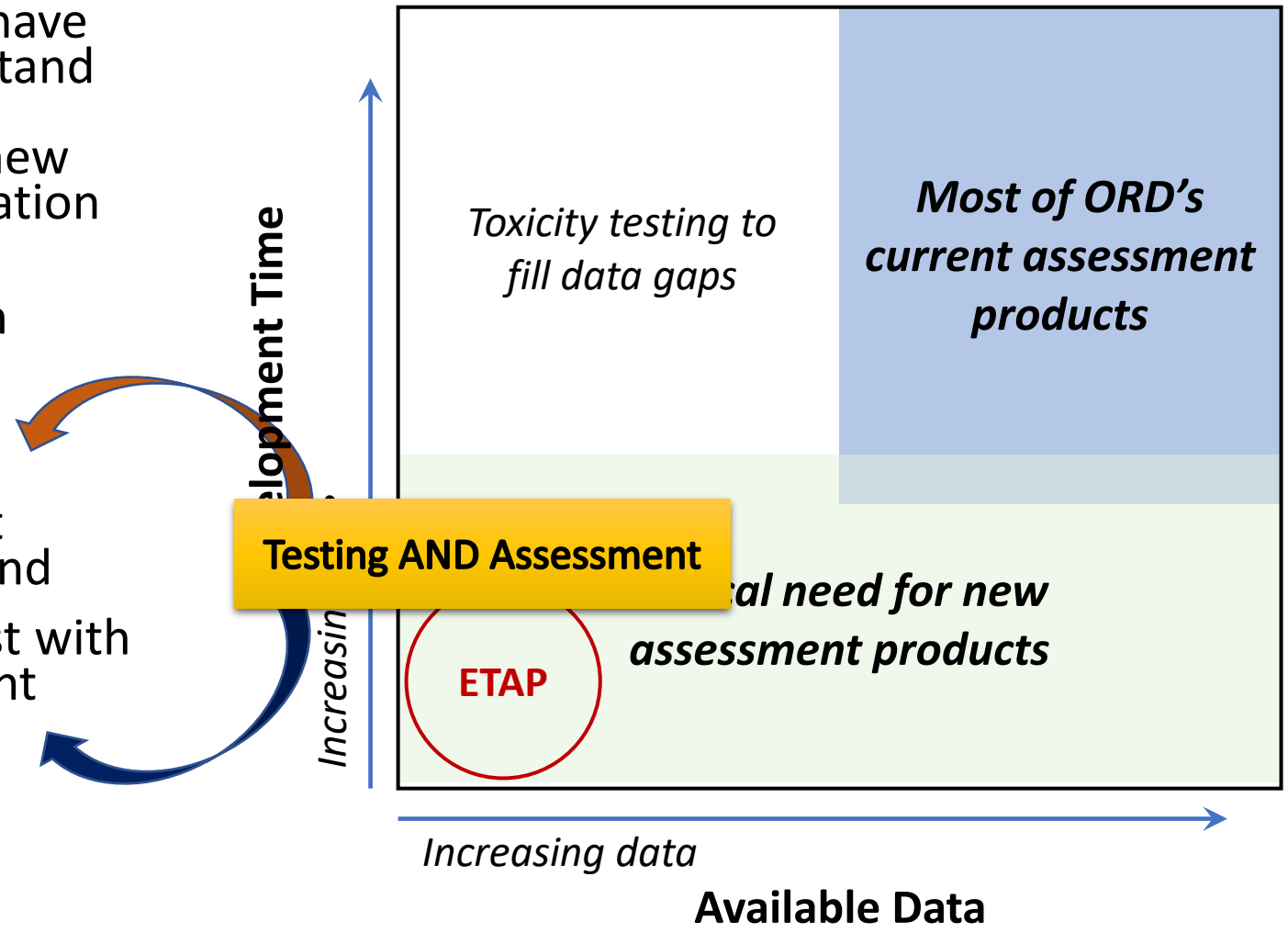
Case Study Objective

- The present report uses the VOI framework developed by EPA ORD (Hagiwara et al. 2022) in a case study to evaluate the human health and economic trade-offs associated with the timeliness, uncertainty reduction, and costs of different toxicity testing and assessment approaches

The Case Study

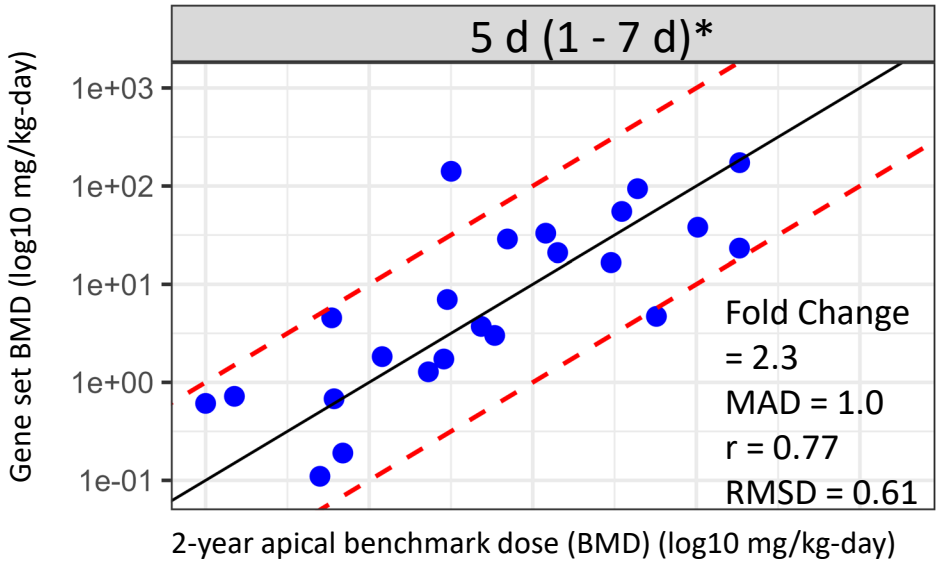
- For regulatory agencies, case studies have served as an important tool to understand the strengths and weaknesses of new methods and to gain familiarity with new methods or approaches before application (Kavlock *et al.* 2018)
- The case study focuses on comparison between two options:

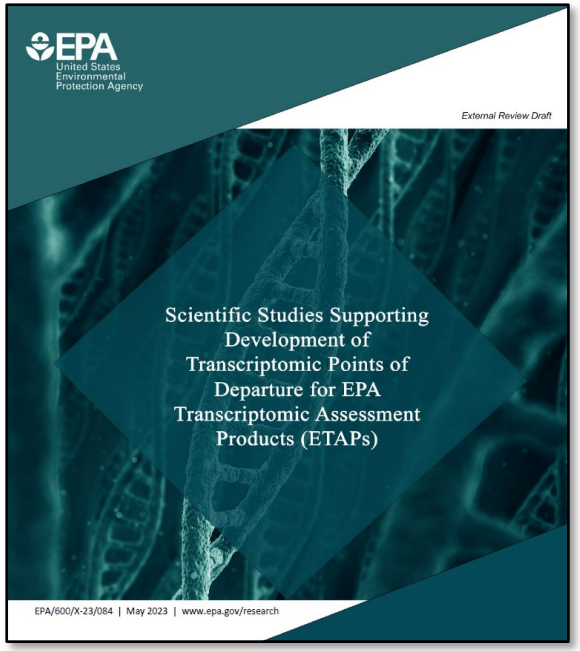
1. five-day, repeated dose *in vivo* transcriptomic study and the EPA Transcriptomic Assessment Product process [referred to as the **ETAP**]; and
2. two-year rodent chronic toxicity test with traditional human health assessment process [referred to as **THHA**].



Why Compare ETAP to the Bioassay?

- The two-year rodent chronic toxicity test was selected as the basis for comparison since the PODs from the five-day, repeated dose in vivo study showed robust concordance with the PODs from the chronic studies
- For the purposes of the case study, the THHA is assumed to be the gold standard that the ETAP is compared against





POD: point of departure | BMD: Benchmark dose | MAD: median absolute difference | RMSD: root mean squared difference

Traditional Human Health Assessment (THHA)

- Two-year rodent bioassay toxicity testing method is used to determine adverse health effects that may arise due to prolonged and repeated exposure to a substance
  - 3 dose levels + vehicle group
  - 50 male and 50 females per group
  - clinical observations, clinical chemistry, and histopathology

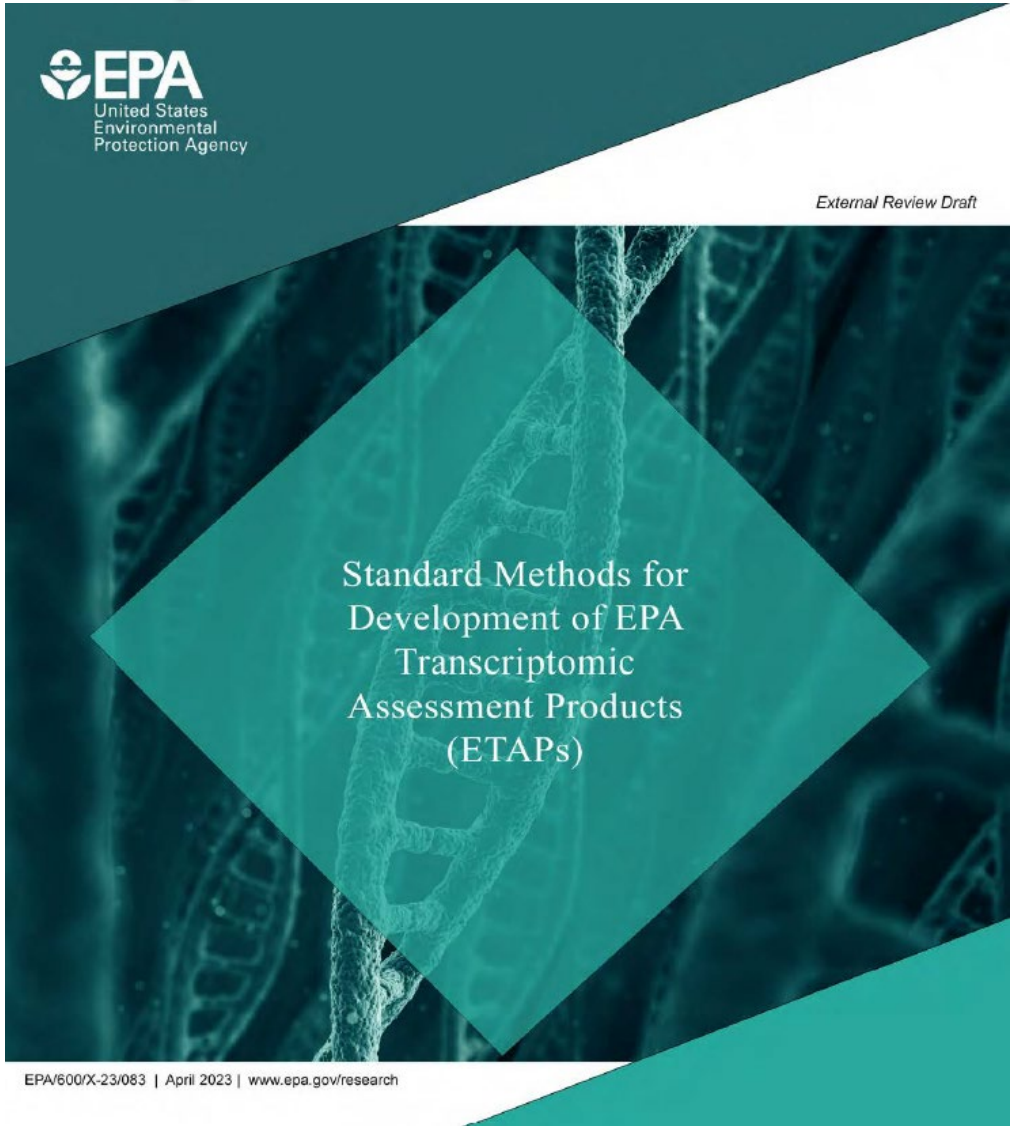
- Histopathology findings are frequently subjected to additional independent review by a pathology working group to gain agreement on the endpoints and responses identified (Bucher 2002)

Traditional Human Health Assessment (THHA)

- The process within the EPA to develop a human health assessment for existing substances involves multiple steps:
  - Problem formulation and scoping to identify the regulatory need, specific environmental or exposure conditions, and specific assessment questions to be answered
  - Relevant animal and human studies compiled and evaluated for quality, consistency, and relevance, often using systematic review principles
  - The hazard evidence is integrated for each health outcome and the studies are selected for dose-response assessment
  - Critical effect(s) is identified and used to derive reference values using appropriate uncertainty factors (UFs) that capture important experimental, variability, and extrapolation considerations
  - Human health assessments undergo a multi-step intra- and inter-organization review process, external peer review, public comment period, revision process, and finalization of the document for publication
- The case study performed in this report assumes that a two-year rodent bioassay was used as the basis of the critical effect(s) to derive the reference value

The ETAP is a Short-Duration Study that Derives a Transcriptomic POD

- The ETAP rationale and methods are under consideration by the EPA's ORD as a new human health assessment product and documentation are undergoing parallel review by an *ad hoc* BOSC panel (July 11-12, 2023)



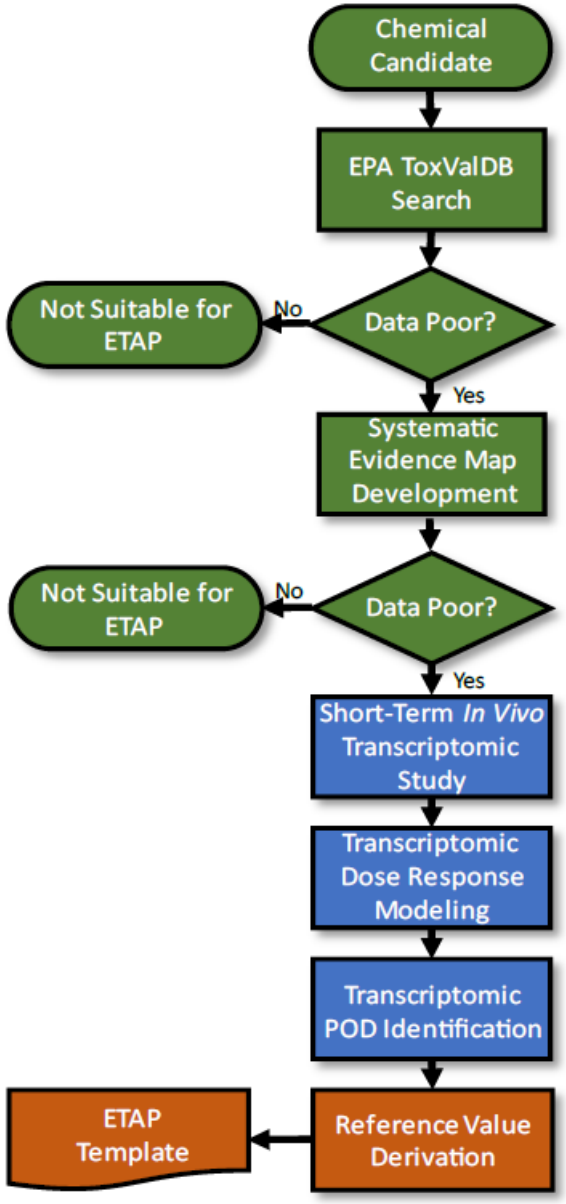
Purpose and Applicability

- *Standard Methods for Development of EPA Transcriptomic Assessment Products (ETAPs)* (EPA 2023) details methods used to derive a transcriptomic reference value (TRV) for use in the ETAP by EPA's ORD.
  - Transcriptomics entails large-scale measurement of gene expression changes and application to toxicology enables broad characterization of biological processes impacted following chemical exposure
  - TRV is defined as an estimate of a daily oral dose that is likely to be without appreciable risk of adverse effects following chronic exposure
  - While a TRV is expressly defined as a chronic value in an ETAP, it may also be applicable across other exposure durations of interest including short-term and subchronic.

- The scientific rationale is provided in EPA report *Scientific Studies Supporting Development of Transcriptomic Points of Departure for EPA Transcriptomic Assessment Products (ETAPs)* (EPA 2023).

Purpose and Applicability

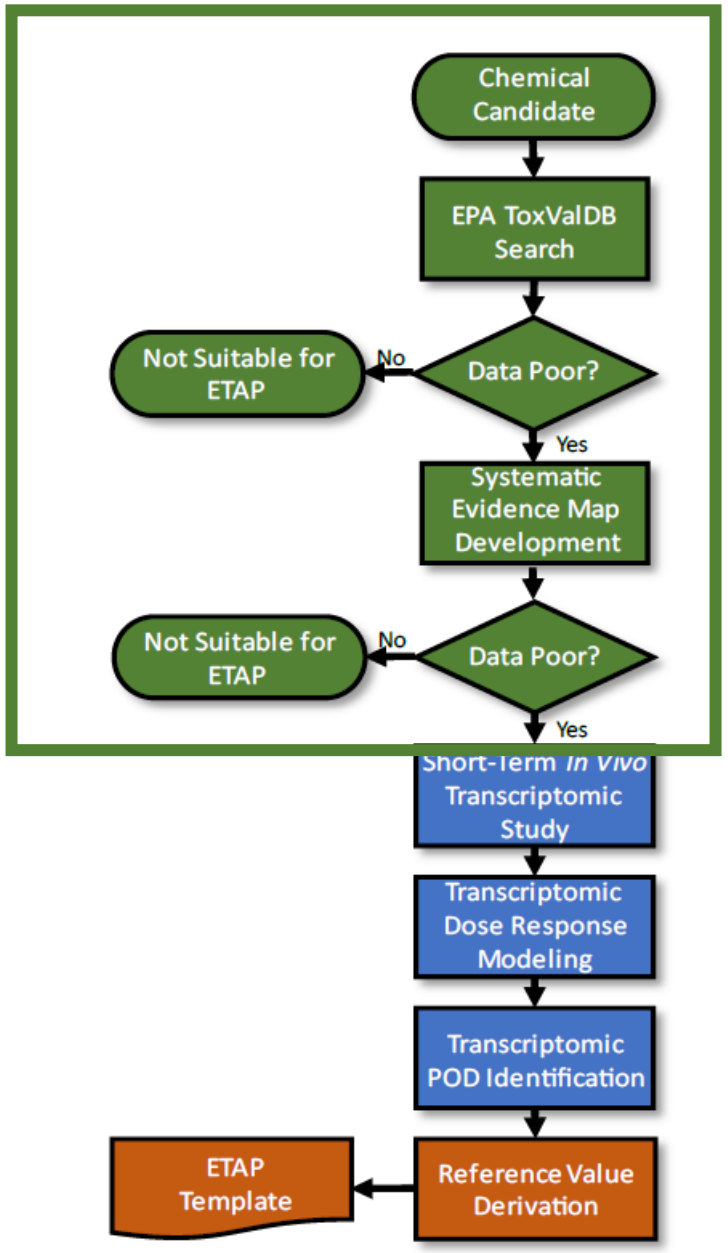
- The ETAP is intended to be applied to data poor substances
  - No existing or publicly accessible repeated dose toxicity studies or suitable human evidence
- ETAP TRVs may be updated to incorporate new data or methods that might impact the estimated reference values
- ETAP TRVs may be retired if traditional toxicity studies and an associated human health assessment are published



Method Overview

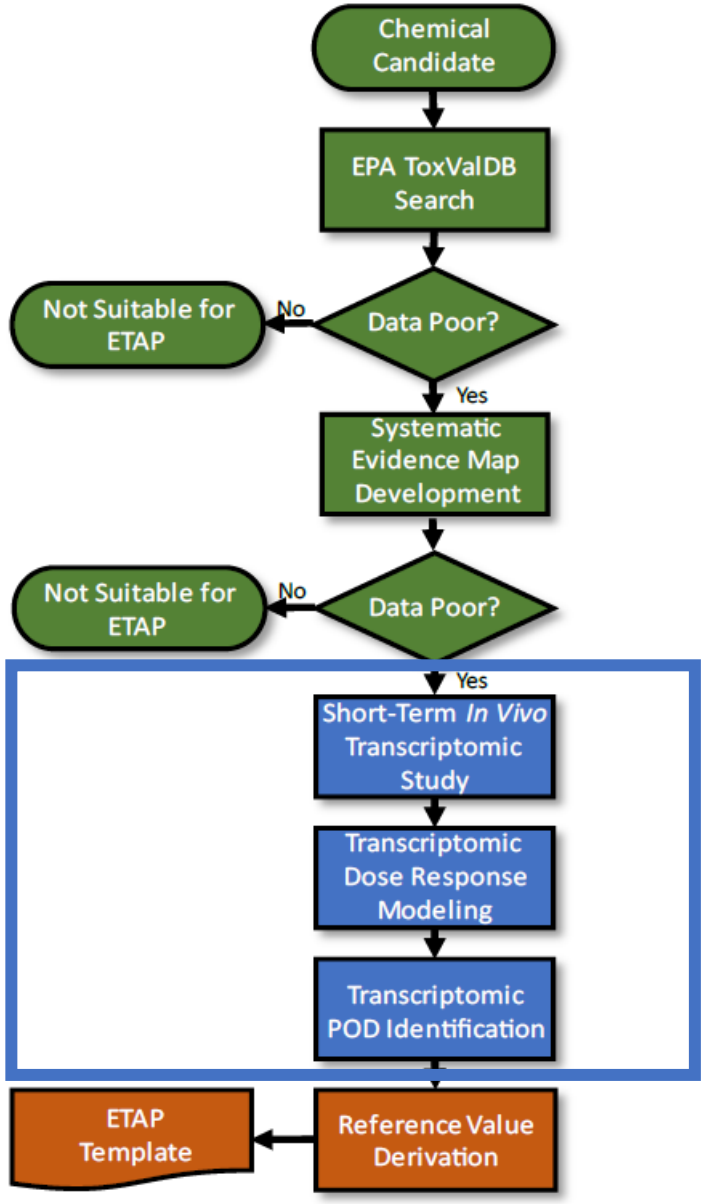
- The combination of standardized methods and streamlined review process is intended to facilitate expedient development, execution, and release of the assessment

- ETAP consists of 3 primary components:
  1. Initial database search and systematic evidence map development
  2. Short-term *in vivo* transcriptomic study for point-of-departure (POD) identification
  3. Assessment development and reporting



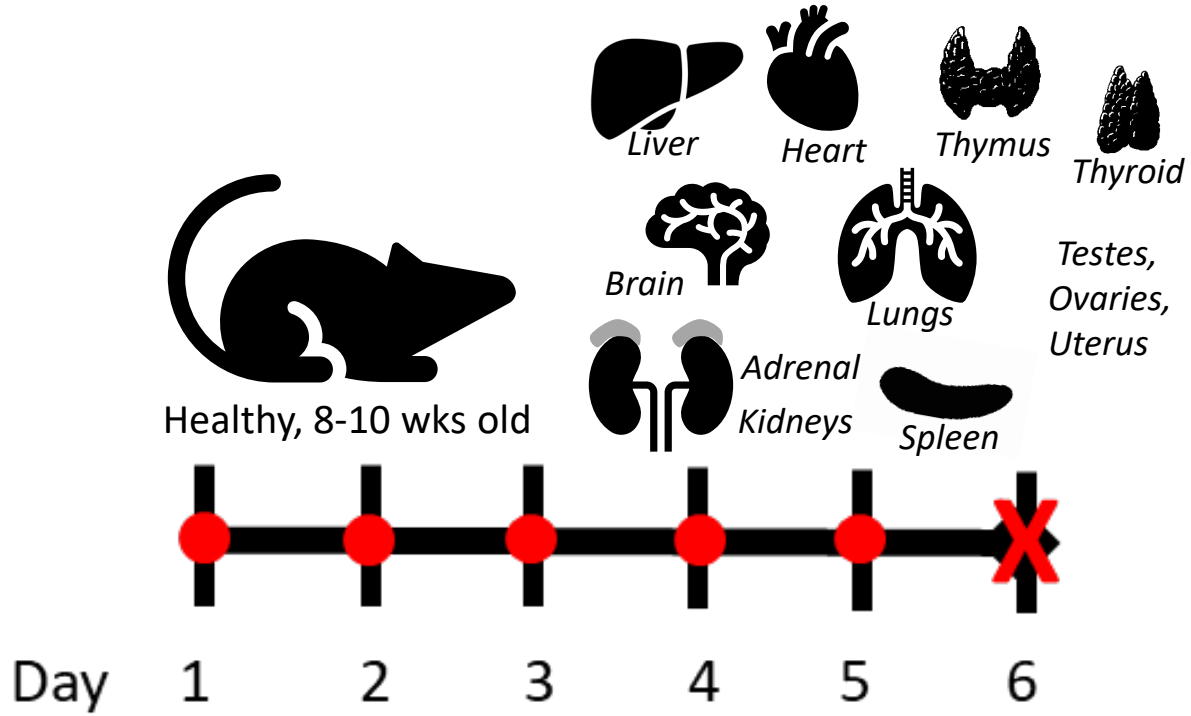
First Component

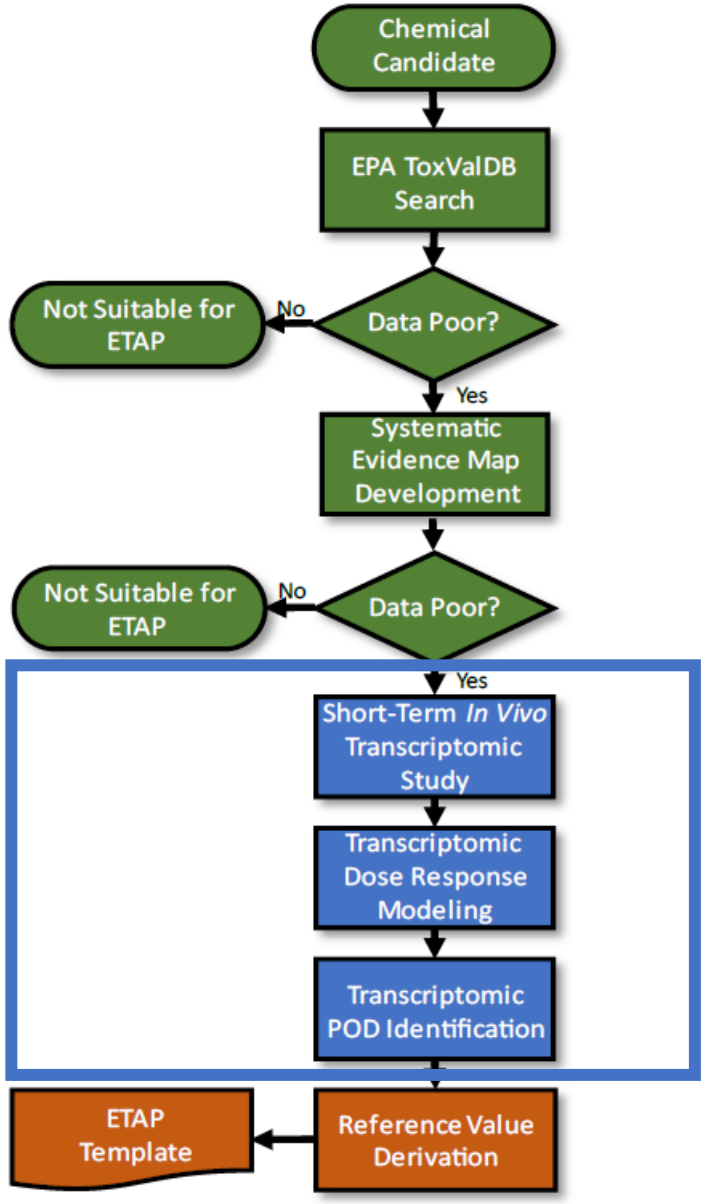
- The first component of an ETAP is identifying potentially relevant toxicological studies
- Candidate substances for ETAP are screened for publicly available repeated dose toxicity data using the US EPA ToxVal database (ToxValDB)
- If no suitable studies are identified in the ToxValDB, then systematic evidence map (SEM) methods are used to identify and organize the research available on a specific substance



Second Component

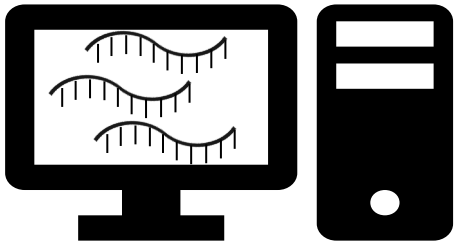
- 5-day *in vivo* rat study in males and females (N=4/group)
  - Oral exposure only
  - Targeted RNA-seq in a variety of tissues



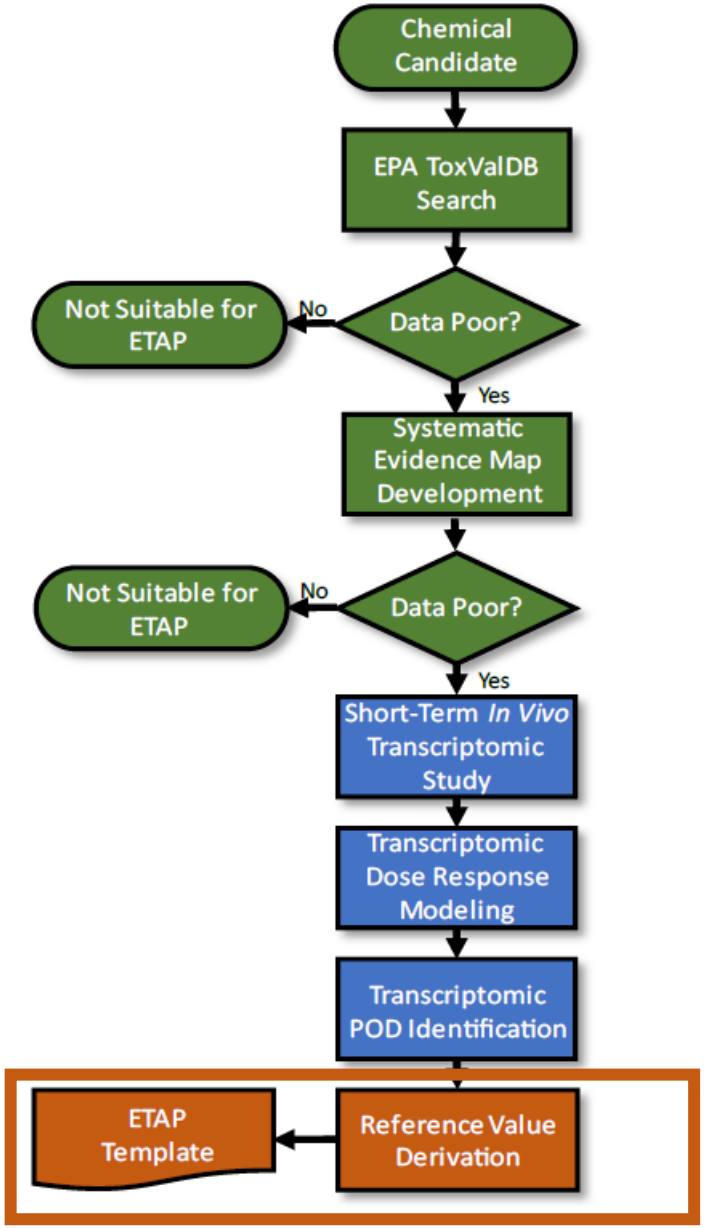


Second Component

- Identification of transcriptomic POD
  - Transcriptional changes can provide a quantitative assessment of disruptions to signaling pathways, biological processes, and molecular functions by a chemical substance and the doses at which these disruptions occur
  - Defined as the experimentally determined dose at which there were no coordinated transcriptional changes that would indicate a potential toxicity of concern



RNA Seq S1500+ → Data pre-processing QC → Dose response modeling and summarization BMDExpress2 → Identify benchmark dose BMD(L) for each tissue and sex



Third Component

- Assessment development and reporting
  Transcriptomic POD obtained from the 5-day in vivo oral exposure study is used in the derivation of a **TRV** through application of uncertainty factors (UFs)
  - Because the ETAP process is used only for data poor chemicals, a standardized composite uncertainty factor will be applied for most tested substances*

    BMDL is derived from the lowest value across sex|tissue combinations

    BMDL * DAF = $BMDL_{HED}$

    $BMDL_{HED}$ / Composite UF = TRV

- The results from the systematic evidence mapping, 5-day transcriptomic study, and TRV derivation are compiled and reported in a standardized ETAP reporting template
- The assessment undergoes extensive QA/QC review; due to the highly standardized nature of the testing paradigm, each assessment does not undergo external peer review

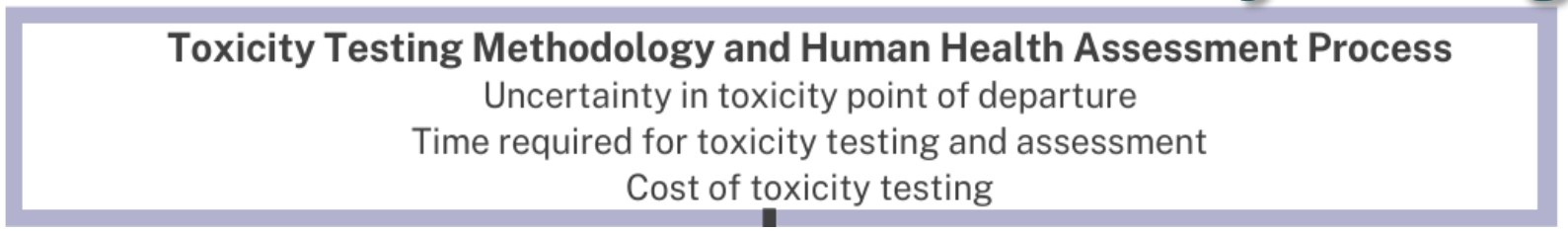
DAF: Dose Adjustment Factor | HED: Human Equivalent Dose| UF: Uncertainty Factor | TRV: Transcriptomic Reference Value

Case Study Considerations

- To evaluate the relative benefits driving the choice between two processes (ETAP or THHA), case study inputs included components from the published VOI framework paper (Hagiwara et al. 2022) as well as others that were unique to the comparison being performed
- The case study was constructed to evaluate VOI under a variety of chemical exposure and decision contexts that could impact the costs of exposure mitigation (*i.e.* control costs) and overall public health burden (*i.e.* health costs)

	ETAP	or	THHA	?
Time to decision	Short		Long	
Cost of testing	Less		More	

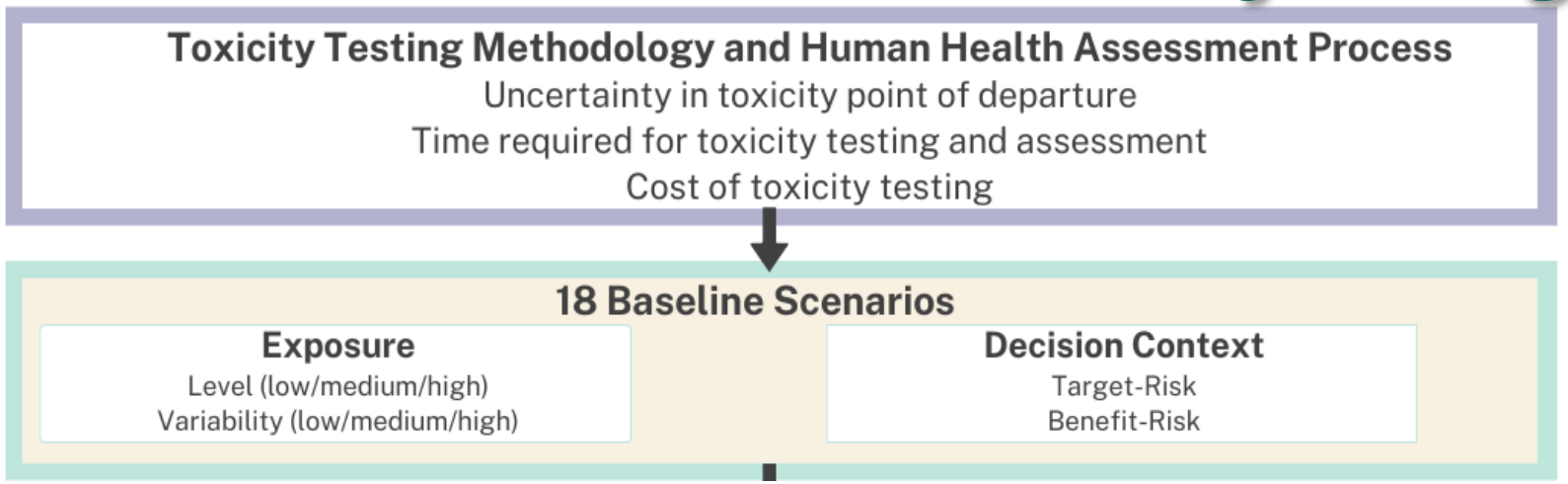
Case Study Design



Toxicity testing methodology and human health assessment process:

- Uncertainty around the experimentally determined point of departure
- The time required for toxicity testing and developing the assessment
- The costs associated with conducting each type of toxicity test

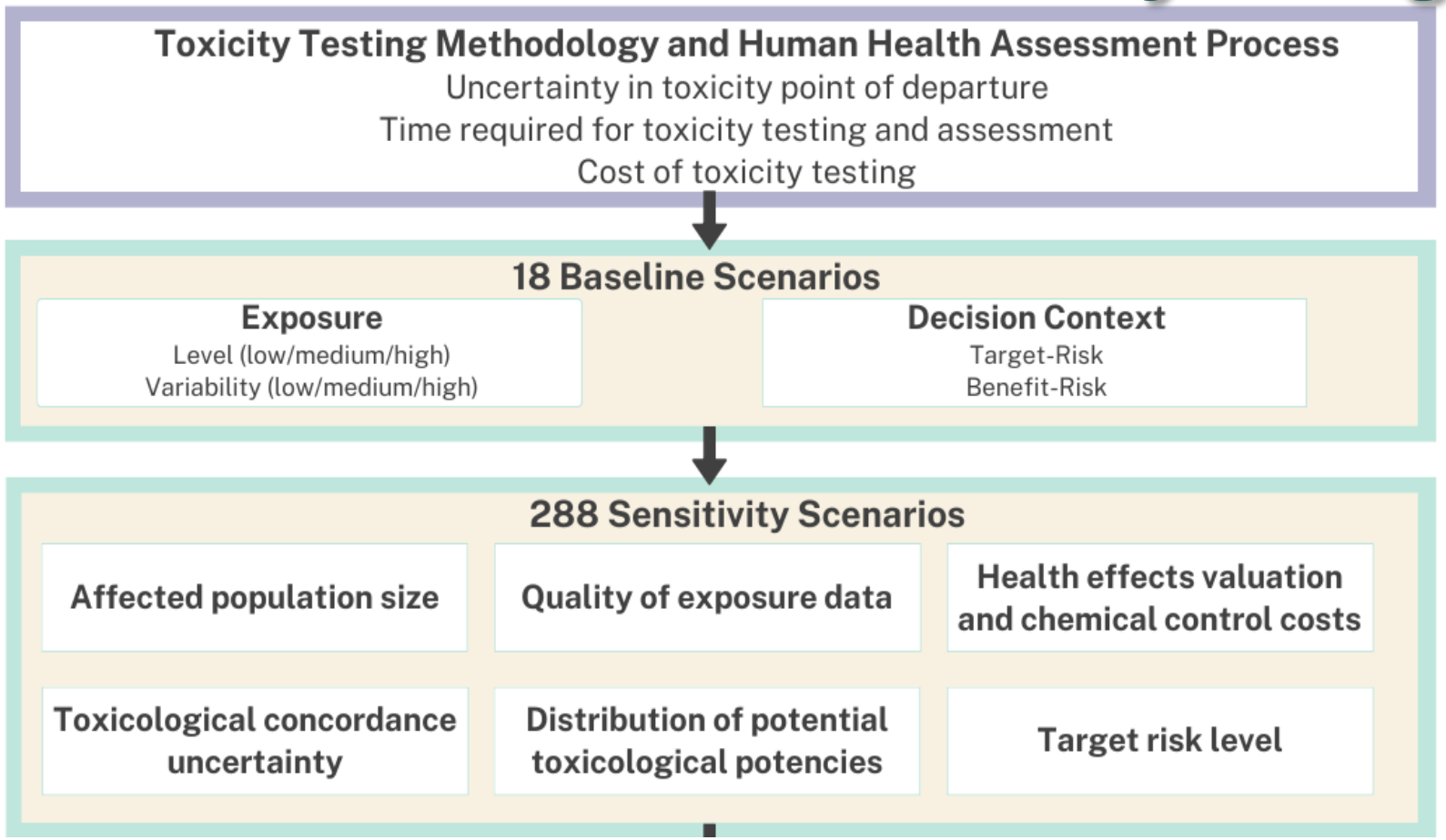
Case Study Design



Baseline Scenarios

- **Exposure**: Chemical exposure defined by the mean population exposure level and population variability in exposure
- **Decision type**: Target-risk and benefit-risk decision makers

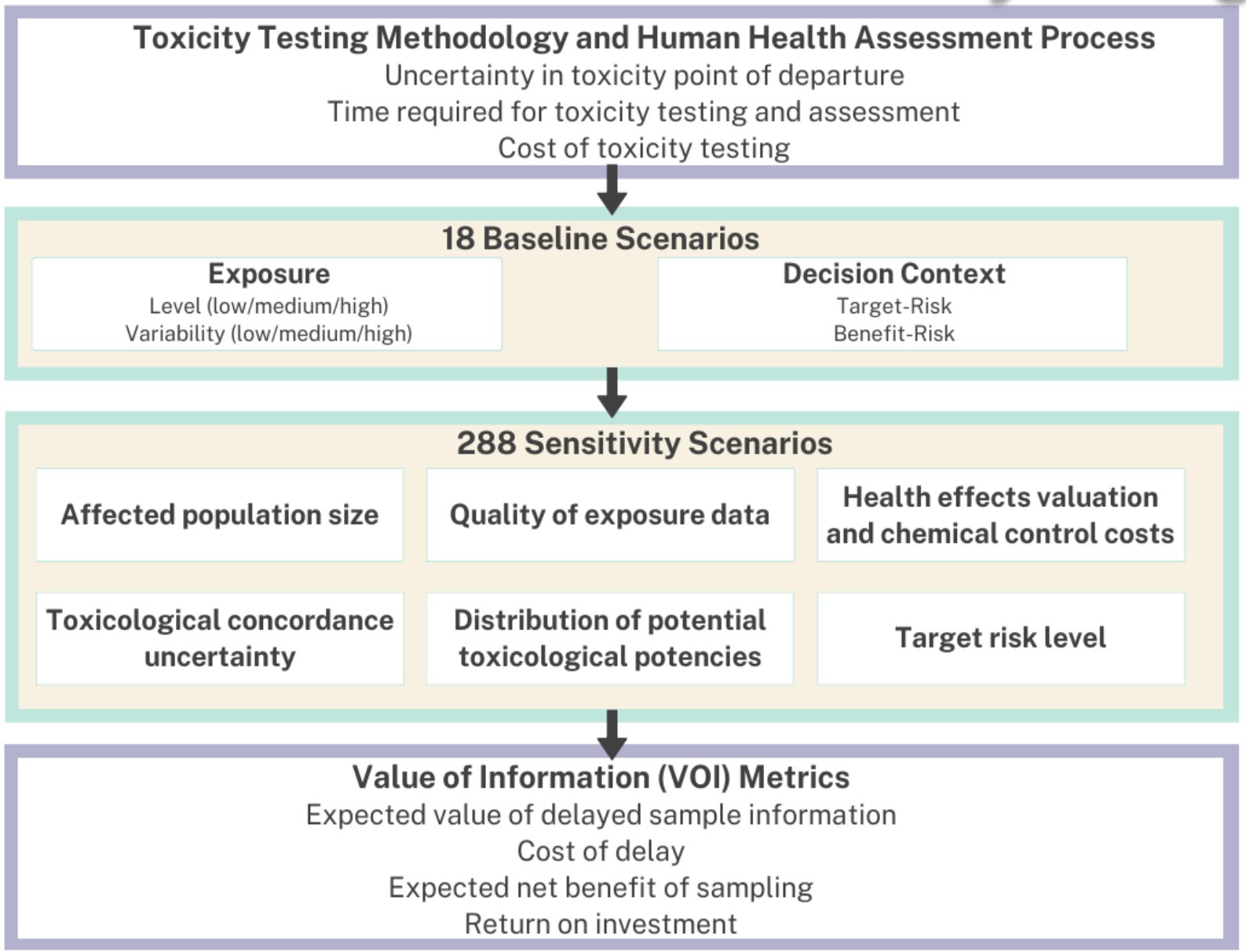
Case Study Design



Sensitivity Scenarios

- **Affected population size**: Size of the exposed population
- **Quality of exposure data**: Consideration of more accurately knowing mean population exposure level and population variability in exposure
- **Health effects and chemical control costs**: Economic valuation for the adverse health effects resulting from exposure and costs of exposure mitigation actions
- **Toxicological concordance uncertainty**: Uncertainty associated with the five-day, repeated dose in vivo transcriptomic study
- **Distribution of potential toxicological potencies**: Range of potential toxicological effect levels of an untested chemical
- **Target risk level**: The specified target risk level required for the target-risk decision maker to take action

Case Study Design



VOI Metrics

- Reporting of key VOI metrics to assess trade-offs between choosing ETAP or THHA under each scenario