

**Value of Information
Case Study: Human Health
and Economic Trade-offs
Associated with the
Timeliness, Uncertainty, and
Costs of the Draft EPA
Transcriptomic Assessment
Product (ETAP)**

EPA/600/X-23/082 | July 2024 | www.epa.gov/research
<https://doi.org/10.23645/epacomptox.26093572>



EPA/600/X-23/082

Value of Information Case Study on the Human Health and Economic Trade-offs Associated with the Timeliness, Uncertainty, and Costs of the Draft EPA Transcriptomic Assessment Product (ETAP)

July 2024

Center for Computational Toxicology and Exposure (CCTE)
Office of Research and Development
U.S. Environmental Protection Agency

TABLE OF CONTENTS

ABBREVIATIONS.....	iv
CONTRIBUTORS REVIEWERS.....	vi
1. EXECUTIVE SUMMARY.....	7
2. BACKGROUND.....	10
2.1. CHEMICAL INVENTORIES AND CURRENT LANDSCAPE OF TOXICITY TESTING AND HUMAN HEALTH ASSESSMENTS.....	10
2.2. VALUE OF INFORMATION ANALYSIS	12
3. VOI CASE STUDY	15
3.1. DESIGN OF THE CASE STUDY.....	15
3.2. CHARACTERISTICS OF THE TESTING AND ASSESSMENT PROCESSES CONSIDERED IN THE CASE STUDY.....	17
3.2.1. TWO-YEAR RODENT BIOASSAY AND HUMAN HEALTH ASSESSMENT.....	17
3.2.2. SHORT-TERM <i>IN VIVO</i> TRANSCRIPTOMIC STUDY AND EPA TRANSCRIPTOMIC ASSESSMENT PRODUCT (ETAP)	18
4. VALUE OF INFORMATION	21
4.1. VOI ANALYTIC FRAMEWORK.....	21
4.2. DECISION MAKING CONTEXTS.....	23
4.3. VOI CONCEPTS AND METRICS.....	25
5. PARAMETERIZATION OF VOI MODELS	29
5.1. TOXICOLOGICAL PARAMETERIZATION	29
5.1.1. PRIOR UNCERTAINTY IN TOXICITY	29
5.1.2. CONDITIONAL POSTERIOR UNCERTAINTY ABOUT μ_{tox} FOR THHA	30
5.1.3. CONDITIONAL POSTERIOR UNCERTAINTY ABOUT μ_{tox} FOR ETAP	32
5.2. EXPOSURE PARAMETERIZATION	33
5.3. OTHER PARAMETERS.....	35
5.3.1. ADVERSE HEALTH OUTCOME VALUATION.....	35
5.3.2. CONTROL COSTS.....	36
5.3.3. AFFECTED POPULATION SIZE	37
5.3.4. DISCOUNT RATE	37
5.3.5. TOXICITY TESTING AND ASSESSMENT DURATION	38
5.3.6. TIME HORIZON.....	39

5.3.7. STUDY AND ASSESSMENT COSTS.....	39
5.3.8. ADDITIONAL CONSIDERATIONS FOR TARGET-RISK DECISION-MAKING.....	40
6. VOI CASE STUDY RESULTS.....	42
6.1. VOI ANALYSIS OF ETAP VERSUS THHA.....	42
6.1.1. BENEFIT-RISK DECISION MAKING	42
6.1.2. TARGET-RISK DECISION-MAKING	46
6.2. SENSITIVITY ANALYSES	50
6.2.1. EFFECT OF QUALITY OF EXPOSURE INFORMATION.....	50
6.2.2. EFFECT OF ADVERSE HEALTH OUTCOME AND COST OF CONTROL.....	53
6.2.3. EFFECT OF TOXICITY TESTING AND ASSESSMENT DURATION AND TIME HORIZON	54
6.2.4. EFFECT OF STUDY COST.....	57
6.2.5. EFFECT OF AFFECTED POPULATION SIZE.....	59
6.2.6. EFFECT OF TARGET RISK LEVEL.....	60
6.2.7. DISCORDANCE AS A SOURCE OF ADDITIONAL UNCERTAINTY.....	62
7. SUMMARY AND CONCLUSIONS.....	64
8. SUPPLEMENTAL MATERIAL	71
9. REFERENCES.....	72

ABBREVIATIONS

AHC	Annualized Health Cost
ACC	Annualized Control Cost
ASD	Autism Spectrum Disorders
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark Dose
BMDL	Benchmark Dose Lower Confidence Bound
BOSC	Board of Scientific Counselors
BRDM	Benefit-Risk Decision Maker
CCED	Chemical Characterization and Exposure Division
CCTE	Center for Computational Toxicology and Exposure
COD	Cost of Delay
COT	Cost of Testing
CPHEA	Center for Public Health and Environmental Assessment
DAF	Dosimetric Adjustment Factor
ECHA	European Chemicals Agency
ED ₅₀	Median Effective Dose
ENBS	Expected Net Benefit of Sampling
EPA	U.S. Environmental Protection Agency
ETAP	EPA Transcriptomic Assessment Product
ETHC	Expected Total Health Cost
ETSC	Expected Total Social Cost
EV CI	Expected Value Given Current Information
EVDSI	Expected Value of Delayed Sample Information
EVIPPI	Expected Value of Immediate Partial Perfect Information
EVISI	Expected Value of Immediate Sample Information
GO	Gene Ontology
GM	Geometric Mean
GSD	Geometric Standard Deviation
HD _{M^I}	Human Dose at Magnitude (M) and Incidence (I)
HED	Human Equivalent Dose
ID	Intellectual Disability
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
K	Thousand(s)
LOAEL	Lowest Observed Adverse Effect Level
M	Million(s)
MRL	Minimum Risk Level
NASEM	U.S. National Academies of Sciences, Engineering, and Medicine
NCEE	U.S. EPA National Center for Environmental Economics
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program

OM	Orders of Magnitude
OPP	Office of Pesticide Programs
ORD	Office of Research and Development
ORE	Optimal Reduction in Exposure
OW DWS	Office of Water Drinking Water Standards
PM	Particulate Matter
POD	Point of Departure
PPI	Partial Perfect Information
PPRTV	EPA Provisional Peer Reviewed Toxicity Value
REACH	European Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals
RfD	Reference Dose
RMSD	Root Mean Squared Difference
RNA	Ribonucleic Acid
RNA-seq	RNA Sequencing
ROI	Return on Investment
RSL	Regional Screening Level (Superfund)
SAB	U.S. EPA Science Advisory Board
SEM	Systematic Evidence Map
SHEDS-HT	U.S. EPA's High-Throughput Stochastic Human Exposure and Dose Simulation Model
TCC	Total Control Cost
TD	Toxicodynamic
TH	Time Horizon
THC	Total Health Cost
THHA	Traditional Human Health Assessment
TK	Toxicokinetic
ToxValDB	U.S. EPA Chemicals Dashboard ToxVal database
TRDM	Target-Risk Decision Maker
TRL	Target Risk Level
TSC	Total Social Cost
TSCA	Toxic Substances Control Act
TRV	Transcriptomic Reference Value
UF	Uncertainty Factor
VOC	Volatile Organic Compounds
VOI	Value of Information
VSL	Value of a Statistical Life

CONTRIBUTORS | REVIEWERS

EPA Office of Research and Development (ORD) Authors

Mike DeVito	U.S. EPA/ORD/CCTE
Alison Harrill	U.S. EPA/ORD/CCTE
Russell Thomas	U.S. EPA/ORD/CCTE

Risk Sciences International EPA Contract 68HE0B22P0318

Shintaro Hagiwara	RSI
Daniel Krewski	RSI
Greg Paoli	RSI
Patrick J. Farrell	RSI

EPA ORD Executive Direction

Russell Thomas	CCTE Center Director
Reeder Sams	CCTE Deputy Center Director
Alison Harrill	CCTE Associate Director
Mike DeVito	CCTE/CCED Division Director

EPA Contributors and Reviewers

Timothy Buckley	U.S. EPA/ORD/CCTE
Chris Dockins	U.S. EPA/NCEE
Peter Egeghy	U.S. EPA/ORD/CCTE
Katie Paul-Friedman	U.S. EPA/ORD/CCTE
Joshua Harrill	U.S. EPA/ORD/CCTE
Bryan Hubbell	U.S. EPA/ORD/NPD for Air, Climate, and Energy
Kristin Isaacs	U.S. EPA/ORD/CCTE
Richard Judson	U.S. EPA/ORD/CCTE
Jason Lambert	U.S. EPA/ORD/CCTE
Esra Mutlu	U.S. EPA/ORD/CCTE
Jon Sobus	U.S. EPA/ORD/CCTE
Ravi Subramaniam	U.S. EPA/ORD/CPHEA
Kristina Thayer	U.S. EPA/ORD/CPHEA
Daniel Villeneuve	U.S. EPA/ORD/CCTE

1. EXECUTIVE SUMMARY

Time is an important, but underappreciated component in chemical safety decisions. An estimated 15% of the chemicals in domestic commerce have traditional repeated dose toxicity testing data and even fewer have human health assessments that can be used to inform regulatory actions. The time and resources required to perform traditional toxicity testing and develop a human health assessment are substantial and, for many chemicals, human exposure continues to occur while toxicity data are collected, interpreted, and integrated into a human health reference value. Although new methods and approaches are increasingly available to more rapidly and cost effectively evaluate toxicity and develop human health assessments, there is hesitation to utilize newer approaches as compared with traditional paradigms. Objective approaches are needed to evaluate the potential trade-offs between timeliness of the toxicity testing and human health assessment, uncertainty of the information, and the associated costs and benefits of the testing and assessment approaches.

The United States Environmental Protection Agency (EPA) Office of Research and Development (ORD) recently developed a value of information (VOI) framework for comparing human health and economic benefits of toxicity-testing methodologies ([Hagiwara et al. 2022](#)). VOI analysis is a decision analytic method for objectively quantifying the expected value of collecting additional information to reduce uncertainty when considering the benefits of improved outcomes against the associated costs. The ORD VOI framework incorporates a series of input parameters relevant to chemical risk assessment that would be considered by risk managers, including chemical exposure, associated adverse health effects, costs of potential exposure mitigation actions, the size of affected populations, and the amount of uncertainty reduced in human health assessments by performing additional toxicity tests. The VOI framework builds on previous work in this field by explicitly incorporating the value of additional toxicity testing data in reducing the uncertainty of human health risks while accounting for the cost of delay in decision making that results from the time required for testing and assessment.

This report outlines a case study using the VOI framework to evaluate the human health and economic trade-offs between uncertainty, timeliness, and costs associated with a recently released five-day *in vivo* transcriptomic-based toxicity study and EPA Transcriptomic Assessment Product (ETAP) compared to a two-year rodent bioassay and traditional human health assessment (THHA) process. Both the ETAP and the THHA result in the derivation of a reference value that represents the daily dose of a chemical substance for which exposure to humans would be unlikely to result in an adverse health effect following oral exposure. The ETAP and THHA processes differ in the cost of the study, duration of the study and assessment process, and the degree of uncertainty around the

point-of-departure (POD)¹, with ETAP having the inherently shorter-duration and lower cost assay, but with the trade-off of presumed greater uncertainty. The ETAP is intended to be applied to substances with no existing or publicly accessible repeated dose toxicity studies or human evidence suitable for use as a POD and reference value derivation. The comparison was performed for various combinations of exposure conditions, health endpoints, control costs, population characteristics, and decision types using a range of values informed by real-world data. For the exposure and decision type, the range of values for each component were combined into a set of baseline scenarios to capture the multiple exposure characteristics and decision contexts for a chemical for which ETAP may be applicable. In addition, a separate set of sensitivity analyses (*i.e.*, sensitivity analysis scenarios) were performed to evaluate additional chemical characteristics and other potential sources of uncertainty. A total of 360 baseline and sensitivity analysis scenarios were summarized across multiple VOI metrics to bound the relative difference in value between the ETAP and THHA across the diverse range of characteristics and contexts for chemicals that are suitable for ETAP.

The results of the case study showed that ETAP was favored over THHA in most of the scenarios examined and across multiple VOI metrics. The 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. For the BRDM, 83% of the scenarios favored ETAP, while the remaining 17% favored neither ETAP nor THHA. The target-risk decision maker (TRDM) takes regulatory action to mitigate exposure whenever the risk exceeds a prespecified target risk level. For the TRDM, 7% of the scenarios required neither ETAP nor THHA, while between 87 and 99% of the remaining scenarios favored ETAP, depending on the VOI metric evaluated. Across the scenarios examined, the median difference in the expected net benefit of sampling (ENBS), which considers the reduction in total costs from the additional testing and assessment activities adjusted for delay and the cost of testing (COT), was approximately \$44 billion for the benefit-risk decision context and \$81 billion for the target-risk decision context². Negative values for ENBS were frequently observed for THHA in the benefit-risk decision context, suggesting that the delay and costs associated with decision-making for the traditional toxicity testing and human health assessment process are greater than the eventual benefit. In contrast, the ETAP less frequently had a negative ENBS for the benefit-risk decision

¹ In human health risk assessment practice, a point-of-departure (POD) represents the dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (*e.g.*, Benchmark Dose; BMD), or a No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) for an observed incidence or change in level of response. For BMD values, this is typically the BMD lower confidence bound (BMDL).

² Total benefits over the twenty-year time horizon for which the costs were calculated. To put these numbers in perspective, as an example, preventing a chronic health condition (costing \$10,000 per year) among 330,000 people (approximately 1/10th of 1% of the US population) would provide a benefit of \$66B over a 20-year time horizon.

context, suggesting that the benefit gained by collecting toxicity information via ETAP outweighed both the delay and the COT for most scenarios evaluated.

Overall, the results of the case study indicate that under the exposure scenarios and assumptions considered, the ETAP was more frequently preferred over the traditional toxicity testing and human health approach for more rapidly and cost effectively evaluating chemicals with no existing or publicly accessible repeated dose toxicity studies or human evidence suitable for use as a POD and reference value derivation. The amount of time needed to conduct the toxicity testing and develop the human health assessment was particularly important when the risks were high, as the delay in implementing regulatory action resulted in significant health costs.

2. BACKGROUND

2.1. CHEMICAL INVENTORIES AND CURRENT LANDSCAPE OF TOXICITY TESTING AND HUMAN HEALTH ASSESSMENTS

The worldwide inventory of commercial and industrial chemicals is substantial and continues to grow. In a survey of 19 countries or regions, more than 350,000 chemicals and mixtures of chemicals were registered in one or more inventories ([Wang et al. 2020](#)). In the United States (U.S.), the 2022 Toxic Substances Control Act (TSCA) inventory contained more than 86,000 chemicals, of which approximately 42,000 are considered commercially active.³ Both the global and domestic inventories are anticipated to expand in the future. Global chemical production has increased 50-fold since 1950, and is projected to triple again by 2050 compared to 2010 ([EEA 2018](#)). Domestically, annual chemical production increased an average of 3% per year between 2012 and 2019 ([NASEM 2022](#)). While much of the worldwide and domestic chemical production on a volume basis is attributed to a relatively small number of commodity chemical classes, the diversity in chemical structures on various inventories is due to the rising demand for specialty chemicals across a range of industries. For regulatory agencies such as the U.S. Environmental Protection Agency (EPA), the overall consequence of the historical, current, and future trends in chemical production is a substantial and increasing number of chemicals requiring toxicity testing to evaluate potential for human health risks.

Toxicity testing in experimental laboratory settings is an important component in assessing potential human health impacts of chemicals. Traditional methods for characterizing the toxicity of chemicals typically involve the use of animal models in standard guideline studies. These guideline studies cover a range of exposure durations (*e.g.*, acute, subacute, subchronic, chronic) and health effect domains (*e.g.*, general systemic toxicity, reproductive, developmental, immunotoxicity). Chemical testing requirements vary depending on the intended use and the specific statutes governing those uses. For example, a full battery of toxicology studies is required for a food-use pesticide under 40 CFR Part 158⁴, whereas no specific toxicology studies are required for commercial and industrial chemicals under TSCA. Under the current toxicity testing requirements, a relatively small portion of chemicals in commercial use (15%) have been evaluated with traditional animal-based toxicity tests (**Figure 2-1**). A smaller percentage of chemicals have toxicity testing data for more specialized endpoints such as developmental (10%), reproductive (2%), and neurotoxicity

³ US EPA TSCA Inventory: <https://www.epa.gov/tscainventory>

⁴ EPA Data Requirements for Pesticide Registration: <https://www.epa.gov/pesticide-registration/data-requirements-pesticide-registration>

(1%). The lack of toxicity data poses significant challenges for EPA in evaluating potential human health impacts of the large number of chemicals within its regulatory purview.

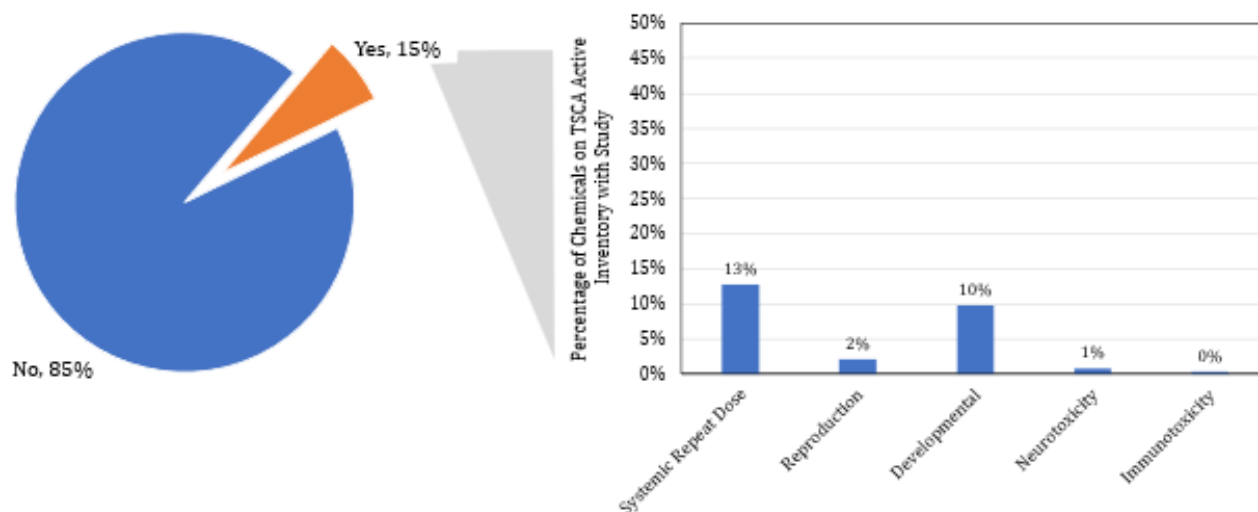


Figure 2-1. The percentage of chemicals on the 2022 TSCA active inventory with available information from traditional animal-based toxicity tests. The pie chart represents chemicals on the TSCA active inventory with any repeated dose toxicity study ('Yes'; Orange). The bar chart on the right provides a breakdown of the repeated dose toxicity tests health outcome domains by endpoint. The total percentage may not add up to 15% since some chemicals may have been tested for more than one type of health outcome. Data were obtained from ToxValDB v9.4.

Human health assessments integrate the results of human epidemiological and experimental animal toxicity tests and other relevant information to identify exposure levels at which no adverse health effect(s) is anticipated over a given duration of exposure (*e.g.*, lifetime). Within the EPA, human health assessments inform a broad range of regulatory decisions such as setting water quality standards, establishing remediation levels at contaminated sites, identifying standards for manufacturing, disposal, and air emissions, and determining safe uses. To develop a human health assessment, significant effort is required to identify and assemble the various sources of experimental animal toxicology and human studies, and to systematically examine the studies for quality and relevance. Once the studies are reviewed and evidence assembled, the candidate critical toxicological effects are identified for dose-response modeling and point of departure (POD)⁵ identification. Based on considerations such as quantitative sensitivity across the candidate PODs, a POD is selected and then divided by a number of uncertainty (or safety) factors that address important experimental, variability, and extrapolation considerations ([EPA 2002](#)). The resulting study review, hazard and dose-response assessment, reference value derivation, and assessment

⁵ In human health risk assessment practice, a point-of-departure (POD) represents the dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (*e.g.*, Benchmark Dose; BMD), or a No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) for an observed effect.

conclusions are summarized, undergo requisite review, and are published. Each step in this process is time and resource intensive, such that the development of human health assessments typically takes at least 4 years (Krewski et al. 2020), while more complex assessments can take substantially longer (NASEM 2009). Due to the lack of toxicity testing data for many chemicals in commerce and the time required to develop human health assessments, few chemicals have published reference values. Among chemicals on the TSCA active inventory, only 1.8% have a published human health assessment from EPA or the Agency for Toxic Substances and Disease Registry (ATSDR) (Figure 2-2). None of the individual federal sources have developed human health assessments on more than 1% of chemicals on the TSCA active inventory.

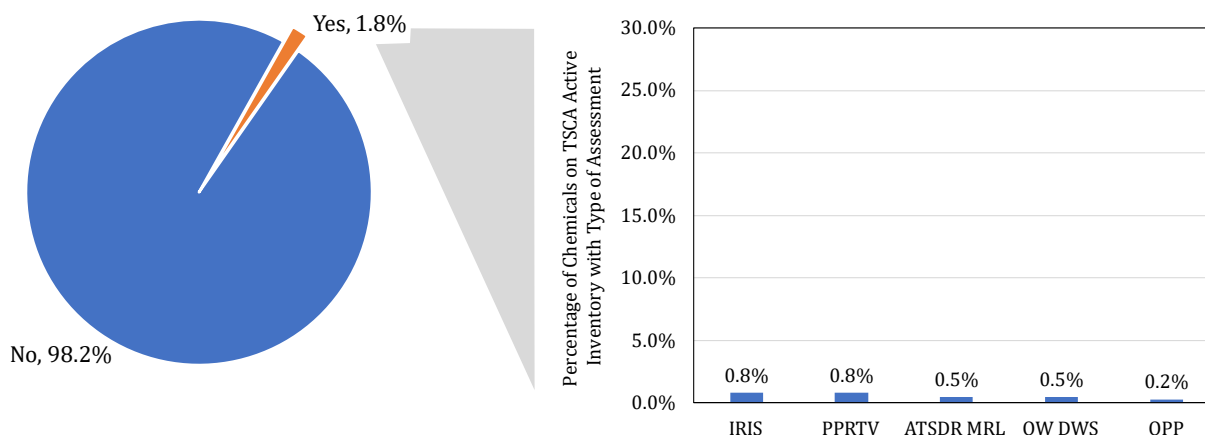


Figure 2-2. The percentage of chemicals on the 2022 TSCA active inventory with human health assessments from representative US federal agencies. The pie chart represents chemicals on the TSCA active inventory with any human health assessment ('Yes'; Orange). The bar chart on the right provides a breakdown of the human health assessments from different sources including the EPA Integrated Risk Information System (IRIS) database, EPA Provisional Peer Reviewed Toxicity Values (PPRTV), Agency for Toxic Substances and Disease Registry (ATSDR) Minimum Risk Levels (MRL), EPA Office of Water Drinking Water Standards (OW DWS), and Office of Pesticide Program (OPP). The total percentage may not add up to 1.8% since some chemicals may have an assessment from more than one source.

2.2. VALUE OF INFORMATION ANALYSIS

To address the gap in availability of human health assessments, the EPA has committed to developing and refining scientifically robust methods for characterizing chemical hazard and exposure with the specific goal of making risk assessments more expedient and economical (Cote et al. 2012; Krewski et al. 2014). Moving the science of human health risk assessment forward will require both the development of novel toxicity testing methods and approaches, as well as associated frameworks to assess their value for informing decision making in a variety of decision contexts. A key aspect of assessing that value involves the decision to take an immediate action with currently available information versus delaying until additional data are collected and analyzed. This choice is often informed by the urgency of the public health need and the costs, in terms of both time and resources, of acquiring additional relevant information that may lead to decisions with less

uncertainty. The U.S. National Academies of Sciences, Engineering, and Medicine (NASEM), in its report *Science and Decisions: Advancing Risk Assessment*, reflected that time is a major and rarely acknowledged factor in risk assessment and that additional studies may reduce uncertainty, but the delay can have significant impact on society and communities who are exposed to a chemical or substance while awaiting the results ([NASEM 2009](#)). The NASEM Committee recommended the development and application of Value of Information (VOI) analysis to provide a more objective decision framework to evaluate the potential impact of information on a particular decision or proposed changes in risk assessment activities ([NASEM 2009](#)).

VOI analysis is a decision analytic methodology for quantifying the expected gain in reducing uncertainty through the collection of additional data or information ([Howard 1966](#); [Raiffa 1968](#)). In general terms, the value of the information is calculated based on the expected reduction in probability of making the wrong decision multiplied by the consequences of being wrong. The result of the calculation is compared with the expected cost of the information. If the expected value obtained is favorable with respect to the costs incurred, then the additional information should be collected. If not, then the value of additional information is not worth the cost and should not be collected. Like traditional sensitivity and uncertainty analysis, VOI analyses capture the influence of uncertain parameters and model structures on model outcomes. However, in VOI, the focus is not necessarily on individual model outputs, but rather the focus is on a specific decision to be made and the potential impacts of collecting additional information ([Zabeo et al. 2019](#)). For toxicology, exposure characterization, and human health risk assessment, VOI has been applied or proposed in a variety of decision contexts ([Finkel and Evans 1987](#); [Lave and Omenn 1986](#); [Lave et al. 1988](#); [Leontaridou et al. 2016](#); [Taylor et al. 1993](#); [Thompson and Evans 1997](#); [Yokota et al. 2004](#); [Yokota and Thompson 2004](#)).

The EPA Office of Research and Development (ORD) recently developed a VOI framework for comparing human health and economic benefits of toxicity-testing methodologies ([Hagiwara et al. 2022](#)). The ORD VOI framework focuses on the value of collecting toxicity testing information based on two types of risk management strategies: the target-risk decision maker (TRDM) whose objective is to control potential health risks whenever it is thought to exceed a specified target risk level (TRL); and the benefit-risk decision maker (BRDM) whose objective is to balance the cost of exposure mitigation and the resulting health benefits. To calculate the human health and economic value of the toxicity testing information, the framework incorporates a series of input parameters relevant to chemical risk assessment that would be considered by risk managers, including chemical exposure, associated adverse health effects, costs of potential exposure mitigation actions, the size of affected populations, and the amount of uncertainty reduced in human health assessments by performing the toxicity tests. The ORD VOI framework builds on previous work in the field by explicitly incorporating the value of additional toxicity testing data while accounting for the cost of delay in decision making that results from the time required for testing. To illustrate its potential application, the publication outlining the VOI framework considered two different hypothetical toxicity tests (a low-cost and

short-duration test with greater uncertainty and a high-cost long-duration test with less uncertainty). The results from the comparison considered in the framework paper indicated that the time required to perform the toxicity testing was a strong determinant of the VOI, even when the degree of uncertainty reduction was less than could be achieved with a more time and resource intensive toxicity testing method.

3. VOI CASE STUDY

3.1. DESIGN OF THE CASE STUDY

For regulatory agencies, case studies have been an important tool to understand the strengths and weaknesses of new methods and gain familiarity with new methods or approaches before application ([Kavlock et al. 2018](#)). 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, and costs of different toxicity testing and assessment approaches. The case study focuses on a VOI comparison between two options: 1) a five-day, repeated dose *in vivo* transcriptomic study and the EPA Transcriptomic Assessment Product process [hereafter, the combination is referred to as the ETAP]. The ETAP incorporates a standardized and structured data collection and analysis procedure, reporting template, and review process that is intended to facilitate the rapid development and release of the assessment. The ETAP is intended to be applied to substances with no existing or publicly accessible repeated dose toxicity studies or human evidence suitable for use as a POD and reference value derivation; and 2) two-year rodent chronic toxicity test with traditional human health assessment process [hereafter, the combination is referred to as THHA]. The two-year rodent chronic toxicity test was selected as the basis for comparison since the transcriptomic PODs from the five-day, repeated dose *in vivo* study showed robust concordance with the traditional apical PODs from the chronic studies ([EPA 2024b](#)). The concordance between the transcriptomic and apical POD values was approximately equivalent to the observed inter-study variability in the repeated dose toxicity studies ([EPA 2024b](#)). For the purposes of the case study, the THHA is assumed to be the gold standard that the ETAP is compared against. The ETAP was chosen as the comparator because it underwent parallel review by the EPA Board of Scientific Counselors (BOSC) ([EPA 2024b](#)) and has recently been released as a new EPA human health assessment product.

The case study was constructed to evaluate the 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). To evaluate the relative benefits driving the choice between two processes, the case study inputs included important components from the VOI framework paper as well as others that were unique to the comparison being performed, including (**Figure 3-1**):

- **Toxicity testing and human health assessment:** The costs associated with conducting each type of toxicity test, uncertainty around the experimentally determined point of departure, and the time required for toxicity testing and developing the assessment.
- **Exposure:** Chemical exposure defined by the mean population exposure level and population variability in exposure.

- **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.
- **Decision type:** Benefit-risk and target-risk decision makers.
- **Target risk level:** The specified target risk level required for the target-risk decision maker to take action.

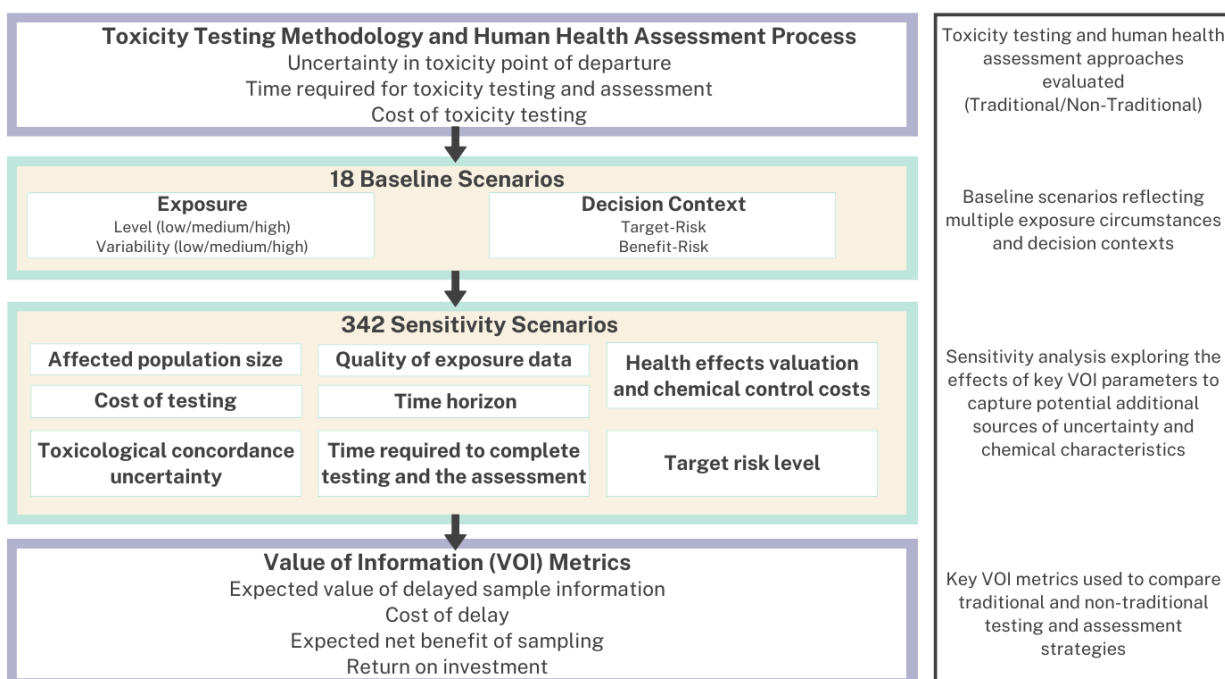


Figure 3-1. Overview of the VOI analysis case study comparing the ETAP and THHA. The two toxicity testing and human health assessment approaches were compared across multiple exposure characteristics and decision contexts to capture the range of values for a chemicals for which ETAP may be applicable. Sensitivity analyses were performed to evaluate additional chemical characteristics and other potential sources of uncertainty. The results of the case study were reported via multiple VOI metrics.

For components above, a range of values informed by real-world data was evaluated to understand the relative sensitivity of the results to the inputs. For the exposure and decision type, the range of values for each component were combined into a set of baseline scenarios to capture the multiple exposure characteristics and decision contexts for a chemical for which ETAP may be applicable. In addition, a separate set of sensitivity analyses (*i.e.*, sensitivity analysis scenarios) were performed to evaluate additional considerations, including chemical characteristics and other

potential sources of uncertainty. The results of the baseline and sensitivity analysis scenarios were summarized across multiple VOI metrics to bound the relative difference in value between the non-traditional and traditional toxicity testing and human health assessment process.

The report is organized to present the following information:

- Description of the toxicity testing and human health assessment methods and processes for ETAP and THHA.
- The analytical framework used for VOI analysis, as well as the decision-making paradigms used to evaluate the VOI from the two toxicity tests and human health assessment processes.
- Parameterization of the VOI analytic framework informed by real-world inputs.
- Results of the VOI analysis across baseline scenarios that are defined by the mean population exposure level, variability in exposure across the population, and the type of decision maker.
- Results of the sensitivity analysis scenarios defined by quality of exposure information, valuation of adverse health effects, costs of exposure mitigation actions, prevalence of exposure in a population, target risk level, distribution of potential toxicological potencies for an untested chemical, the degree of uncertainty reduction achieved using the ETAP, the time horizon considered, variation in the testing costs incurred, and differences in the time required to complete the testing and associated human health assessments.
- Overall conclusions from the case study and implications for application of the ETAP.

3.2. CHARACTERISTICS OF THE TESTING AND ASSESSMENT PROCESSES CONSIDERED IN THE CASE STUDY

3.2.1. TWO-YEAR RODENT BIOASSAY AND HUMAN HEALTH ASSESSMENT

The two-year rodent bioassay is a standard toxicity testing method that is used to determine adverse health effects that may arise due to prolonged and repeated exposure to a substance. Most bioassays expose rodents to at least three dose levels of the test substance or vehicle control for up to two years, beginning at 5-6 weeks after birth, and ending prior to the natural lifespan of the animal [*i.e.*, approximately three years for rats ([Huff et al. 2008](#)), which is the typical species of choice for combined chronic toxicity and carcinogenicity studies]([Bucher 2002](#)). At least 100 rodents (50 male and 50 female) are used for each dose group and the vehicle control group, with additional numbers added for interim sacrifices at earlier time points to investigate temporality, as the design may require. Typical studies involve analysis of clinical observations, hematology, clinical chemistry, and urinalysis on a subset of animals. In addition, changes in body weight over time, organ weights and gross examination, and histopathologic assessment of a wide variety of organs are performed to ensure adequate biological coverage. 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](#)).

The process within the EPA to develop a human health assessment for existing substances involves multiple steps that have evolved over time ([EPA 2014, 2022c](#))⁶. The process usually begins with problem formulation and scoping to identify the regulatory need, specific environmental or exposure conditions, and the specific assessment questions to be answered. Following problem formulation, relevant animal and human studies are compiled and evaluated for quality, consistency, and relevance. In recent years within the EPA ORD, the literature survey and study evaluations may be conducted using systematic review principles ([NASEM 2021; Whaley et al. 2020](#)). The hazard evidence is integrated for each health outcome and the studies are selected for dose-response assessment. The critical effect(s) is identified and used to derive reference values using appropriate uncertainty factors (UFs) that capture important experimental, variability, and extrapolation considerations ([EPA 2002](#)). In large federal agencies such as EPA, the human health assessments often undergo a multi-step intra- and inter-organization review process, external peer review, and public comment period. The human health assessments are then revised based on the reviews and public comments prior to final 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.

3.2.2. SHORT-TERM *IN VIVO* TRANSCRIPTOMIC STUDY AND EPA TRANSCRIPTOMIC ASSESSMENT PRODUCT (ETAP)

The ETAP was developed to provide timely information to support decision making for chemicals lacking existing or publicly accessible repeated dose toxicity studies or human evidence suitable for use as a POD and reference value derivation. The proposed methods are summarized in this document to orient the reader as to the derivation of values pertinent to the VOI case study. Detailed methods and the scientific studies supporting the development of the ETAP are available in separate EPA reports ([EPA 2024b, c](#)).

Briefly, the ETAP Scientific Support Document evaluates the relationship between transcriptomic PODs from short-term exposures and their concordance to apical PODs from traditional two-year toxicity studies in rodents. Data from 33 independent studies of over 140 chemicals with diverse physicochemical and toxicological properties demonstrated that transcriptomic benchmark dose (BMD) and benchmark dose lower confidence bound (BMDL) values, when integrated at a gene set level, were concordant with BMD and BMDL values for apical responses in traditional subchronic and chronic rodent toxicity studies. The error associated with the concordance between the transcriptomic BMD values versus apical BMD values was approximately equivalent to the inter-study variability in the repeated dose toxicity study itself. The transcriptomic

⁶ TSCA risk evaluation process: <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluations-existing-chemicals-under-tsca#publication>

and apical dose concordance was robust across different exposure durations, exposure routes, species, sex, target tissues, physicochemical properties, toxicokinetic half-lives, and technology platforms.

As described in the ETAP Standard Methods Document, the ETAP consists of three primary components with associated processes and decision points within each component. The three primary components consist of: 1) initial database searches and systematic evidence map development; 2) short-term (five-day) *in vivo* transcriptomic study and POD determination; and 3) assessment development and reporting. The main concepts of the ETAP are that the underlying methods and data analysis procedures are highly standardized and structured, and the decision context is narrowly focused on chemicals with no existing or publicly accessible repeated dose toxicity studies or human evidence suitable for use as a POD and reference value derivation. Candidate chemicals for ETAP are screened for publicly available repeated dose toxicity data using the 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 ([Thayer et al. 2022a](#); [Thayer et al. 2022b](#)). For the ETAP, a SEM is developed to identify and evaluate the literature base associated with the candidate substance for mammalian *in vivo* repeated dose toxicity studies or suitable human evidence. Resources searched include databases of published research (*e.g.*, PubMed, Web of Science, ProQuest) as well as repositories of studies that may not have been peer-reviewed, such as those summarized in European Chemicals Agency (ECHA) registration dossiers or EPA's ChemView database. In addition, searches may be conducted to discern whether studies exist in such regulatory reporting databases but are classified as confidential business information. Based on the SEM, chemicals confirmed to have no publicly available mammalian *in vivo* repeated dose toxicity studies or suitable human studies may be eligible for development of an ETAP.

The next component of an ETAP is a short-term (five-day) *in vivo* transcriptomic study and POD identification. Transcriptomics is the characterization of gene expression changes in a cell, tissue, organ, or organism of interest. When analyzed following dose-response treatment with a chemical substance, transcriptional changes provide an understanding of the signaling pathways, biological processes, and molecular functions that are disrupted and the dose at which this occurs ([Thomas et al. 2007](#)). In the ETAP, a five-day repeat dose design in both male and female rats is used as the basis for the transcriptomic study. Transcriptomic measurements for ETAP development are performed using targeted ribonucleic acid (RNA) sequencing (RNA-seq) in twelve tissues. Additional endpoints typically assessed for the purposes of the THHA, such as clinical chemistry and histopathology, are not assessed for the ETAP.

Transcriptomic BMD modeling is performed consistent with the expert-reviewed, National Toxicology Program's (NTP) Approach to Genomic Dose-Response Modeling ([NTP 2018](#)), but adapted for the targeted RNA-seq gene expression platform used for the ETAP. A comprehensive series of analyses was performed to identify and support the choices and parameters used in each

step of the transcriptomic dose-response modeling process to promote detection of transcriptional changes concordant with adverse apical effects, maximize inter-study reproducibility, and minimize detection of false dose response changes ([EPA 2024c](#)). A combination of dose-response modeling parameters was identified that resulted in transcriptomic BMD values with a concordance to apical BMD values from a two-year rodent bioassay that was approximately equivalent to the combined inter-study variability from both studies. To select the transcriptomic POD, the BMDL from the gene ontology (GO) biological process class with the lowest median BMD in the most sensitive sex (male or female) and across all the tissues examined is identified. No determination of a specific type of hazard caused by the substance nor mechanistic interpretation of the gene expression changes is performed.

For the development of the assessment product and reporting, the transcriptomic POD obtained from the five-day *in vivo* oral exposure study is converted to a human equivalent dose (HED) using an oral dosimetric adjustment factor (DAF) based on allometric cross-species scaling ([EPA 2011a](#)). The POD_{HED} is used in the derivation of a chronic transcriptomic reference value (TRV) through application of UFs that are consistent with traditional human health assessment guidance and practice. The quantitative values of the individual UFs and the overall composite value are the same across the individual ETAP assessments due to the standardized nature of the studies and data analysis procedures. The TRV is defined as an estimate of a daily oral dose to the human population that is likely to be without appreciable risk of adverse non-cancer health effects over a lifetime. The results from the SEM, five-day transcriptomic study, and TRV derivation are compiled and reported in a standardized ETAP reporting template, which is made available at a target date within six months of initiating the experiments. The analysis detailed in the series of ETAP documents provide scientific support for considering a short-term transcriptomic study as an alternative method for chemicals lacking existing or publicly accessible repeated dose toxicity studies or human evidence suitable for use as a POD and reference value derivation ([EPA 2024b, c](#)).

4. VALUE OF INFORMATION

The present EPA report focuses on the use of VOI analysis to evaluate the utility of gathering additional evidence on the toxicity of chemicals. Specifically, a VOI analytic case study is presented using a framework that builds on previous methodological work in this field, explicitly incorporating the value of additional test data resulting from reductions in the uncertainty associated with estimates of the dose at which a chemical is not anticipated to cause adverse health effects over a specific exposure duration, the cost of delay in decision making that results from the time required for testing and assessment, and the monetary expense associated with toxicity testing and assessment. This case study is motivated by the need to evaluate the large number of chemicals that are present in commerce and the environment with no existing or publicly accessible repeated dose toxicity studies or human evidence suitable for use as a POD and reference value derivation. The VOI framework employed in this case study provides a basis for evaluating the trade-offs among the degree of uncertainty reduction, timeliness, and costs associated with ETAP and THHA. A flowchart for the VOI framework is presented in **Figure 4-1**. Definitions of all key concepts and terms involved in VOI analysis are provided in **Table 4-1** at the end of this section.

4.1. VOI ANALYTIC FRAMEWORK

Let R represent the population average risk of an adverse health effect due to exposure to a specified chemical within a given population. This risk can be defined as the fraction of the people exhibiting the adverse health effect due to chemical exposure. Let θ_{tox} and θ_{exp} denote the sets of parameters that govern the distribution of chemical toxicity and chemical exposure, respectively. Conditional on θ_{tox} and θ_{exp} , the population average risk R can be modelled as

$$R = R(\theta) = \int G_{\text{tox}}(x|\theta_{\text{tox}})f_{\text{exp}}(x|\theta_{\text{exp}})dx, \quad (1)$$

where $G_{\text{tox}}(x|\theta_{\text{tox}})$ denotes the cumulative probability of observing an adverse effect at or below exposure level x , and $f_{\text{exp}}(x|\theta_{\text{exp}})$ denotes the probability density function of the exposure within the population of interest.

Given R , the decision maker decides whether a chemical warrants exposure mitigation action, and if so, to what extent the level of exposure needs to be reduced. When there exists uncertainty in θ_{tox} and/or θ_{exp} , the uncertainty propagates to the population risk, which in turn leads to uncertainty in risk-based decision making. Uncertainty in toxicity may be reduced by collecting additional toxicity data, thereby reducing uncertainty in decision making.

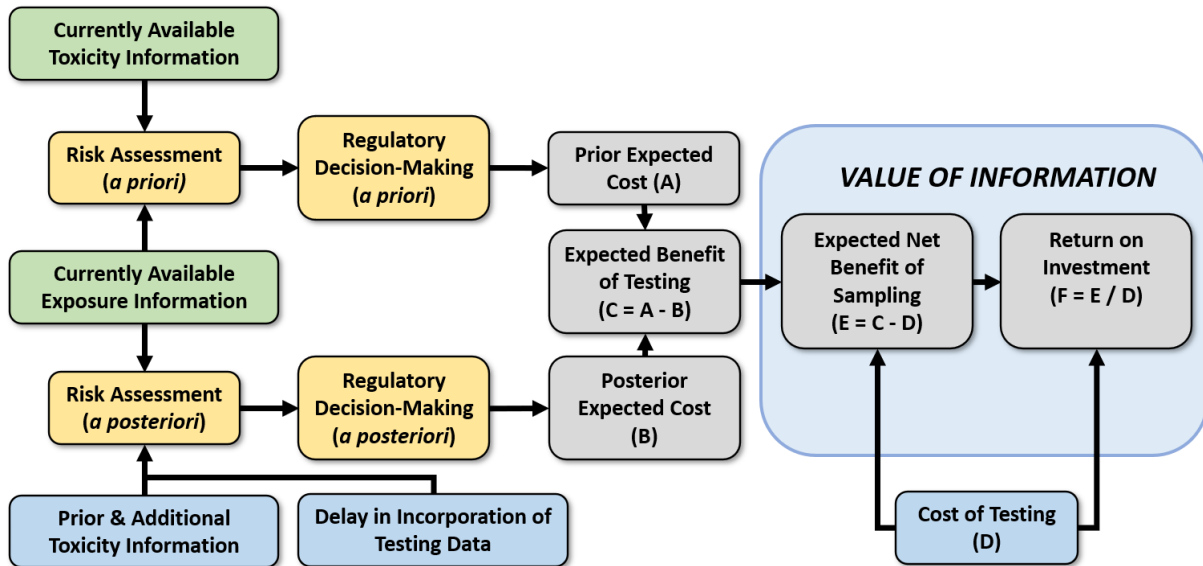


Figure 4-1: Flowchart for the VOI framework. The value of additional toxicity testing is evaluated by comparing the impact of risk decisions with and without this additional information. Without the additional toxicity information, a decision-maker would perform a risk assessment with currently available toxicity and exposure information. The result of this risk assessment would then lead to a regulatory decision (*a priori*) with an associated expected societal cost (denoted as A). A decision-maker may decide to obtain additional toxicity information and perform risk assessment using this information along with currently available exposure information. This would lead to a delayed regulatory decision (*a posteriori*), with a posterior expected societal cost (denoted as B). The difference between the two is the expected benefit of additional toxicity testing (denoted as $C = A - B$). Considering the cost of performing additional toxicity testing (denoted as D), key VOI metrics (denoted as E and F) that incorporate the effects of uncertainty reduction, timeliness, and uncertainty reduction of the additional toxicity testing are calculated. Green nodes in the framework represent information available without additional testing; blue nodes denote parameters associated with additional toxicity testing; yellow nodes correspond to risk assessments and associated regulatory decisions; grey nodes represent the VOI metrics used to evaluate the value of additional toxicity testing.

The VOI analysis in this study aims 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? The VOI framework presented in [Hagiwara et al. \(2022\)](#) provides a method to answer this question by explicitly considering the quality of the information provided by one of the two alternative toxicity tests considered here (*i.e.*, two-year rodent bioassay versus five-day *in vivo* transcriptomic rodent assay), the cost of running such a test, and the delay in decision-making due to the additional testing and human health assessment process.

In applying the VOI framework, the associated costs and benefits of various decision-making approaches need to be defined to determine the ‘value’ of collecting additional toxicity testing data. As part of this process, an economic value is assigned to the costs associated with adverse health effects as well as exposure mitigation. The VOI is calculated over a pre-specified time horizon (which includes the pre- and post-regulation periods), as reflected by the reduction in total social cost (TSC) (which includes the health cost prior to regulation, the reduced health cost after regulation, and the

control cost associated with regulation). The sum of the health costs associated with both the pre- and post-regulation periods is termed the total health cost (THC).

In the presence of uncertainty, TSC and THC are estimated using expected total social cost (ETSC) and expected total health cost (ETHC), where the expectation is taken with respect to the uncertainty distribution about population risk. Since both the ETSC and ETHC depend on the degree of uncertainty in risk, there exists a trade-off amongst the benefits of reduced uncertainty, the costs of testing, and delays in decision making.

The VOI framework quantifies the reduction in uncertainty in toxicity, and ultimately in risk, when additional toxicity tests are performed. This is achieved using Bayesian updating, in which the prior uncertainty distribution for toxicity (represented by the parameter θ_{tox}) is updated given the new toxicity data. This approach ultimately allows for evaluation of the reduction in ETSC/ETHC for different toxicity testing paradigms.

The time required to collect additional toxicity testing data is another important factor in VOI analysis. The delay in reaching a decision pending the collection and analysis of additional data results in a delay in implementing exposure mitigation action, with health costs accruing during this period of inaction. Earlier decisions to control chemical exposure can be advantageous since the TSC is reduced due to an earlier reduction in health costs. The benefit of an earlier decision is quantified by the economic value of this reduction.

The VOI framework integrates all the costs and consequences noted above, with consideration of the timeliness and value of new toxicity testing information collected in support of decision making and the human health assessment process. The framework can be applied to quantify the VOI of different toxicity testing strategies within multiple decision-making contexts, via consideration of context-specific goals. These goals may include the desire to minimize the TSC, to maximize a reduction in the THC, and/or to reduce uncertainty in order support an unambiguous assessment of risk relative to the regulatory objectives [See [Hagiwara et al. \(2022\)](#) for details].

4.2. DECISION MAKING CONTEXTS

The VOI framework requires specification of the decision rules by which the decision makers would choose regulatory action to reduce chemical exposures. These rules determine the specific circumstances under which VOI metrics associated with different testing strategies are quantified and compared. Following [Hagiwara et al. \(2022\)](#), two types of decision makers are considered, the BRDM and the TRDM. The BRDM makes choices to mitigate exposure when the reduction in health cost (or improvement in health benefit) outweighs the associated cost of control, as depicted in **Figure 4-2**. The proportionate level of exposure mitigation that minimizes the TSC is called the optimal reduction in exposure (ORE). In the presence of uncertainty, the BRDM chooses an action (or inaction) that would minimize the ETSC, with the assumption that the associated control cost monotonically increases with increasing exposure reduction. It should be noted that the BRDM is able to make a decision regardless of the degree of uncertainty in the available toxicity and exposure

information. Therefore, the value of additional toxicity information is evaluated against the ETSC with the ORE based on currently available information.

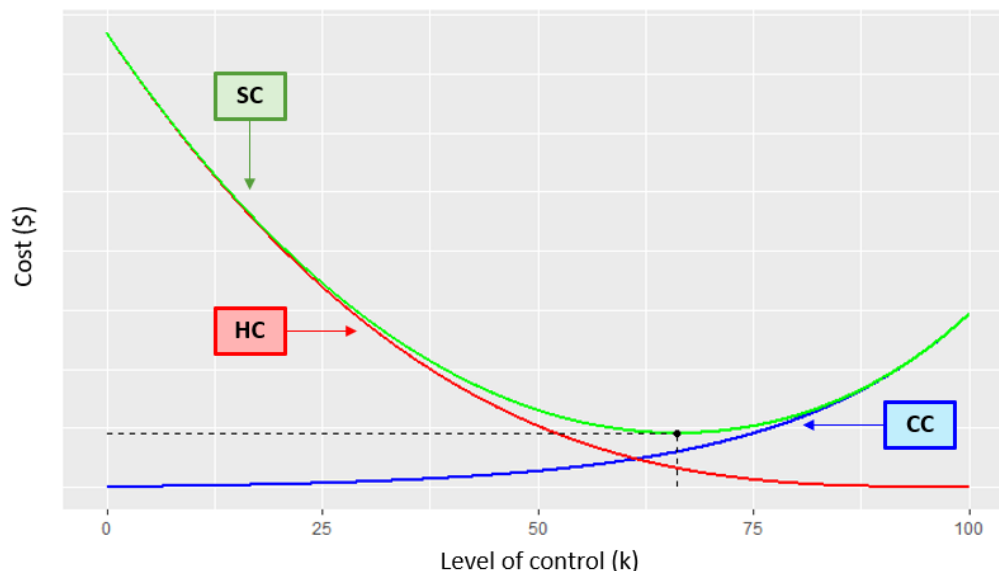


Figure 4-2. Illustration of social cost (SC) as a function of increasing control cost (CC) and decreasing health cost (HC). Optimal reduction in exposure (ORE) that minimizes social cost is denoted by black solid circle.

The TRDM takes regulatory action when the average population risk exceeds a prespecified TRL. The TRDM must consider uncertainty when determining whether the risk is above or below the TRL. Specifically, the TRDM chooses to regulate a chemical if a prespecified lower quantile, q_L , of the uncertainty distribution for risk exceeds the TRL. Similarly, the TRDM would conclude that exposure mitigation is not required when a prespecified upper quantile, q_U , of the uncertainty is below the TRL. Unlike the BRDM, the TRDM cannot determine whether the chemical requires a regulatory action without collection of further evidence when the TRL lies in between the q_L and q_U . A graphical representation of three types of situations, which the TRDM could encounter, is given in **Figure 4-3** below.

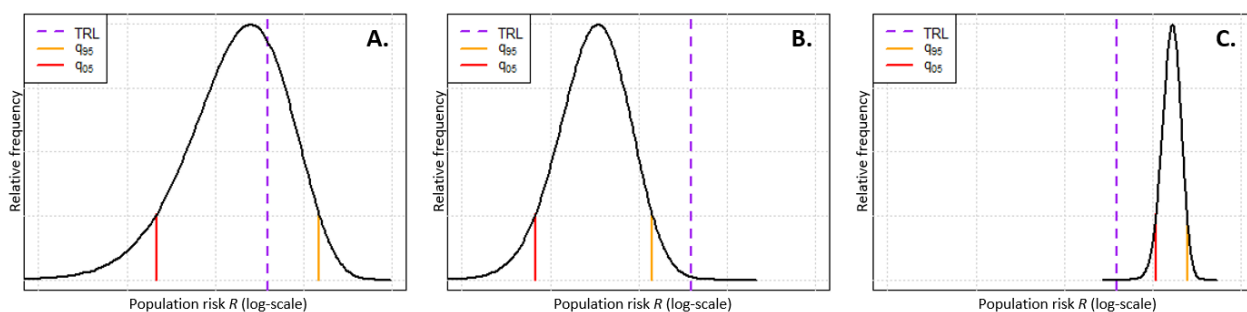


Figure 4-3. Illustration of three types of scenarios that the TRDM may encounter. (A) The TRL is in between the 5th and 95th percentiles of the uncertainty distribution about risk and therefore TRDM cannot make decision whether to implement exposure mitigation action without additional evidence. (B) The TRL is greater than the 95th percentile of the uncertainty distribution and therefore the TRDM would conclude that no regulatory action is required. (C) The TRL is below the 5th percentile of the uncertainty distribution and therefore TRDM would conclude that regulatory action is required. [Reproduced from Figure 2 from Hagiwara et al. (2022)]

4.3. VOI CONCEPTS AND METRICS

As noted in Section 4.1, the TSC is a sum of the THC, which reflects costs accrued prior to regulation and reduced costs after the implementation of regulation, and the total control cost (TCC) over a given time horizon [see [Hagiwara et al. \(2022\)](#), Eq. (10)]. The THC is a function of both the risk and the economic valuation of the adverse health effect(s) of interest, in addition to the time required to implement regulation, while the TCC is the cost of exposure mitigation once such action is implemented. The THC is reduced when exposure mitigation action is taken (and reduced more when action is taken earlier); however, the TCC increases as the reduction in exposure increases. When the time required to implement the regulation is fixed, there exists an ORE that minimizes the TSC.

In the presence of uncertainty, the ETSC is the objective function that the BRDM seeks to optimize when performing VOI analysis. In contrast, the TRDM uses the ETHC to calculate VOI. Both the ETSC and ETHC are the expected values of TSC and THC, respectively, for a given time horizon and decision-making paradigm. To assess the value of new information, a baseline expected value of current information, denoted as $EV|CI$, is calculated for each decision-making context. For the BRDM, $EV|CI$ is the minimal value of the ETSC based on ORE obtained using the current level of uncertainty about the population average risk [see [Hagiwara et al. \(2022\)](#), Eq. (18)]. For the TRDM, $EV|CI$ is the ETHC when uncertainty about toxicity and exposure is sufficiently great to preclude a regulatory decision, in which case no exposure mitigation action is taken based on the current level of uncertainty.

The expected value of immediate partial perfect information (EVIPPI) is the expected reduction in ETSC or ETHC (compared to the $EV|CI$ case) achieved through immediate perfect information about one or more of the parameters that govern the population risk. In the present report, the term ‘partial perfect information’ is used to refer to an elimination of uncertainty about μ_{tox} , as toxicity testing can only reduce uncertainty about μ_{tox} , and not uncertainty about exposure. Thus, EVIPPI can serve as an upper limit on the VOI for any alternative toxicity-testing strategy that may be contemplated.

In practice, it is impossible to eliminate uncertainty completely. The expected value of immediate sample information (EVISI) measures the reduction in ETSC or ETHC achieved by a toxicity test that reduces uncertainty in μ_{tox} by a known degree or proportion. This VOI metric does not consider the delay in decision-making due to testing and human health assessment process. Therefore, it serves as an upper limit on the VOI for the specific toxicity-testing method under consideration.

The expected value of delayed sample information (EVDSI) differs from the EVISI in that it acknowledges that both the ETSC and ETHC are impacted by the delay in decision-making due to toxicity testing and human health assessment process. A positive EVDSI value implies that the reduction in uncertainty due to testing is beneficial after taking this delay into account. The difference between the EVISI and EVDSI, which is the loss in value solely due to the delay component, is referred to as the cost of delay (COD).

The cost of toxicity testing needs to be considered when determining the VOI. The expected net benefit of sampling (ENBS), defined as the difference between the EVDSI and the cost of testing (COT), reflects these costs. Finally, the return on investment (ROI), defined as the ratio between ENBS and COT, reflects the economic benefits per dollar spent in testing.

In practice, implementing VOI analyses requires careful consideration of the health endpoint or endpoints to be included in the analysis and the methods used to evaluate each of these endpoints in economic terms. With multiple health endpoints, consideration will also need to be given to the nature of the dose-response relationship for each endpoint. The BRDM and TRDM may also be subject to different constraints in real-world decision making, which may need to be considered in conducting VOI analyses in specific circumstances.

It should be noted that additional toxicity testing has value when the information obtained through testing results in a posterior decision that differs from the prior decision that would have been taken in the absence of collecting additional toxicity data. By reducing uncertainty about the toxicity of the chemical of interest, it is possible to make a better decision on the need for regulatory action, within the context of the decision-making paradigm being used. For the BRDM, if the additional information results in a posterior ORE that is different from the prior ORE, the additional toxicity testing data has provided value by virtue of the reduction in uncertainty. For the TRDM, the value of uncertainty reduction is realized when the additional toxicity testing information leads to a decision to regulate the chemical of interest, resulting in a concomitant socio-economic benefit expressed as a reduction in health cost. In other words, if additional toxicity testing information cannot alter the decision under either of our two decision rules (benefit-risk or target-risk), such information does not provide value under the VOI framework used here.

The key concepts in VOI analysis are summarized in **Table 4-1**. Precise mathematical definitions of these concepts can be found in [Hagiwara et al. \(2022\)](#). A visual illustration of the quantitative relationships among the output parameters discussed in this section is provided in **Figure 4-4**.

Table 4-1. VOI concepts and their definitions

Concept	Definition
Indicators of public health impact	
THC – Total health cost	A sum of health cost over a pre-specified time horizon, which include both pre- and post-regulation periods.
TCC – Total control cost	A sum of control cost over a pre-specified time horizon, which incur only during the post-regulation period.
TSC – Total social cost	A sum of THC and TCC.
ETHC – Expected total health cost	An expected value of THC, which is integrated over the uncertainty distribution about risk.
ETSC – Expected total social cost	An expected value of TSC, which is integrated over the uncertainty distribution about risk.
Decision making styles	
BRDM – benefit-risk decision maker	A decision maker who would regulate a chemical if exposure mitigation action results in a reduced (E)TSC.
TRDM – target-risk decision maker	A decision maker who would regulate a chemical if the (lower quantile of) risk is greater than the pre-specified TRL.
VOI metrics	
ORE – Optimal reduction in exposure	An amount of exposure reduction that would minimize ETSC. (Applicable only to BRDM.)
EV CI – Expected value given current information	BRDM: Minimum reference ETSC achieved by choosing an ORE based on currently available information. TRDM: Reference ETHC without implementing exposure mitigation action.
EVIPPI – Expected value of immediate partial perfect information	Reduction in ETSC/ETHC from EV CI when perfect information is immediately available for toxicity parameters. [Larger EVIPPI values are preferred.]
EVISI – Expected value of immediate sample information	Reduction in ETSC/ETHC by collecting sample information about toxicity parameters that reduces uncertainty by a known amount without delay. [Larger EVISI values are preferred.]
EVDSI – Expected value of delayed sample information	Reduction in ETSC/ETHC by collecting sample information about toxicity parameters while incorporating costs associated with delay in decision-making (and thus mitigation) due to the time required to collect new data. [Larger EVDSI values are preferred.]
COD – Cost of delay	Difference between EVISI and EVDSI. [Smaller COD values are preferred.]
COT – Cost of testing	Direct cost associated with obtaining additional toxicity information. [Smaller COT values are preferred.]
ENBS – Expected net benefit of sampling	EVDSI minus COT. [Larger ENBS values are preferred.]
ROI – Return on investment	ENBS divided by COT. [Larger ROI values are preferred.]

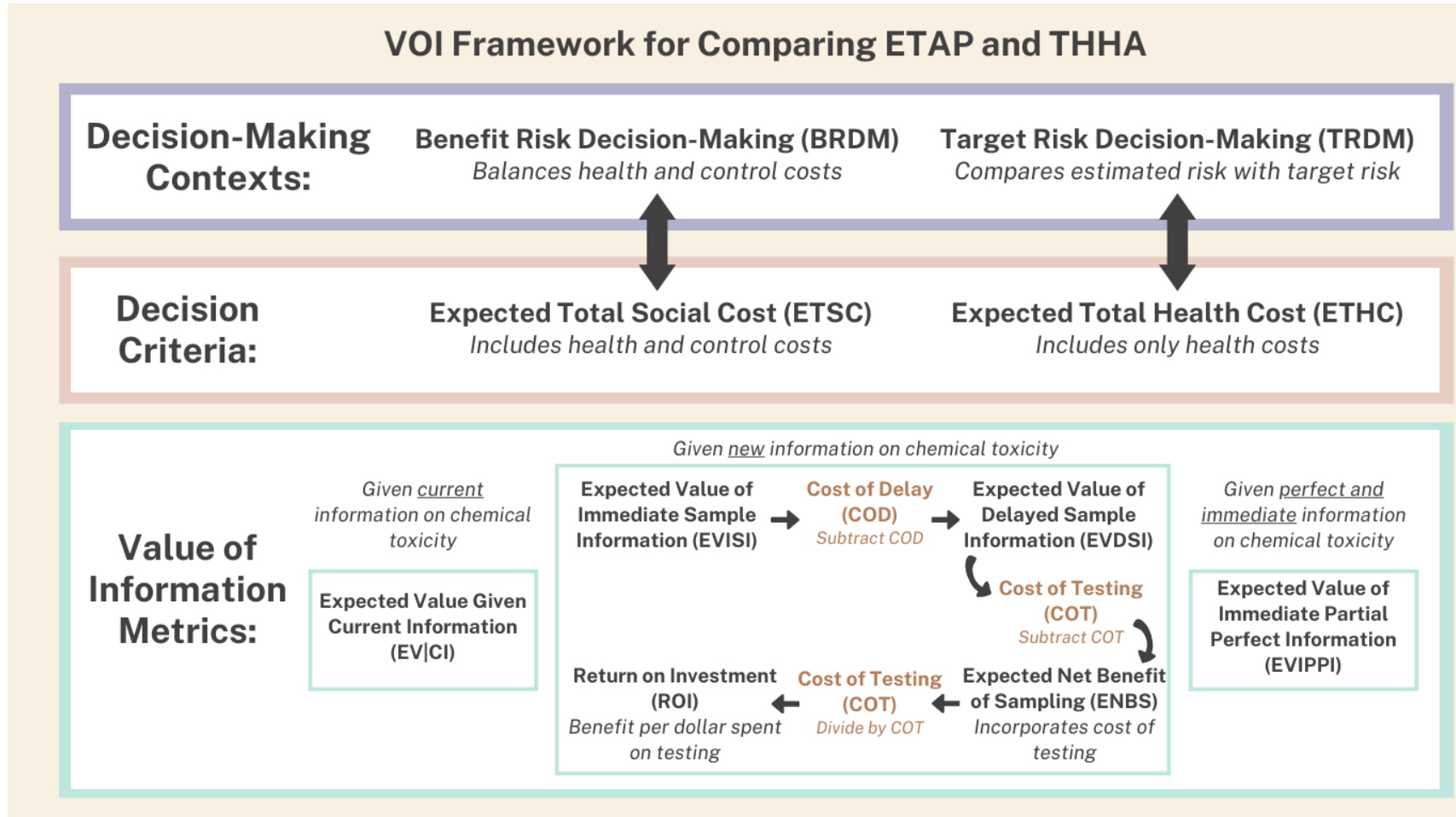


Figure 4-4. Illustration of the decision contexts and VOI metrics used in the current case study to compare ETAP and THHA.

5. PARAMETERIZATION OF VOI MODELS

Parameterization of the decision-making scenarios in the VOI analysis is informed, where possible, by realistic data on toxicity, exposure, chemical mitigation actions, health economics, and decision making. The parameterization is broken down into a core set of baseline scenarios and a complementary set of sensitivity analysis scenarios (**Fig. 3-1**). The core set of baseline scenarios reflect potential differences in exposure characteristics and decision contexts while the sensitivity analysis scenarios were developed to investigate potential impacts of varying other important parameters in the VOI analyses. The range in parameter values in both the baseline and sensitivity analysis scenarios were designed to evaluate potential differences in VOI across the diverse set of chemicals that could be candidates for human health assessment by ETAP or THHA.

5.1. TOXICOLOGICAL PARAMETERIZATION

5.1.1. PRIOR UNCERTAINTY IN TOXICITY

In order to apply the VOI framework discussed in Section 2, it is necessary 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. The original VOI framework used data previously considered by [Krewski et al. \(1993\)](#) on variation on the potency of the chemical carcinogens as well as data used by [Chiu et al. \(2018\)](#) on variation in toxicity reflected in distribution of PODs for non-cancer, critical effects. To characterize the prior distribution of chemical toxicity in this case study, we utilize data on 608 chemicals considered previously by [Chiu et al. \(2018\)](#). These chemicals include substances evaluated under the EPA Integrated Risk Information System (IRIS), the Office of Pesticide Programs (OPP), Superfund Regional Screening Levels (RSLs) programs, as well as substances evaluated by California EPA Office of Environmental Health Hazard Assessment. With more than one endpoint evaluated for many of these chemicals, there are a total of 1,522 chemical-endpoint combinations in this database. As indicated in **Figure 5-1**, the 1,522 chemicals and endpoints considered by [Chiu et al. \(2018\)](#) reflect a variety of subchronic and chronic toxicity (non-cancer) endpoints.⁷

The median human dose (HD_M^I) associated with an effect of magnitude (M) and population incidence (I) across the 1,522 chemicals and endpoints considered by [Chiu et al. \(2018\)](#) is $HD_M^{50} = 3.26$ mg/kg-day using the average human body weight of 80kg ([EPA 2011c](#)), corresponding to a value of $\mu_{tox} = \log_{10}(HD_M^{50}) = 0.51$. Excluding chemicals with extremely high potencies, such as 2,3,7,8-

⁷ Although a subset of the chemicals considered by Chiu et al. (2018) may also increase cancer risk, only the non-cancer outcomes were considered in their analysis of this dataset.

tetrachlorodibenzo-*p*-dioxin and those chemicals tested above the limit dose of 1,000 mg/kg-day, the distribution of toxic potency spans approximately 6 orders of magnitude (OM). Assuming this represents approximately 99.9% of the variation in the PODs for non-cancer endpoints expressed by these chemicals, the \log_{10} prior uncertainty standard deviation in chemical toxicity of an untested chemical $u^0(\mu_{tox})$ is given by $6/(2z_{0.9995}) = 6/6.58 = 0.912$.

Information on σ_{tox} , which is the logarithm of the geometric standard deviation [$\log_{10}(\text{GSD})$] of human susceptibility, is provided by the International Programme on Chemical Safety (IPCS) [WHO (2017), Table 4.4]⁸. The value of σ_{tox} is calculated to be 0.424 using the midpoint of 5th and 95th percentiles ($P_{05} = 0.151$ and $P_{95} = 0.697$), with uncertainty about σ_{tox} being $u(\sigma_{tox}) = 0.166$. Since σ_{tox} cannot be negative, the VOI framework currently integrates uncertainty distribution between $\pm 6u(\cdot)$ about the mean, $u(\sigma_{tox})$ as $\sigma_{tox}/6 = 0.0706$.

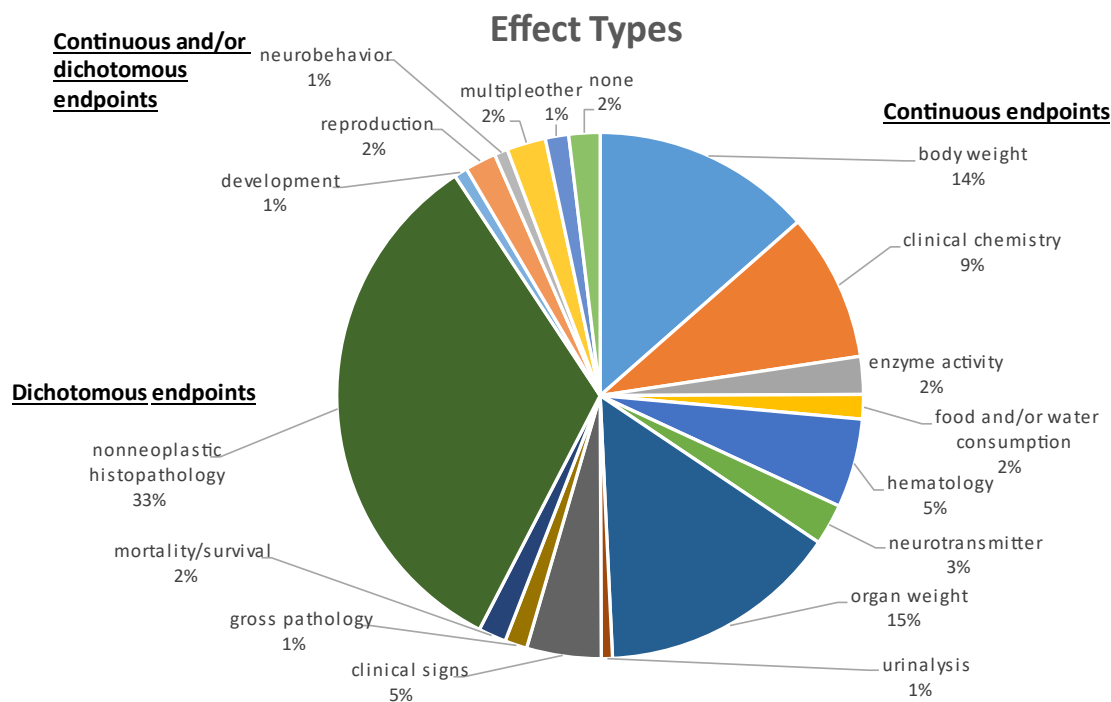


Figure 5-1. Overview of toxicological effect types represented by 1,522 chemicals and endpoints. [Reproduced from Chiu et al. (2018), Figure 5A, originally published in *Environmental Health Perspectives*, with permission from the authors.]

5.1.2. CONDITIONAL POSTERIOR UNCERTAINTY ABOUT μ_{tox} FOR THHA

In order to extrapolate the results of two-year rodent bioassays to humans, it is necessary to translate the value of μ_{tox} to an HED. This is done using the HD_M^1 , as outlined by Chiu et al. (2018). In

⁸ IPCS obtained the variability in human susceptibility by combining toxicokinetic (TK) and toxicodynamic (TD) variability in equipotent dose distributions for humans.

addition to providing a best estimate of the HED, the uncertainties associated with the various steps in this extrapolation need to be considered. As indicated in **Table 5-1**, key sources of uncertainty include variation among animals within a given bioassay, uncertainties in allometric scaling in extrapolating from animals to humans, and differences in toxicokinetics (TK) and toxicodynamics (TD) between animals and humans, after adjusting for differences in body weight.

The sources of uncertainty summarized in **Table 5-1** are characterized by the ratio, P_{95}/P_{50} , of the 95th to 50th percentiles of the respective uncertainty distributions. Intra-study variation is reflected in the BMD/BMDL ratio. The BMDL is the lower confidence limit of the estimated BMD. As a result, toxicity tests with less uncertainty will result in the BMDL being closer to the BMD, and correspondingly smaller BMD/BMDL ratios. To estimate the uncertainty associated with the BMD values derived from animal bioassay, data from 584 two-year rodent bioassays are used to determine the distribution of BMD₁₀/BMDL₁₀ ratios ([Sand et al. 2011](#)), where BMD(L)₁₀ corresponds to BMD(L) values associated with a benchmark response (BMR) of 10% extra risk. The mean BMD₁₀/BMDL₁₀ ratio across 584 datasets was 1.803 and is used as the estimated intra-study variability shown in **Table 5-1**. The uncertainty due to allometric scaling (1.235) is based on results reported by [Chiu et al. \(2018\)](#), and the uncertainty in differences in TK/TD between animals to humans (3.000), is taken from published work by the IPCS [[WHO \(2017\)](#), Table 4.3].

Table 5-1. Sources of uncertainty for two-year rodent bioassays in THHA

Source of Uncertainty	Uncertainty (P_{95}/P_{50})	$[\text{Log}_{10}(P_{95}/P_{50})]^2$
Intra-study (BMD/BMDL) ^a	1.803	0.066
Allometric scaling ^b	1.235	0.008
Animal-human TK/TD ^c	3.000	0.228
Total		0.302

^a Calculated based on the distribution of 584 BMD₁₀/BMDL₁₀ ratios for rodent bioassays presented in Sand et al. (2011).

^b Taken from Chiu et al. (2018).

^c Taken from Table 4.3 in IPCS (WHO 2017).

Let HD denote the HD_M⁵⁰. Following [Chiu and Slob \(2015\)](#), the uncertainty standard deviation for HD using the three sources of uncertainty about HD in **Table 5-2** can be obtained by first calculating the ratio P_{95}/P_{50} for the HD as

$$\frac{P_{95\text{HD}}}{P_{50\text{HD}}} = 10^{\left\{ \sum_{i=1}^3 \left[\log_{10} \left(\frac{P_{95,i}}{P_{50,i}} \right) \right]^2 \right\}^{1/2}} = 10^{(0.302)^{1/2}} = 3.541, \quad (2)$$

and then converting the ratio to the GSD as

$$\text{GSD}_{\text{THHA}} = \left(\frac{P_{95\text{HD}}}{P_{50\text{HD}}} \right)^{1/1.645} = 2.157. \quad (3)$$

The sample standard deviation σ_B for the bioassay is obtained by taking the logarithm of the GSD, with

$$\sigma_{\text{THHA}} = \log_{10}(\text{GSD}_{\text{THHA}}) = 0.334. \quad (4)$$

Under the assumption of lognormality in both the prior uncertainty in μ_{tox} and variability in the sample information, application of Bayesian updating leads to the conditional posterior uncertainty standard deviation of

$$u_{\mu_{\text{tox}}}^{\text{THHA}} = \left(\frac{\sigma_B^2 (u_{\mu_{\text{tox}}}^0)^2}{\sigma_B^2 + (u_{\mu_{\text{tox}}}^0)^2} \right)^{\frac{1}{2}} = \left(\frac{0.334^2 \times 0.912^2}{0.334^2 + 0.912^2} \right)^{\frac{1}{2}} = 0.313. \quad (5)$$

5.1.3. CONDITIONAL POSTERIOR UNCERTAINTY ABOUT μ_{tox} FOR ETAP

The information required to derive the posterior conditional uncertainty about μ_{tox} following a five-day transcriptomic study is summarized in **Table 5-2**. This source of uncertainty is gauged in terms of intra-study variability, estimated by the average of the transcriptomic BMD₁₀/BMDL₁₀ ratios for 14 chemicals for which both five-day *in vivo* transcriptomic and chronic rodent bioassay dose-response data are available and analyzed as described in the ETAP scientific support document (EPA 2024c; Gwinn et al. 2020)⁹. Since both the two-year bioassay and five-day transcriptomic studies are *in vivo* toxicity testing strategies using rodents, the uncertainty due to allometric scaling and animal-human TK/TD remains the same for both methods.

Table 5-2. Sources of uncertainty for five-day transcriptomic studies in ETAP

Source of Uncertainty	Uncertainty (P ₉₅ /P ₅₀)	[Log ₁₀ (P ₉₅ /P ₅₀)] ²
Intra-study (BMD/BMDL) ^a	3.476	0.293
Allometric scaling ^b	1.235	0.008
Animal-human TK/TD ^c	3.000	0.228
Total		0.529

^a Calculated based on the distribution of 14 BMD₁₀/BMDL₁₀ ratios for ETAP considered by EPA (EPA 2023a).

^b Taken from Chiu et al. (2018).

^c Taken from Table 4.3 in IPCS (WHO 2017).

Using the VOI parameters in **Table 5-2** and performing the same calculations presented in Section 5.1.2 for the bioassay, the sample standard deviation of the five-day transcriptomic studies in ETAP is obtained as

$$\sigma_{\text{ETAP}} = \log_{10}(\text{GSD}_{\text{ETAP}}) = 0.442, \quad (6)$$

with the posterior conditional uncertainty about μ_{tox} being

$$u^{\text{ETAP}}(\mu_{\text{tox}}) = 0.398. \quad (7)$$

⁹ The primary data from the Gwinn *et al.*, 2020 study that was utilized for the analysis are accessible online at: <https://cebs.niehs.nih.gov/cebs/paper/14731>. The transcriptomic BMD analysis files from the ETAP scientific support document are available at: <https://clowder.edap-cluster.com/datasets/660ad607e4b063812d700fe6>

It should be noted that, for both methods, toxicity testing reduces the uncertainty in μ_{tox} , but not σ_{tox} , as the latter parameter reflects inter-individual variation in susceptibility in the target population.

5.2. EXPOSURE PARAMETERIZATION

In order to ensure that the case study reflects realistic chemical exposures, the EPA's High-Throughput Stochastic Human Exposure and Dose Simulation Model (SHEDS-HT) ([Isaacs et al. 2014](#)) was used to obtain exposure estimates for 1,578 chemicals from the TSCA active inventory. Exposure estimates were generated for a simulated population of 10,000 individuals using published parameterizations of consumer products ([Ring et al. 2019](#)) and food contact pathways ([Biryol et al. 2017](#); [Ring et al. 2019](#)).¹⁰

Although the majority of the U.S. population is expected to be exposed to most of these chemicals, the exposed population can be quite small for other chemicals. SHEDS-HT makes two key assumptions in its predictions of chemical exposures: first, the prevalence of any chemical within food contact materials (*i.e.*, the fraction of foods contacting materials containing chemical) is assumed to be 100%; and second, the prevalence of any specific chemical within all products is assumed to be 100%, as the market penetration of any given product formulation is unknown. These two assumptions provide conservative estimates of exposure for a broad array of chemicals, but likely overestimating actual real-world exposures. It should be noted that these two routes do not cover all possible exposure pathways (excluding, for example, food chemicals such as food additives and contaminants). As such, the exposure profiles developed using SHEDS-HT may not reflect total exposure to the chemical of interest from all possible sources and routes. Nonetheless, SHEDS-HT does provide a rich source of exposure data spanning a broad range of chemical exposure profiles. As the VOI analyses focus on impacts on the exposed population, the logarithm (\log_{10}) of the geometric mean (GM) for exposed individuals across the 1,578 chemicals and the logarithm of the GSD averaged across chemicals are used as the μ_{exp} (-2.271) and σ_{exp} (0.493), respectively.¹¹ In order to calibrate uncertainty about the true value of μ_{exp} , the variation in mean exposure across chemicals, given by $u(\mu_{\text{exp}}) = 1.401$, was used as a proxy indicator of uncertainty in μ_{exp} , in much the same way as the uncertainty in μ_{tox} was gauged by variation in toxicity of chemicals that have been previously tested. Similarly, the uncertainty in the true value of σ_{exp} is given by $u(\sigma_{\text{exp}}) = 0.183$, calculated as the standard deviation of the values of the σ_{exp} across chemicals. As discussed in Section 5.1.1, $u(\sigma_{\text{exp}})$ is set to $\sigma_{\text{exp}}/6 = 0.0305$ to avoid negative σ_{exp} value in the VOI calculation.

¹⁰ Included in these 1,578 chemicals were 665 chemicals present in consumer products, 625 chemicals in food contact materials, and 288 chemicals present in both consumer products and food contact materials. The aggregated population exposure estimates were generated using SHEDS-HT version v.0.1.8.

¹¹This calculation assumes a lognormal distribution of exposure within the exposed population, so that the GMs and GSDs in SHEDS-HT can be converted to logarithmic exposures to be used within the VOI framework.

Because of the extremely large variation in exposure estimates across all 1,578 chemicals from the SHEDS-HT model, using the entire dataset as the basis for gauging prior uncertainty in exposure would introduce substantial uncertainty into the VOI analysis that is not reduced by toxicity testing. Expecting that some prior information about exposure will be available for most chemicals based on intended use and other information, the SHEDS-HT dataset was partitioned into nine domains. The chemicals were first partitioned, into three tertiles based on their μ_{exp} values (representing low, medium, and high average exposure), with 526 (=1,578/3) chemicals in each level of average exposure. Chemicals were further sub-partitioned into three tertiles based on their σ_{exp} values (representing low, medium, and high variability in exposure). Each of the resulting 3x3=9 exposure domains contain approximately 175 (=526/3) chemicals.

For the i th domain ($i = 1, \dots, 9$), $\mu_{exp,i}$ and $\sigma_{exp,i}$ are estimated by taking the means within the subgroup as summarized and represented graphically in **Figure 5-2**. The corresponding uncertainty standard deviations $u(\mu_{exp,i})$ and $u(\sigma_{exp,i})$ are also summarized in **Table 5-3**.

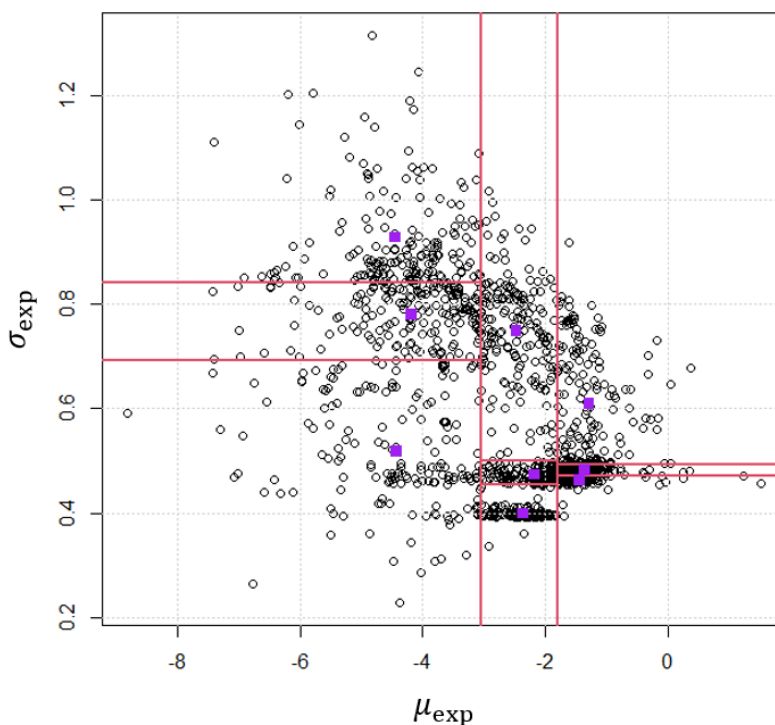


Figure 5-2. Scatter plot showing μ_{exp} and σ_{exp} for the exposed population across 1,578 chemicals from SHEDS-HT. The exposure estimates are partitioned into nine domains by dividing μ_{exp} and σ_{exp} into tertiles (*i.e.*, low/medium/high). The purple squares denote the average $\mu_{exp,i}$ and $\sigma_{exp,i}$ for each partitioned domain.

Table 5-3. Exposure parameters for nine conditional exposure scenarios

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 ^a
$\mu_{exp,i}$	-4.419	-4.180	-4.438	-2.358	-2.175	-2.469	-1.439	-1.357	-1.282
$u(\mu_{exp,i})$	1.076	0.965	0.881	0.307	0.341	0.365	0.423	0.325	0.417
$\sigma_{exp,i}$	0.517	0.780	0.927	0.399	0.473	0.748	0.463	0.482	0.609
$u(\sigma_{exp,i})$	0.086	0.042	0.093	0.013	0.010	0.100	0.008	0.006	0.101

^a $\mu(\sigma_{exp,i})$ is reduced to $\sigma_{exp,i}/6$

5.3. OTHER PARAMETERS

The VOI analysis requires selecting parameters that govern not only the toxicity and exposure information on the range of chemicals for which the two toxicity testing and assessment processes may be applied, but also the economic valuation of various outcomes and timelines. This section summarizes the rest of the parameters used in the VOI analysis presented in Section 6.1.

5.3.1. ADVERSE HEALTH OUTCOME VALUATION

The economic value associated with adverse health outcomes varies widely with the severity of the outcome, including whether the outcome is acute or chronic, non-life-threatening or fatal, and irreversible or reversible. Health economists have estimated and applied a value of a statistical life (VSL) of \$8.8M¹² (EPA 2022b). Most valuations of non-fatal adverse health effects focus on direct medical costs, lost productivity, and direct non-medical costs such as education or transportation.¹³ In an international review of the economic costs associated with childhood disabilities, Shahat and Greco reported a range of annualized values from \$450 to \$69,500, corresponding to \$36,000 to \$5.6M over the course of an 80-year lifetime (Shahat and Greco 2021). While the range of valuations is informative, the lower values in this range may not be directly relevant in the U.S. context, because of the higher cost of the U.S. health system compared to other developed countries. Economic values have also been estimated for specific diseases in the U.S. including autism at \$69,530 annually (Ganz 2007), asthma at \$36,500 (Belova et al. 2020), Down syndrome at \$15,311 (Peng et al. 2009), and pervasive developmental disorders at \$10,538 (Peng et al. 2009). Buescher et al. (2014) estimated the annual costs (in 2011 dollars) for children with autism spectrum disorders (ASD) and intellectual disability at \$86,000 - \$107,000 annually (depending on age) and for children with ASD and no

¹² VSL given in 2016 USD, based on a base value of \$7.4M in 2006 USD (EPA 2022a).

¹³ These estimates are based on costs of illness rather than the willingness to pay measure of value for changes in health risks that focus on changes in individual well-being, referred to as welfare or utility. For more information, consult EPA’s Guidelines for Preparing Economic Analyses (EPA 2010).

intellectual disability at \$52,000 - \$63,000. Although these examples do not constitute a systematic review of the literature on health effects valuations, they provide useful benchmarks for determining the range of economic values for adverse health outcomes to be used in the present VOI analysis.

In the previously published VOI analyses, [Hagiwara et al. \(2022\)](#) considered annualized valuations of \$110,000 for a fatal outcome.¹⁴ Acute adverse health effects, such as a restricted airway event, were valued at \$70 per occurrence¹⁵ ([EPA 2013, 2021](#)). Assuming an expected rate of occurrence of one event per week, this corresponds to an annualized cost of \$2,600. Considering the range of valuations discussed above, values of \$110,000, \$10,000, and \$1,000 are used in the present VOI analysis to capture the potentially broad range of adverse outcomes following exposure to an untested chemical. As the great majority (>98%) of the adverse health effects caused by the 1,522 chemicals and endpoints considered by [Chiu et al. \(2018\)](#) are not fatal, a value of \$10,000 is used in the baseline scenarios in the analysis, with the other two values presented as sensitivity analyses (Section 6.2).

5.3.2. CONTROL COSTS

Control costs were evaluated that would capture both the high and low ends in the range of costs for a chemical that may be evaluated by ETAP. At the high end, the maximum annualized control cost, denoted by ACC_{\max} , for reducing emissions of key air pollutants in the United States was considered. EPA estimated an average annual control cost of \$2.0B for individual air pollutants such as acid gas, mercury (Hg), particulate matter less than 2.5 microns in aerodynamic diameter ($PM_{2.5}$), and sulfur dioxide (SO_2) ([EPA 2011b](#)). Trends in emission rates demonstrated a reduction of 25% between 1990 and 2021 across the following seven key air pollutants: carbon monoxide (CO), ammonia (NH_3), nitrogen oxides (NO_x), $PM_{2.5}$, PM_{10} , SO_2 , and volatile organic compounds (VOCs) ([EPA 2022a](#)). As the cost of exposure reduction is expected to increase as exposure is reduced to lower and lower levels, the annualized control is modelled as

$$ACC_k = ACC_{\max} \left(\frac{10^{\eta k} - 1}{10^{\eta} - 1} \right). \quad (8)$$

where $0 \leq k \leq 1$ denotes the proportionate reduction in mean exposure and $\eta > 0$ governs the steepness of this relationship. Setting $\eta = 1$ and solving Eq. (8) for ACC_{\max} gives \$23.1B, which is used as the default value for this cost parameter.

At the lower end of the range of control costs, a recent evaluation of the costs of chemical restriction proposals between January 2010 to May 2020 under the European Union's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) indicated an annualized total

¹⁴ The value of \$110,000 does not correspond to the value of a single life year, but rather to the annualized value of a risk reduction action that is assumed to occur over an 80-year period, based on the VSL of \$8.8M used by EPA.

¹⁵ This estimate is based on willingness-to-pay to avoid a single asthma attack.

expenditure of €1.7B across all the proposals ([ECHA 2021](#)). The annualized control cost associated with each of the 33 risk management programs considered in this evaluation are shown in **Figure 5-3**. Annualized control cost ranges from a low of €12K associated with substitution of trifluoroacetate salts in spray products to a high of €955M for reformulation and compliance cost for intentionally added microplastics.¹⁶ The mean and median control cost across all chemical control programs included in this program were €53.3M and €6M, respectively, corresponding to \$50.6M and \$5.7M, based on average 2022 exchange rates. Excluding those programs with zero cost, the mean and median values increased to €60.7M (\$57.6M) and €17.6M (\$16.7M), respectively. Based on the diverse set of chemical control programs, a control cost using ACC_{max} of \$578M (using Eq. (8) with a \$50M ACC at 25% reduction and $\eta = 1$) is included for the sensitivity analysis in addition to the \$23.1B used for the baseline scenarios discussed above.

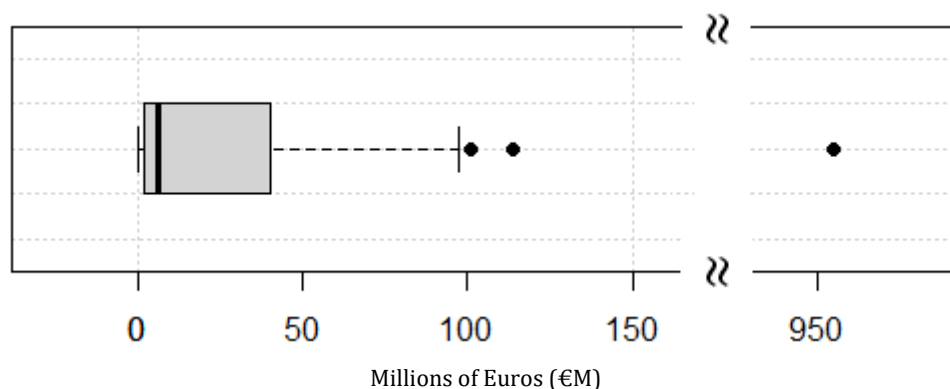


Figure 5-3. Boxplot of annualized control cost associated with 33 risk management programs under the REACH registration (in €M). The overall median and mean control costs are €6M and €53.3M, respectively.

5.3.3. AFFECTED POPULATION SIZE

For the baseline scenarios, the size of the affected population is set to be $N = 330M$ people, representing essentially the entire U.S. population. To investigate the impacts associated with only a subset of the population being exposed, two sensitivity analysis scenarios were evaluated for population sizes in which 165M (50% of the U.S. population), and 33M (10%) people are exposed.

5.3.4. DISCOUNT RATE

To account for the fact that costs and benefits realized in the future are of less economic value than those realized immediately, a discount rate of $r = 5\%$ is applied in the calculation of the TSC to standardize all costs and benefits to their net present values at the beginning of the time horizon. The present case study employed a discount rate of 5%, consistent with the recommendation of the EPA Science Advisory Board (SAB)([EPA 2004](#)) and current economic conditions. Other discount rates

¹⁶ Several control programs with zero cost, such as an industry decision to move away from use of long-chain perfluorinated substances, are excluded from this range.

could also be considered, such as the value of 3% subsequently recommended by the 2010 EPA economic analysis guidelines (EPA 2010). Sensitivity analyses previously conducted by Hagiwara et al. (2022) using discount rates of 3, 5, and 7% showed that choice of discount rate did not dramatically alter VOI.

5.3.5. TOXICITY TESTING AND ASSESSMENT DURATION

The baseline analysis relies on estimates that the THHA requires 8 years from the start of toxicity testing to reaching a regulatory decision. This timeline was based on observations that the traditional two-year rodent bioassay takes an average of 4 years to complete (Faustman and Omenn 2015; NTP 1996; Pastoor and Stevens 2005), and the typical human health assessment process is estimated to take an additional 4 years (Krewski et al. 2020). To investigate the effect of shortening the testing and assessment time of THHA, a sensitivity analysis scenario was considered that reduces the human health assessment process to 2 years, thereby encompassing a 6-year timeframe for testing and decision making. The 2-year timeframe is consistent with the targets for implementation of the streamlined IRIS assessment process for less challenging assessments¹⁷. The effects of a longer time frame for THHA were also considered. The NTP routinely establishes and conducts high quality toxicity testing studies on chemicals selected for analysis via a nomination process. For the most recent chemicals tested that evaluated effects of chronic exposure to adult animals as the primary focus, the completion time from the start of the 2-year bioassay and issuance of the report was on average 8 years, with a standard deviation of approximately 1 year, and with a maximum duration of 9.5 years¹⁸. Based on this information, sensitivity analysis was performed on the approximate maximum of 10 years for toxicity testing and the 4 years required to complete the assessment with the total time resulting in a delay in decision making as long as 14 years with THHA.

For the ETAP, the baseline analysis assumes that the studies and human health assessment can be completed in 6 months¹⁹. It is possible that delays may be encountered when performing an ETAP due to issues such as chemical purity, stability, or selecting the appropriate dose range. To investigate the effects of lengthening the time required for testing and developing the human health

¹⁷ Refers to GAO Report GAO-12-42 assessing the EPA's 2009 revisions to the IRIS program, accessible via <https://www.gao.gov/products/gao-12-42>.

¹⁸ Time frame estimates were derived from the time elapsed between the start of dosing for the two-year rodent bioassay and the publication date of the technical reports for TR-585 through TR-594 published between September 2014 and January 2019. Estimates do not include project scoping, pre-study evaluations, or the 90-day subchronic study. For more information on NTP technical reports, visit <https://ntp.niehs.nih.gov/data/tr>.

¹⁹ While the average production time for an ETAP has been 6 months, the Agency anticipates that ETAPs will be issued within 9 months of chemical procurement to issuance of the assessment. For those chemicals that meet the ETAP applicability domain, but for which orthogonal data suggests a change to the standard methods, the Agency has established an external peer review process that may impact the time to issue the assessment for those rare cases.

assessment for ETAP, additional sensitivity analyses were performed assuming 1-year and 2-year timeframes.

5.3.6. TIME HORIZON

The time horizon, denoted by TH, over which the TSC is calculated, is set to 20 years in the baseline scenarios since it is a time frame commonly used in health economics. In sensitivity analysis scenarios, additional time horizons of 40 years and 75 years were considered for evaluating impacts of health effects that may be encountered by the exposed population over a generation or over a lifetime.

5.3.7. STUDY AND ASSESSMENT COSTS

In the baseline scenarios, the costs of performing a chronic rodent bioassay was estimated to be \$4M and derived from multiple sources ([Faustman and Omenn 2015](#); [NTP 1996](#); [Pastoor and Stevens 2005](#)). To evaluate the impact of alternative assumptions about the cost of toxicity testing, an additional sensitivity analysis was conducted using different study costs. Bottini and Hartung estimated the cost of a traditional chronic rodent bioassay to be €780K, or \$845K ([Bottini and Hartung 2009](#)). Typically, a traditional chronic bioassay is conducted following a subchronic or other short-term study to set the appropriate dose range. When combined with a subchronic toxicity study (€116K, or \$126K) or a short-term study (€49K, or \$53K), the total cost of testing for THHA may be between \$898K and \$971K. For the sensitivity analysis, the cost of THHA was reduced to \$1M.

For the ETAP, the five-day *in vivo* transcriptomic study and ETAP process currently costs approximately \$200,000 for the baseline scenario²⁰. The most variable cost component of an ETAP assessment is chemical procurement, which can range from less than \$5K to over \$50K. In the sensitivity analysis, the effect of changing the study cost was investigated by assuming that the cost associated with ETAP is increased to \$250K.

Although it is recognized that there are labor costs associated with the review of available data and with the composition and issuance of the human health assessment, in the absence of authoritative quantitative information on the relevant average labor costs, the cost associated with development of the traditional human health assessment is presumed to be \$0 for the purposes of the case study. In the case of ETAP, the assessment labor costs are expected to be significantly less than with THHA due to the ETAP standardized reporting format and significantly shorter time required for data review and quality assurance steps, which would impact the VOI to favor ETAP.

²⁰ Cost estimates related to the ETAP are based on EPA ORD experience with conducting the transcriptomic studies (2022 estimates).

5.3.8. ADDITIONAL CONSIDERATIONS FOR TARGET-RISK DECISION-MAKING

The decision rule for the TRDM requires specification of the q_L and q_U to determine whether the chemical of interest warrants exposure mitigation action. In the present analysis, the q_L and q_U are set to 5% and 95%, respectively. Unlike the BRDM, who considers the cost of exposure reduction, leading to an optimal reduction in exposure, decisions taken by the TRDM are driven by achieving the TRL regardless of exposure reduction cost. Acknowledging that it is not always possible to eliminate exposure, it is assumed that the TRDM reduces the GM of the population exposure by 90% when exposure mitigation is deemed necessary ([Hagiwara et al. 2022](#)). While EPA does not have a recommended TRL for non-cancer effects, a value of 10^{-6} is often used for cancer-related effects ([EPA 2009](#)). The baseline scenarios were conducted using a $TRL = 10^{-6}$. For the sensitivity analysis, a $TRL = 10^{-4}$ was also considered. [Chiu et al. \(2018\)](#) noted that the median residual risk at the traditional reference dose (RfD) for most of the 1,522 chemicals and endpoints included in their analysis is less than 0.01%.

A summary of the parameter values governing prior information on toxicity and exposure, toxicity testing and assessment, economic valuation of health impact, and decision making contexts used in the baseline scenarios of ETAP versus THHA presented in Section 6.1 is given in **Table 5-4**. Results from the variations in these parameter values were used in the sensitivity analyses presented in Section 6.2.

Table 5-4. Summary of parameter values used in the baseline VOI analysis of ETAP versus THHA.

Parameter	Description	Value
Toxicity and exposure information		
μ_{tox}	$\log_{10}(HD_M^{50})$	0.51 (log ₁₀ -mg/kg-day)
$u(\mu_{tox})$	Uncertainty standard deviation about μ_{tox}	0.91 (log ₁₀ -mg/kg-day)
σ_{tox}	\log_{10} (GSD) for human susceptibility	0.424 (unitless)
$u(\sigma_{tox})$	Uncertainty standard deviation about σ_{tox}	0.07 (unitless)
μ_{exp}	\log_{10} (GM) for population exposure	-4.42 ~ -1.28 (log ₁₀ -mg/kg-day)
$u(\mu_{exp})$	Uncertainty standard deviation about μ_{exp}	0.31~1.08 (log ₁₀ -mg/kg-day)
σ_{exp}	\log_{10} (GSD) for population exposure	0.40~0.93 (unitless)
$u(\sigma_{exp})$	Uncertainty standard deviation about σ_{exp}	0.006~0.10 (unitless)
Toxicity testing and assessment process information		
σ_{ETAP}	Sampling variability for ETAP	0.442 (unitless)
COT_{ETAP}	Cost of running ETAP	\$200,000
t_{ETAP}	Time required to obtain ETAP information	6 months
σ_{THHA}	Sampling variability for THHA	0.334 (unitless)
COT_{THHA}	Cost of running THHA	\$4M
t_{THHA}	Time required to obtain THHA information	8 years
Economic valuation		
N	Affected population size	330 million persons
t_{imp}	Time required to implement regulation	2 years
TH	Time horizon	20 years
AHC	Annualized health cost	\$10,000
ACC_{max}	Maximum annualized control cost	\$23.1B
η	Steepness parameter for control cost function	1 (unitless)
r	Discount rate	5%
TRDM specific information		
q_L	Lower quantile for uncertainty distribution about risk	5 th percentile
q_U	Upper quantile for uncertainty distribution about risk	95 th percentile
TRL	Target risk level	10^{-6} (unitless)
k_{TRDM}	Proportion of exposure reduction	90%

6. VOI CASE STUDY RESULTS

6.1. VOI ANALYSIS OF ETAP VERSUS THHA

6.1.1. BENEFIT-RISK DECISION MAKING

The BRDM seeks an optimal reduction in exposure to balance the costs associated with exposure mitigation against the corresponding public health benefit. The results of the VOI analysis for the BRDM and the nine baseline scenarios corresponding to each of the nine categories in the 3×3 grid of SHEDS-HT exposures (**Figure 5-2**) are summarized in **Figure 6-1** and **Table 6-1**. The results for Baseline Scenario 5, in which both μ_{exp} and σ_{exp} are assigned to the middle categories in this grid, are used as the starting point for the discussion of the results, followed by evaluation of the results for lower and higher values of μ_{exp} and σ_{exp} .

In Baseline Scenario 5, EV|CI is \$293B. This value represents the ETSC minimized over the 20-year time horizon, without collecting any additional information, obtained by proportionately reducing exposure by the optimal value of 78% (*i.e.*, the ORE is 78%). The EVIPPI, which represents the reduction in the ETSC obtained with immediate perfect information about μ_{tox} for the chemical of interest, is \$154B. This implies that the ETSC may be reduced by up to 52% by eliminating uncertainty in μ_{tox} .

In the presence of experimental error (neither test can completely eliminate uncertainty), ETAP and THHA can reduce the ETSC by as much as \$133B and \$143B, respectively, as indicated by their EVISIs values. These EVISIs account for 87% and 93% of EVIPPI value, respectively, indicating that the value of information for both ETAP and THHA is high. What distinguishes these two approaches is the time required to obtain the results of the toxicity testing and human health assessment. As the delay associated with ETAP is only 6 months, with the THHA taking 8 years to complete, their CODs – \$12B for ETAP and \$169B for THHA – are notably different. In fact, the COD for THHA is greater than its EVISI, resulting in a negative value for $\text{EVDSI}_{\text{THHA}}$ of -\$26B, while $\text{EVDSI}_{\text{ETAP}}$ remains positive at \$121B. The comparison of EVDSI values for these two toxicity testing strategies indicates that the greater timeliness of ETAP provides a distinct advantage over THHA, despite the smaller uncertainty reduction associated with ETAP. As the direct COT for ETAP is only \$200K per test, the value of $\text{ENBS}_{\text{ETAP}} = \121B indicates that ETAP is preferable when the delay and costs of testing are considered. When the VOI is assessed in terms of ROI, the ETSC is reduced by \$603,877 for every \$1 spent on ETAP. For THHA, since the EVDSI is negative, so are the ENBS and ROI.

In considering scenarios for which μ_{exp} and σ_{exp} are higher or lower than their central values (**Figure 6-1**), Baseline Scenario 8 - where μ_{exp} is taken from the highest SHEDS-HT exposure

category while σ_{exp} remains in the medium category - shows an increase in both ORE and EV|CI due to the shift to the right in the prior uncertainty distribution for the population average risk R compared to Baseline Scenario 5. Since the BRDM cannot take regulatory action while waiting for the results of ETAP or THHA, the CODs for both assays are increased by more than 5-fold compared to Baseline Scenario 5, whereas the EVIPPI and EVISI values are reduced in Baseline Scenario 8. Therefore, EVDSI, ENBS, and ROI are all reduced in Baseline Scenario 8.

In Baseline Scenario 2, on the other hand, where μ_{exp} is in the lowest SHEDS-HT exposure category, the ORE and EV|CI are reduced compared to Baseline Scenario 5, leading to much smaller CODs for both ETAP and THHA. In this case, the reduced COD for THHA translates to positive EVDSI, ENBS, and ROI values; however, ETAP remains the preferred testing and assessment strategy in this scenario.

As shown in **Figure 6-1**, the relative performance of the two toxicity testing and assessment approaches for increased or decreased values of σ_{exp} is less impactful than the increase/decrease in μ_{exp} (Baseline Scenarios 7, 8, and 9 show similar VOI metrics). However, both ETAP and THHA produced negative EVDSI values (along with ENBS and ROI values) in Baseline Scenario 9. This indicates that there are situations where immediate exposure mitigation action based on current information may be preferable to collecting additional toxicity information.

The timeliness of toxicity testing appears to be the dominant factor in determining the VOI of ETAP and THHA, despite $\text{EVISI}_{\text{THHA}}$ accounting for at least 79% of EVIPPI in all nine scenarios. Timeliness is especially critical when the potential risk is high, as earlier intervention can provide a substantial reduction in health cost. This is consistent with negative EVDSI, ENBS, and ROI values for THHA in more than half of the scenarios considered (Baseline Scenarios 5 to 9), where exposure is higher. In contrast, ETAP, which provides toxicity testing data within 6 months, produced positive EVDSI, ENBS, and ROI values in Baseline Scenarios 1 to 8.

By considering the posterior uncertainty distribution for risk, the probability of making a decision to implement exposure mitigation action can be estimated for any combination of decision-making principle and toxicity test. **Table 6-2** summarizes the probability of making decisions under benefit-risk decision making for the ETAP and THHA; decision-making probabilities in the hypothetical case of partial perfect information (PPI) in which the value of μ_{tox} is assumed to be known are also given for purposes of comparison. Since the ETAP is subject to larger posterior uncertainty about μ_{tox} than THHA, ETAP results in more decisions to regulate in cases where perfect knowledge of μ_{tox} would not lead to regulatory action as compared to THHA.

As discussed in Section 4.3, uncertainty reduction informed by additional toxicity testing data is of value when the prior and posterior decisions differ. This is most likely to be the case in scenarios in which the ORE is neither 0% nor 100% (Baseline Scenarios 4-6), which demonstrate greater EVIPPI, $\text{EVISI}_{\text{ETAP}}$, and $\text{EVISI}_{\text{THHA}}$ values. The COD increases with increasing delay, due to the greater opportunity loss in earlier exposure mitigation; increasing ORE can enhance the increase in the COD.



Figure 6-1. Selected VOI metrics for baseline VOI analysis for BRDM.

Table 6-1. Baseline VOI analysis for BRDM^a

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	
ORE	0		0		0		52		78		88		100		100		100	
EV CI (\$B)	35		71		53		187		293		326		683		718		915	
EVIPPI (\$B)	10		24		15		113		154		146		119		122		74	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI (\$B)	7	8	18	21	11	12	98	105	133	143	126	135	86	101	88	103	47	59
CoD (\$B)	0.3	5	1	12	0.5	7	6	85	12	169	12	172	65	876	70	952	100	1,342
EVDSI (\$B)	6	3	18	9	10	5	92	20	121	-26	113	-36	22	-775	17	-849	-53	-1,283
ENBS (\$B)	6	3	18	9	10	5	92	20	121	-26	113	-36	22	-775	17	-849	-53	-1,283
ROI	32,140	856	87,618	2,226	50,901	1,327	461,668	5,046	603,877	-6,478	566,612	-9,124	107,737	-193,780	86,693	-212,216	-262,718	-320,868

^a EVDSI, ENBS, and ROI are shown with color gradation (*min* → *zero* → *max*, with darker shades of red and blue indicating larger **negative** and larger **positive** values, respectively, of the VOI metric)

Table 6-2. Probability (%) of making a decision to regulate or not regulate a chemical for BRDM^{a,b}

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	
	P(D = 1)	P(D = 0)	P(D = 1)	P(D = 0)	P(D = 1)	P(D = 0)	P(D = 1)	P(D = 0)	P(D = 1)	P(D = 0)	P(D = 1)	P(D = 0)	P(D = 1)	P(D = 0)	P(D = 1)	P(D = 0)	P(D = 1)	P(D = 0)
PPI	10.6	89.4	17.1	82.9	14.7	85.3	19.8	80.2	32.6	67.4	48.0	52.0	67.4	32.6	67.4	32.6	82.9	17.1
ETAP	9.9	90.1	20.0	80.0	15.4	84.6	31.3	68.7	44.7	55.3	58.8	41.2	82.4	17.6	82.4	17.6	91.5	8.5
THHA	10.2	89.8	18.6	81.4	14.0	86.0	24.1	75.9	40.7	59.3	51.9	48.1	75.9	24.1	75.9	24.1	88.0	12.0

^a D = 1 indicates a decision to regulate, and D = 0 denotes a decision not to regulate.

^b Partial perfect information (PPI) assumes perfect knowledge of μ_{tox} .

6.1.2. TARGET-RISK DECISION-MAKING

The results for the VOI analysis for the TRDM, under which decisions are made without consideration of cost, are summarized in **Table 6-3**. In all nine baseline scenarios, the TRL lies between the q_L and q_U of the prior uncertainty distribution for the population average risk R ; consequently, the TRDM must collect additional toxicity test data in order to make a decision on whether or not to regulate. This decision-making paradigm is depicted in **Figure 6-2** under the conditions of Baseline Scenario 5.

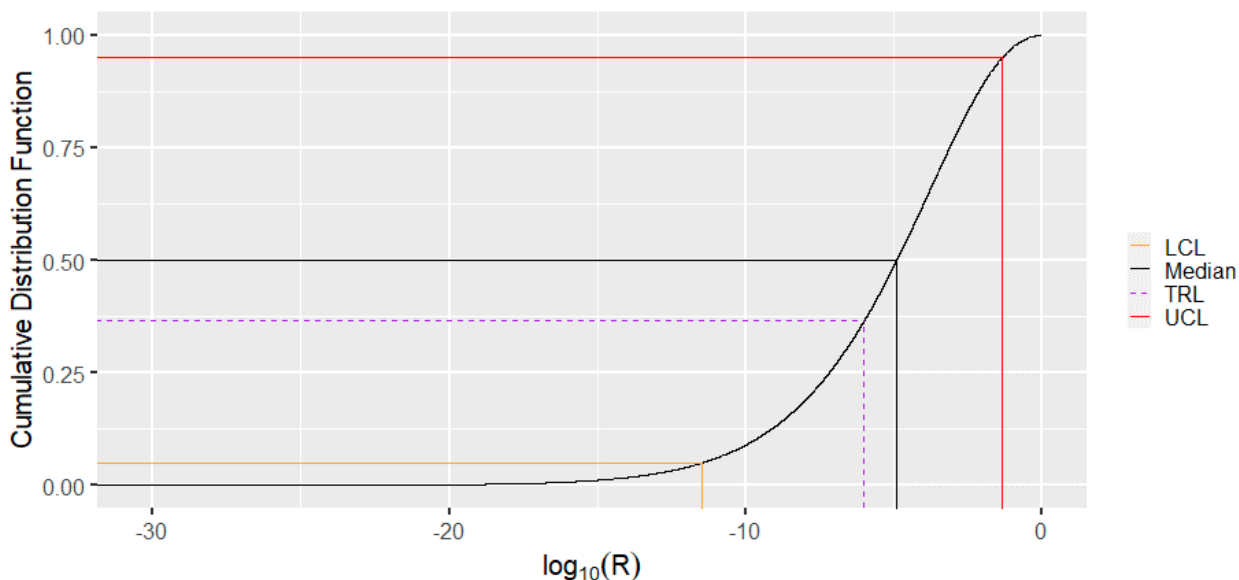


Figure 6-2. Cumulative distribution function for prior uncertainty distribution for R in \log_{10} scale (Baseline Scenario 5). The black vertical line represents the median risk, while the yellow and red vertical lines denote q_{05} and q_{95} , respectively. The purple dotted line represents the $TRL=10^{-6}$.

In Baseline Scenario 5, the $EV|CI$ (corresponding to the ETHC without exposure mitigation action) is \$446B, indicating that some of the chemicals with exposure information within this domain may pose an appreciable risk to the exposed population. As the $EV|PPI$ is \$323B, eliminating uncertainty in μ_{tox} could reduce the ETHC by as much as 72%. From **Table 6-4**, perfect information about μ_{tox} would allow the TRDM to decide to regulate (or not regulate) 35% (or 13%) of the chemicals within this domain. For the remaining 52% of the chemicals, even PPI is insufficient to allow the TRDM to make an unambiguous risk determination relative to TRL and thus a regulatory decision. With the ETAP and THHA, the TRDM can decide to regulate 22% and 28% of chemicals in this domain, respectively. If regulatory action is taken immediately, the ETHC is reduced by $EV|SI_{ETAP} = \$297B$ for the ETAP and $EV|SI_{THHA} = \$314B$ for the THHA. As the delay in obtaining the THHA is longer than ETAP, the CODs differ markedly, with COD_{THHA} being more than 14-fold larger than COD_{ETAP} . Consequently, $EV|DSI_{ETAP}$ is over 2-fold greater than $EV|DSI_{THHA}$. The lower testing cost of the

ETAP further increases the value of information when measured in terms of return on investment, with $ROI_{ETAP} = 1,420,115$ being 42-fold greater than $ROI_{THHA} = 33,678$.

Examination of other exposure scenarios reveals that all VOI metrics increase when either μ_{exp} or σ_{exp} increase. This is due to the associated uncertainty distribution for R being shifted towards higher population risk levels. With the exception of Baseline Scenario 1, EVDSI, ENBS, and ROI are all greater for ETAP than for THHA, due to the shorter testing and assessment development time for ETAP. Although EVDSI and ENBS are greater for THHA in Baseline Scenario 1, ROI for ETAP remains higher (as is the case for all other scenarios).

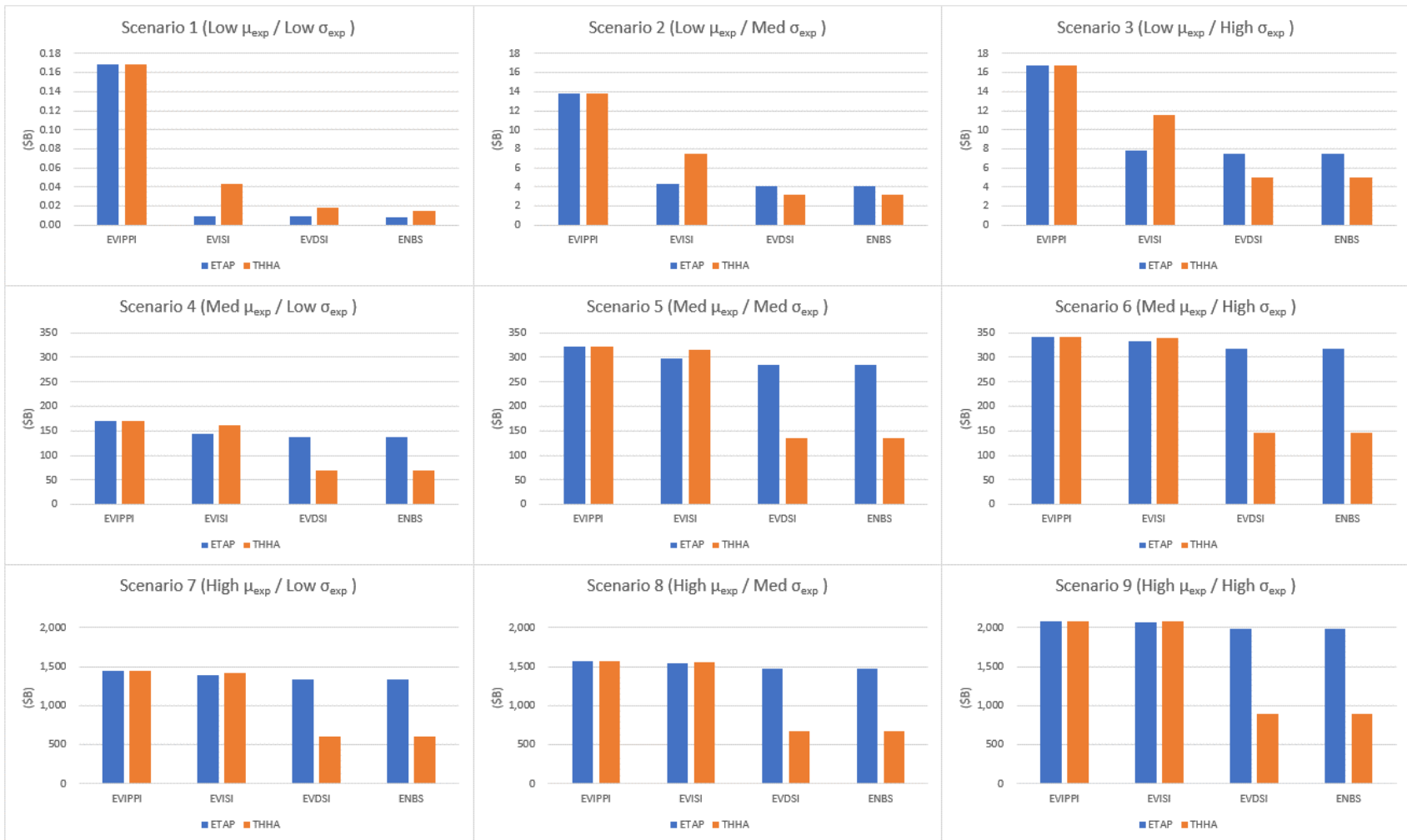


Figure 6-3. Selected VOI metrics for baseline VOI analysis for TRDM.

Table 6-3. Baseline VOI analysis for TRDM^a.

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	
EV CI (\$B)	35		71		53		231		446		492		2,115		2,281		3,205	
EVIPPI (\$B)	0.2		14		17		170		323		342		1,443		1,566		2,086	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI (\$B)	0.01	0.04	4	7	8	12	143	162	297	314	332	339	1,389	1,425	1,545	1,561	2,067	2,078
CoD (\$B)	0.00	0.03	0.2	4	0.3	7	6	92	13	180	14	194	59	814	66	892	88	1,187
EVDSI (\$B)	0.01	0.02	4	3	7	5	137	69	284	135	318	145	1,330	611	1,479	669	1,979	890
ENBS (\$B)	0.01	0.02	4	3	7	5	137	69	284	135	318	145	1,330	611	1,479	669	1,979	890
ROI	44	4	20,556	801	37,362	1,240	685,100	17,308	1,420,115	33,678	1,590,540	36,319	6,650,803	152,671	7,394,078	167,194	9,895,810	222,597

^a EVDSI, ENBS, and ROI are shown with color gradation (*min* → *zero* → *max*, with darker shades of red and blue indicating larger **negative** and larger **positive** values, respectively, of the VOI metric).

Table 6-4. Probability (%) of making a decision to regulate or not regulate a chemical for TRDM^{a,b}.

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	
	P(D = 1)	P(D = 0)	P(D = 1)	P(D = 0)	P(D = 1)	P(D = 0)	P(D = 1)	P(D = 0)	P(D = 1)	P(D = 0)	P(D = 1)	P(D = 0)	P(D = 1)	P(D = 0)	P(D = 1)	P(D = 0)	P(D = 1)	P(D = 0)
PPI	<0.1	43.1	1.1	10.1	3.0	4.7	20.5	26.6	35.4	13.0	56.9	1.1	60.8	2.1	73.4	2.1	79.5	0.1
ETAP	<0.1	37.0	0.3	5.3	1.1	2.0	9.6	13.9	21.9	5.3	47.4	0.2	49.1	0.5	61.3	0.4	75.4	0.0129
THHA	<0.1	39.8	0.5	7.0	1.8	3.2	14.5	19.3	27.9	8.3	52.8	0.5	54.7	1.0	67.2	0.9	76.7	0.0394

^a D = 1 indicates a decision to regulate, and D = 0 denotes a decision not to regulate.

^b Partial perfect information (PPI) assumes perfect knowledge of μ_{tox}

6.2. SENSITIVITY ANALYSES

The baseline scenarios presented in Section 6.1 partitioned the 1,578 chemical exposure datasets from SHEDS-HT into the nine domains shown in **Figure 5-2**, based on cross-classification of tertiles of μ_{exp} and σ_{exp} , thereby allowing an assessment of VOI for lower and higher average exposures and lower and higher variation in population exposure. This analysis was conducted under the assumption that the adverse health outcome has an annualized economic valuation of \$10K per case, the cost of exposure mitigation action is similar to EPA estimates for controlling key air pollutants, and that essentially the entire U.S. population is exposed to the chemical of interest. Recognizing that different chemicals will lead to different adverse health outcomes, require different exposure mitigation actions, and affect the larger or smaller fraction of the general population, a series of sensitivity analyses (*i.e.*, sensitivity analysis scenarios) is provided to illustrate the effects of changes in these parameters. Detailed results of the sensitivity analysis scenarios are presented primarily for Baseline Scenario 5, with results for other scenarios included in the supplementary material.

6.2.1. EFFECT OF QUALITY OF EXPOSURE INFORMATION

Because of the high degree of variability in exposure (as reflected by both μ_{exp} and σ_{exp}) across chemicals within each of these domains, there exists considerable uncertainty about exposure to untested chemicals which is not reduced by toxicity testing (recall that variability in mean exposure is used as a proxy for uncertainty in exposure for chemicals lacking population exposure data). To evaluate the impact of more precise prior information on chemical exposure, each of the nine exposure domains in the baseline analysis is subdivided into nine sub-domains. This results in a total of 81 sub-domains within which the variation in exposure is substantially less than in the baseline analysis which involved only nine domains (see **Figure 6-4**). From a practical perspective, the creation of additional sub-domains from the original nine domains corresponds to having some prior knowledge about the actual levels of population exposure to the specific chemical of interest.

Figure 6-5 identifies exposure domains – or additional scenarios – where ENBS values for ETAP are positive (in light blue) or negative (in orange), under the nine baseline scenarios and a sensitivity analysis with 81 additional scenarios, respectively, for the BRDM. These results indicate that μ_{exp} has a greater impact on whether $\text{ENBS}_{\text{ETAP}}$ is positive or negative than does σ_{exp} . It is also worth noting that one (11%) of the nine exposure scenarios in the baseline scenarios yields negative $\text{ENBS}_{\text{ETAP}}$ values, whereas ten (12%) of 81 additional scenarios in the sensitivity analysis results in negative $\text{ENBS}_{\text{ETAP}}$ values. Similar results are observed for THHA (**Figure 6-6**) where four (44%) baseline scenarios produce positive $\text{ENBS}_{\text{THHA}}$ values, and 38 (47%) of the additional scenarios in the sensitivity analyses produce positive results.

Further comparison of the 81 sensitivity analysis scenarios indicates that ETAP produced greater EVDSI, ENBS, and ROI values than THHA in all scenarios where at least one of these two

toxicity testing and assessment processes had positive values for all three of these VOI metrics (see **Supplementary Table 6.2.1 BRDM**). These results provide further support for the use of ETAP in preference to THHA for chemicals for which exposure estimates are available, but do not have repeated dose toxicity studies or human evidence suitable for use as a POD and reference value derivation.

Results for the TRDM are depicted in **Figure 6-7**, where the regions in blue represent cases where $ENBS_{ETAP}$ is greater than $ENBS_{THHA}$, regions in pink correspond to cases where $ENBS_{THHA}$ is greater than $ENBS_{ETAP}$, and regions in grey reflect cases in which no additional toxicity testing is required. In the Baseline Scenarios 2 to 9, ETAP is the preferred toxicity testing approach in terms of EVDSI, ENBS, and ROI. When the baseline scenarios are further partitioned, there are 12 additional sensitivity analysis scenarios (15%) in which no further testing is required, three (4%) additional scenarios where $ENBS_{THHA} > ENBS_{ETAP}$, and 66 (81%) additional sensitivity analysis scenarios with $ENBS_{ETAP} > ENBS_{THHA}$. These results indicate that knowing that both μ_{exp} and σ_{exp} are large (or small) with relatively high certainty may be sufficient for the TRDM to make a decision. It may also be noted that while two sensitivity analysis scenarios produced greater $ENBS_{THHA}$ values, ROI_{ETAP} is always greater than ROI_{THHA} (see **Supplementary Table 6.2.1 TRDM**).

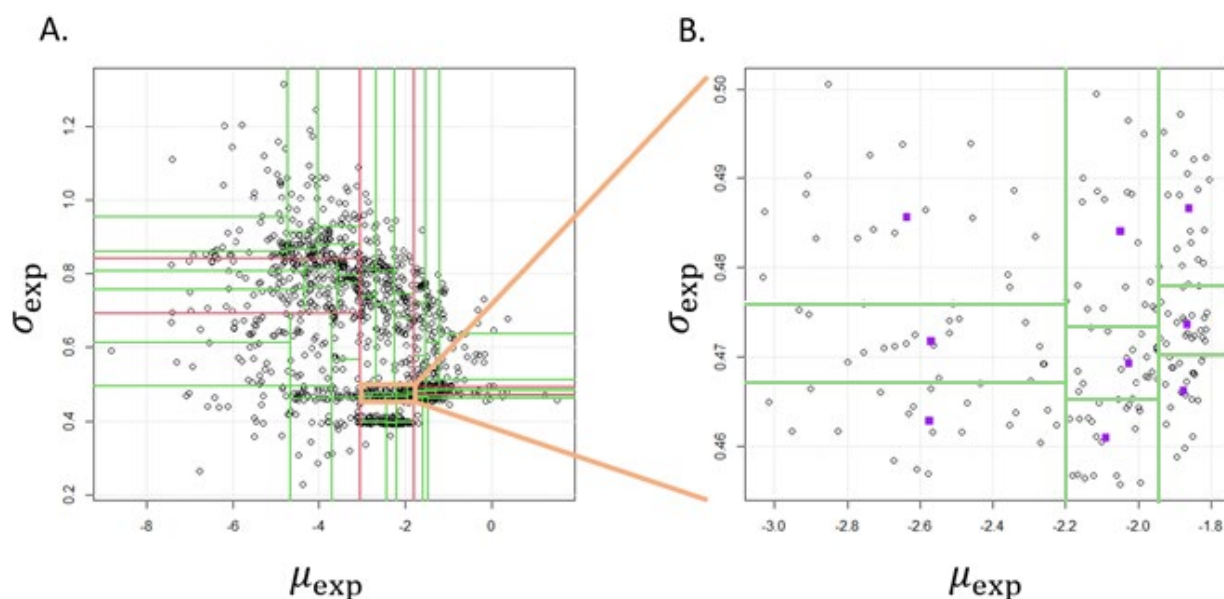


Figure 6-4. Mean (μ_{exp}) and variability (σ_{exp}) of exposure data for 1,578 chemicals in SHEDS-HT. (A) Red lines represent the nine domains to characterize the baseline scenarios. The green lines further partition each baseline scenario into an additional 3x3 = 9 sub-domains, creating a total of 81 domains. (B) Exposure data for the middle tertiles of μ_{exp} and σ_{exp} (Baseline Scenario 5) further partitioned into 3x3 sub-domains to parameterize the sensitivity analysis scenarios. For A and B, individual exposure datapoints are represented by black circles; domain means are represented by solid purple squares.

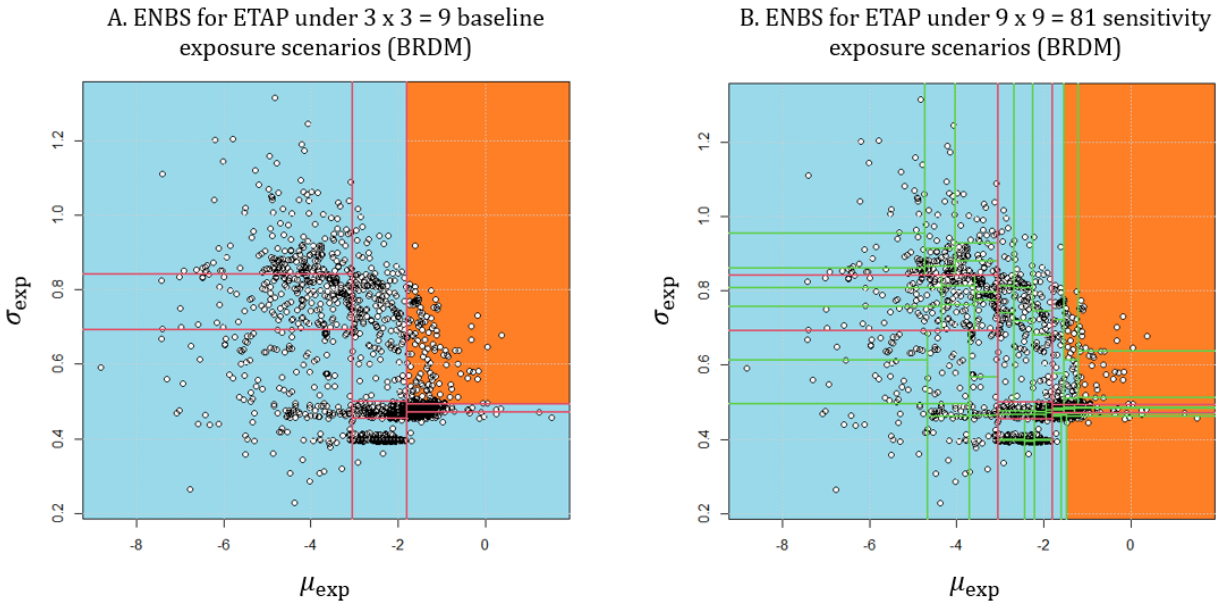


Figure 6-5. ENBS_{ETAP} for BRDM under (A) baseline scenarios with exposure information partitioned into 3x3 domains, and (B) sensitivity analysis scenarios with exposure information partitioned into 9x9 domains. The regions (scenarios) in light blue indicate ENBS values are positive for ETAP. The regions in orange indicate ENBS values are negative for ETAP.

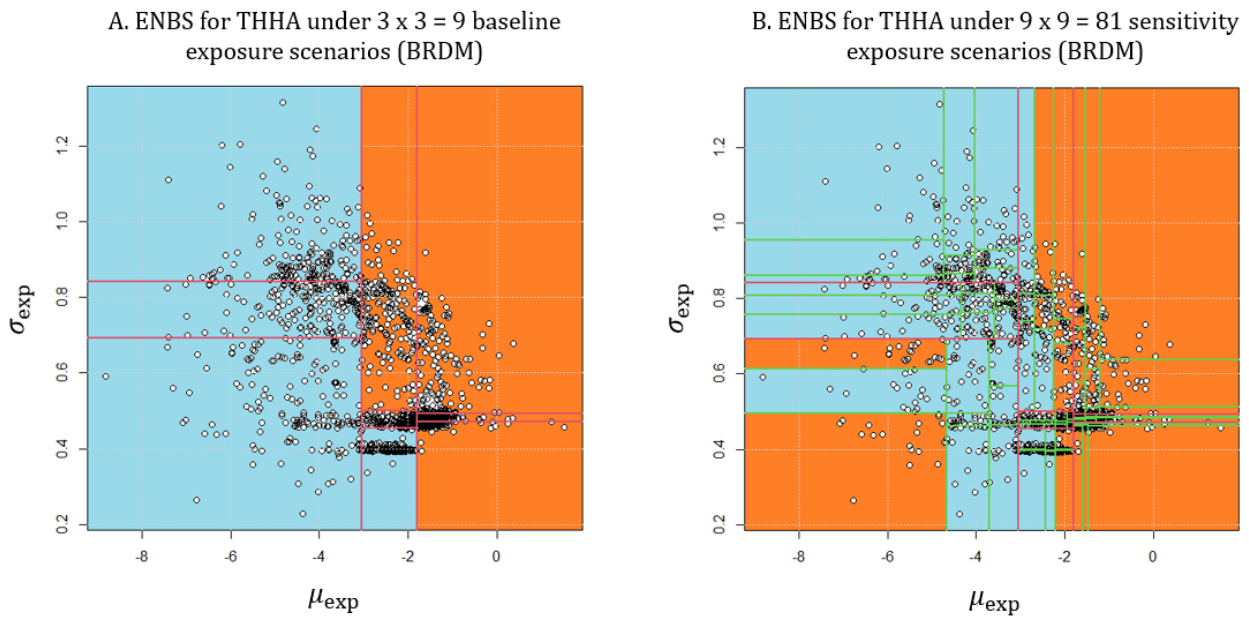


Figure 6-6. ENBS_{THHA} for BRDM under (A) baseline scenarios with exposure information partitioned into 3x3 domains, and (B) sensitivity analysis scenarios with exposure information partitioned into 9x9 domains. The regions (scenarios) in light blue indicate ENBS values are positive for THHA. The regions in orange indicate ENBS values are negative for THHA.

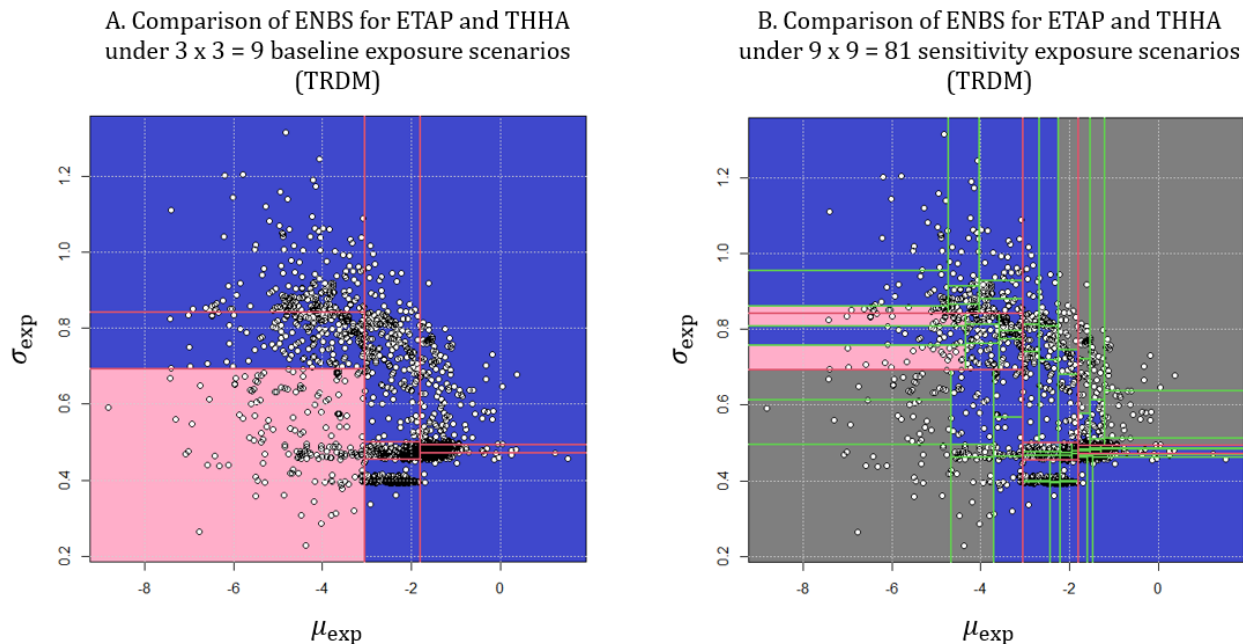


Figure 6-7. Comparison of ENBS values for ETAP and THHA for TRDM under (A) baseline scenarios with exposure information partitioned into 3×3 domains, and (B) sensitivity analysis scenarios with exposure information partitioned into 9×9 domains. The regions (scenarios) in blue indicate $ENBS_{ETAP}$ is greater than $ENBS_{THHA}$; the regions in pink indicate $ENBS_{ETAP}$ is less than $ENBS_{THHA}$; grey regions denote scenarios in which no additional testing is required.

6.2.2. EFFECT OF ADVERSE HEALTH OUTCOME AND COST OF CONTROL

As discussed in Section 5.3.1, health cost valuations may differ substantially, depending on the adverse health outcome of interest. Similarly, the annual cost of control can vary considerably, depending on the physicochemical properties, the toxicity, and the exposure pathways for that chemical. To explore the effect of the valuation of adverse health outcomes and the cost of control, a series of sensitivity analyses scenarios was evaluated varying these two cost parameters.

Table 6-5 summarizes the results of the VOI analysis for the BRDM under the conditions of Baseline Scenario 5²¹, but with changes in the annualized health cost (AHC) and annualized control cost (ACC). When the AHC is increased from \$10K to \$110K and with the ACC_{max} fixed at \$23.1B, the ORE is increased to 100%. This leads to substantially increased CODs for both ETAP and THHA given the opportunity loss in health cost reduction while waiting for the additional toxicity data to make a decision. In particular, COD_{ETAP} is increased to \$159B from \$12B, while the CoD_{THHA} is increased to \$2.1T from \$169B. This results in EVDSI, ENBS, and ROI for both ETAP and THHA being negative, similar to the situation encountered in Baseline Scenario 9 from the baseline analysis. When the AHC is reduced to \$1K, the reduction in ORE - with a concomitant reduction in CODs - results in positive values of EVDSI, ENBS, and ROI for the THHA (these values remain positive for ETAP as well).

²¹ Detailed results for remaining scenarios are provided in the supplemental material.

However, as these same metrics are larger for the ETAP, the BRDM would still prefer ETAP compared with the THHA. These results indicate that as the ratio of AHC-to-ACC_{max} increases, the ORE also increases, as does COD since the benefits of cost-effective exposure mitigation have been delayed.

It may be noted that a reduction in ACC_{max} has a qualitatively similar effect on VOI as an increase in AHC. For example, when the ACC_{max} is reduced from \$23.1B to \$578M (while keeping AHC fixed at \$10K), both the ORE and EV|CI increase. As was observed when the AHC increased from \$10K to \$110K, this change results in negative EVDSI, ENBS, and ROI values for both ETAP and THHA.

As the TRDM does not consider the cost of control, changing the control cost does not affect the resulting VOI analysis (Table 6-5). This also implies that changes in EV|CI, EVIPPI, EVISI, COD, and EVDSI values are proportional to the change in AHC, with ETAP remaining the preferred testing and assessment strategy for the TRDM (See Supplementary Table 6.2.2 for further details).

Table 6-5. Sensitivity analysis scenarios of changing the valuation of annualized health cost (AHC) and annualized maximum control cost (ACC_{max}) under Baseline Scenario 5 (μ_{exp} = medium, σ_{exp} = medium). (A): BRDM, and (B): TRDM^a.

A. VOI analysis results under benefit-risk decision-making									
ACC _{max}	\$23.1B						\$578M		
AHC	\$1K		\$10K		\$110K		\$10K		
ORE	0		78		100		100		
EV CI (\$B)	45		293		1,276		101		
EVIPPI (\$B)	17		154		150		3		
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	
EVISI (\$B)	12	15	133	143	112	129	2	3	
CoD (\$B)	1	8	12	169	159	2,147	15	199	
EVDSI (\$B)	12	6	121	-26	-48	-2,017	-13	-196	
ENBS (\$B)	12	6	121	-26	-48	-2,017	-13	-196	
ROI	59,026	1,563	603,877	-6,478	-237,645	-504,327	-63,327	-49,013	

B. VOI analysis results under target-risk decision-making							
AHC	\$1K		\$10K		\$110K		
EV CI (\$B)	45		446		4,903		
EVIPPI (\$B)	32		323		3,549		
	ETAP	THHA	ETAP	THHA	ETAP	THHA	
EVISI (\$B)	30	31	297	314	3,263	3,458	
CoD (\$B)	1	18	13	180	139	1,976	
EVDSI (\$B)	28	13	284	135	3,124	1,482	
ENBS (\$B)	28	13	284	135	3,124	1,482	
ROI	142,011	3,367	1,420,115	33,678	15,621,276	370,469	

^a EVDSI, ENBS, and ROI are shown with color gradation (*min* → *zero* → *max*, with darker shades of red and blue indicating larger **negative** and larger **positive** values, respectively, of the VOI metric)

6.2.3. EFFECT OF TOXICITY TESTING AND ASSESSMENT DURATION AND TIME HORIZON

The overall time frame for completing the toxicity testing and the human health assessment can vary significantly depending on a number of factors such as the study review processes and assessment complexity. The baseline scenarios rely on estimates that the THHA requires 8 years from

the start of toxicity testing to reaching a regulatory decision. This timeline was based on observations that the traditional two-year rodent bioassay takes an average of 4 years to complete, and the typical human health assessment process is estimated to take an additional 4 years. In the sensitivity analysis scenarios, additional time frames of 6- and 14-years were considered. **Table 6-6** summarizes the results of the VOI analysis for the BRDM and the TRDM under Baseline Scenario 5, but with considerations for the different THHA timeframes. Given that the amount of uncertainty reduction remains the same, changes in assessment duration only affect the cost of delay (COD) and other VOI metrics that incorporate COD. When the THHA takes 14 years, the COD is increased by 95% when compared to the baseline scenario; this increase in COD resulted in reduced values of EVDSI, ENBS, and ROI for the BRDM. On the other hand, when the THHA assessment duration is reduced to 6 years, the corresponding COD is reduced by 30%, leading to increased EVDSI, ENBS, and ROI values. Similar observations can be made for the TRDM. The 14-year assessment timeframe led to a 53% increase in the COD, and a 21% reduction in the COD for the 6-year timeframe, when compared against an assessment duration of 8-years. In all 18 baseline scenarios for both the BRDM and TRDM, ETAP remained the preferred testing strategy, even when the THHA timeline is reduced to the minimum feasible duration of 6 years.

It may also be possible that ETAP could encounter unexpected delays that would extend the average 6-month timeframe for completion²². Additional sensitivity analyses assuming 1-year and 2-year timeframes for ETAP showed an increase in the CoD of 98% and 286%, respectively (**Table 6-6**). When comparing with THHA under the most favorable 6-year timeframe with ETAP under the least favorable 2-year timeframe, there were two scenarios for the TRDM (Scenarios 1 and 2, where the μ_{exp} was low and σ_{exp} was either low or medium) in which THHA was preferred over ETAP using ENBS. For the BRDM, ETAP demonstrated greater VOI than THHA in all nine scenarios. (Full details of the sensitivity analysis of assessment duration are provided in **Supplementary Table 6.2.3 A**).

An extended time horizon beyond 20 years may also be considered, thereby accounting for societal benefits that may continue to accrue after that time. To investigate the impact of extending the time horizon, 40-year and 75-year time horizons were also considered. For the BRDM, ETAP was preferred in all nine scenarios using delay-adjusted VOI metrics under both of these extended time horizons. For the TRDM, on the other hand, Scenarios 1 and 2 (low μ_{exp} and low-to-medium σ_{exp}) preferred THHA based on ENBS under the 40-year time horizon, and Scenarios 1, 2, and 3 (low μ_{exp}) preferred THHA under the 75-year time horizon. For the BRDM, the initial opportunity loss of delayed action reflected in the COD may be the driving factor in preferring ETAP over the THHA,

²² While the average production time for an ETAP has been 6 months, the Agency anticipates that ETAPs will be issued within 9 months of chemical procurement to issuance of the assessment. For those chemicals that meet the ETAP applicability domain, but for which orthogonal data suggests a change to the standard methods, the Agency has established an external peer review process that may impact the time to issue the assessment for those rare cases.

despite the longer time horizon allowing the benefit of THHA to accrue for a greater period of time. For the TRDM, longer time horizons benefit THHA in scenarios where ETAP has difficulty concluding that a chemical requires a regulatory action (*i.e.*, in scenarios where the risk is low and difficult to quantify with sufficient precision to decide). (Full details of the sensitivity analysis of an extended time horizon are provided in **Supplementary Table 6.2.3 B**).

It should also be noted that due to discounting of costs and benefits back to their net present value in VOI analysis, benefits realized far in the future are less valuable than benefits realized in the near term. In particular, under the assumption that it takes 10 years to implement a regulatory decision with THHA (8 years to collect and process information, and 2 years to implement a regulatory decision), 39% of total future benefits would be realized within a 20-year time horizon. Similarly, 77% and 96%, respectively, of total future benefits would be realized within the extended timeframes of 40 or 75 years. (See **Supplementary Table 6.2.3 C** for further details.)

Table 6-6. Sensitivity analysis scenarios of changing the assessment duration under Baseline Scenario 5 (μ_{exp} = medium, σ_{exp} = medium). The baseline analysis is conducted using 8 years for THHA and 6 months for ETAP. (A): BRDM, and (B): TRDM^a.

A. VOI analysis results under benefit-risk decision-making							
ORE							78
EV CI (\$B)							293
	THHA			ETAP			
EVIPPI (\$B)	146			154			
EVISI (\$B)	143			133			
Timeframe	6 Years	8 Years	14 Years	0.5 Years	1 Year	2 Years	
CoD (\$B)	92	132	258	12	24	47	
EVDSI (\$B)	50	10	-116	121	109	86	
ENBS (\$B)	50	10	-116	121	109	86	
ROI	12,546	2,570	-28,880	603,877	544,557	430,172	
B. VOI analysis results under target-risk decision-making							
EV CI (\$B)							445,722
	THHA			ETAP			
EVIPPI (\$B)	322,652			322,652			
EVISI (\$B)	314,381			296,667			
Timeframe	6 Years	8 Years	14 Years	0.5 Years	1 Year	2 Years	
CoD (\$B)	141	180	275	13	25	49	
EVDSI (\$B)	173	135	39	284	272	248	
ENBS (\$B)	173	135	39	284	272	248	
ROI	43,321	33,678	9,804	1,420,115	1,358,420	1,239,456	

^a EVDSI, ENBS, and ROI are shown with color gradation (*min* → *zero* → *max*, with darker shades of red and blue indicating larger **negative** and larger **positive** values, respectively, of the VOI metric).

6.2.4. EFFECT OF STUDY COST

In the baseline scenarios, the costs of performing ETAP and THHA were assumed to be \$200K and \$4M, respectively. To evaluate the impact of alternative assumptions about the cost of toxicity testing, additional sensitivity analyses were conducted with the costs for ETAP increased to \$250K, while the cost of THHA is reduced to \$1M. The results of sensitivity analyses with alternative toxicity testing cost assumptions are summarized in **Table 6-7** for the 18 baseline scenarios represented by the nine exposure domains and two decision makers. With the EVDSI values in billions of dollars, the effect of alternative assumptions for study cost is minimal. Even in Scenario 1 where the EVDSI values for ETAP and TRDM were \$9M and \$19M, respectively, ETAP was preferred over THHA based on both the calculated ENBS and ROI values.

Table 6-7. Sensitivity analysis scenarios using an increased cost of ETAP (\$250K) and a decreased cost of THHA (\$1M)^a. \$200K for ETAP and \$4M for THHA are used in the baseline scenarios.

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	
ORE	0		0		0		52		78		88		100		100		100	
EV CI (\$B)	35		71		53		187		293		326		683		718		915	
EVIPPI (\$B)	10		24		15		113		154		146		119		122		74	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI (\$B)	7	8	18	21	11	12	98	105	133	143	126	135	86	101	88	103	47	59
CoD (\$B)	0.3	5	1	12	0	7	6	85	12	169	12	172	65	876	70	952	100	1,342
EVDSI (\$B)	6	3	18	9	10	5	92	20	121	-26	113	-36	22	-775	17	-849	-53	-1,283
ENBS (\$B)	6	3	18	9	10	5	92	20	121	-26	113	-36	22	-775	17	-849	-53	-1,283
ROI	25,711	3,426	70,095	8,909	40,719	5,313	369,335	20,187	483,103	-25,908	453,291	-36,494	86,191	-775,118	69,355	-848,861	-210,173	-1,283,470

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	
EV CI (\$B)	35		71		53		231		446		492		2,115		2,281		3,205	
EVIPPI (\$B)	0.2		14		17		170		323		342		1,443		1,566		2,086	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI (\$B)	0.01	0.04	4	7	8	12	143	162	297	314	332	339	1,389	1,425	1,545	1,561	2,067	2,078
CoD (\$B)	0.00	0.03	0.2	4	0.3	7	6	92	13	180	14	194	59	814	66	892	88	1,187
EVDSI (\$B)	0.01	0.02	4	3	7	5	137	69	284	135	318	145	1,330	611	1,479	669	1,979	890
ENBS (\$B)	0.01	0.02	4	3	7	5	137	69	284	135	318	145	1,330	611	1,479	669	1,979	890
ROI	35	18	16,443	3,208	29,891	4,963	548,079	69,234	1,136,091	134,715	1,272,431	145,278	5,320,643	610,688	5,915,263	668,781	7,916,647	890,393

^a EVDSI, ENBS, and ROI are shown with color gradation (*min* → *zero* → *max*, with darker shades of red and blue indicating larger **negative** and larger **positive** values, respectively, of the VOI metric)

6.2.5. EFFECT OF AFFECTED POPULATION SIZE

In the baseline scenarios, the affected population size was assumed to be $N = 330\text{M}$, representing the situation in which essentially 100% of the U.S. population is exposed to the chemical of interest. To investigate the impacts associated with only a subset of the population being exposed, while the cost of control remains the same, two sensitivity analysis scenarios are provided for population sizes in which 165M (50% of the U.S. population), and 33M (10%) people are exposed (**Table 6-8**) under Baseline Scenario 5²³. For the BRDM with 50% of the population exposed, the ORE is reduced to 49% as the ratio AHC-to-ACC_{max} per capita is reduced by 50%. EV|CI is also reduced since the expected number of adverse events is reduced by 2-fold. In this case, the difference in the CODs for the two approaches is the dominant factor affecting EVDSI, ENBS, and ROI. The VOI metrics indicate that the ETAP performs better than the THHA; however, unlike the baseline scenario, THHA provides positive EVDSI, ENBS, and ROI values. Similar patterns are observed when N is further reduced to 33M people (10% of the U.S. population).

For the TRDM, reducing the population size is equivalent to a proportional reduction in ETHC. Hence, all VOI metrics that do not consider the COT are halved when the exposed population is reduced by 50% ($N = 165\text{M}$). Similarly, these metrics are reduced by 10-fold when only 10% ($N = 33\text{M}$) of the population is exposed.

²³ Detailed results for remaining scenarios are provided in the supplemental material.

Table 6-8. Sensitivity analysis scenarios of changing the affect population size N under Baseline Scenario 5 ($\mu_{\text{exp}} = \text{medium}$, $\sigma_{\text{exp}} = \text{medium}$). The baseline analysis uses $N=330\text{M}$. (A): BRDM, and (B): TRDM^a.

A. VOI analysis results under benefit-risk decision-making						
Population size	330M		165M		33M	
ORE	78		49		0	
EV CI (\$B)	293		189		45	
EVIPPI (\$B)	154		106		17	
	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI (\$B)	133	143	91	98	12	15
CoD (\$B)	12	169	5	75	1	8
EVDSI (\$B)	121	-26	86	23	12	6
ENBS (\$B)	121	-26	86	23	12	6
ROI	603,877	-6,478	429,503	5,761	59,026	1,563

B. VOI analysis results under target-risk decision-making						
Population size	330M		165M		33M	
EV CI (\$B)	446		223		45	
EVIPPI (\$B)	323		161		32	
	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI (\$B)	297	314	148	157	30	31
CoD (\$B)	13	180	6	90	1	18
EVDSI (\$B)	284	135	142	67	28	13
ENBS (\$B)	284	135	142	67	28	13
ROI	1,420,115	33,678	710,057	16,839	142,011	3,367

^a EVDSI, ENBS, and ROI are shown with color gradation (*min* → *zero* → *max*, with darker shades of red and blue indicating larger **negative** and larger **positive** values, respectively, of the VOI metric)

6.2.6. EFFECT OF TARGET RISK LEVEL

In the baseline scenarios, the TRDM is concerned about risks that exceed a TRL of 10^{-6} , a benchmark often used for carcinogens (EPA 2009). While EPA does not have a recommended TRL for non-cancer effects, higher risks may be inadvertently present, as reflected by the median estimated residual risks on the order of 10^{-4} for traditional RfDs (Chiu et al. 2018). The results of the VOI analysis using a TRL of 10^{-4} is summarized in **Table 6-9**. With this increase in the TRL, when both μ_{exp} and σ_{exp} are low (Baseline Scenario 1), q_U for the prior uncertainty distribution is below the TRL and the TRDM concludes that the chemical does not require regulatory action without collecting additional toxicity information. In the remaining sensitivity analysis scenarios, all VOI metrics except EV|CI are reduced for both ETAP and THHA, when compared to baseline scenarios, as it is now less likely that risk exceeds the higher TRL. In all scenarios included in this sensitivity analyses, the EVDSI, ENBS, and ROI favor ETAP over THHA.

Table 6-9. Sensitivity analysis scenarios of changing the TRL to 10^{-4} for TRDM^{a,b}.

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	
EV/CI (\$B)	NA		71		53		231		446		492		2,115		2,281		3,205	
EVIPPI (\$B)	NA		2		3		156		304		317		1,382		1,545		2,035	
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI (\$B)	NA	NA	0.2	0.6	0.5	1.2	85	125	199	255	252	288	1,114	1,267	1,359	1,477	1,840	1,945
CoD (\$B)	NA	NA	0.01	0.3	0.02	0.7	4	72	8	146	11	164	47	724	58	844	78	1,112
EVDSI (\$B)	NA	NA	0.2	0.3	0.5	0.5	82	54	191	109	241	123	1,067	543	1,301	633	1,761	834
ENBS (\$B)	NA	NA	0.2	0.3	0.5	0.5	82	54	191	109	241	123	1,067	543	1,301	633	1,761	834
ROI	NA	NA	991	65	2,385	129	407,931	13,412	954,215	27,329	1,206,013	30,800	5,332,748	135,748	6,503,564	158,274	8,806,044	208,416

^a EVDSI, ENBS, and ROI are shown with color gradation (*min* → *zero* → *max*, with darker shades of red and blue indicating larger **negative** and larger **positive** values, respectively, of the VOI metric)

^b NA: not applicable, as the TRDM has sufficient information to make a decision based on the prior information without the need for additional toxicity testing. When $q_{05} \geq TRL$, the risk is sufficiently high that a regulatory action is warranted; when $q_{95} \leq TRL$, the risk is sufficiently low such that exposure mitigation action is not required.

6.2.7. DISCORDANCE AS A SOURCE OF ADDITIONAL UNCERTAINTY

There may be other sources of uncertainty that would possibly affect the VOI analyses presented in this paper. Because the ETAP and THHA incorporate quite distinct protocols, there may be a degree of discordance between these two approaches not explicitly incorporated in the baseline VOI analyses. Whereas the traditional two-year bioassay involves lifetime exposure to an environmental agent with *in vivo* integration across multiple toxicological systems, ETAP involves *in vivo* exposure over a period of five days, following which dose-responsive changes in the transcriptome are quantitatively examined.

Although the error associated with the concordance between the transcriptomic BMD values versus apical BMD values from the two-year bioassay was shown to be approximately equivalent to the combined inter-study variability, the root mean squared deviation (RMSD) between the estimated BMDs based on the short-term transcriptomic study and two-year bioassay may be used as a conservative upper bound of the additional uncertainty for ETAP due to discordance between these two tests. Based on the 14 chemicals for which BMDs for ETAP and traditional bioassay results are available, the RMSD is 0.567 ([EPA 2024c](#)), which translates to a discordance value of $P_{95}/P_{50} = 8.55$. It may be noted that the additional discordance factor corresponds to the same 8-fold factor recommended by the IPCS in translating from subacute to chronic exposures ([WHO 2017](#)). With this additional source of uncertainty for the ETAP, σ_{ETAP} is 0.741 (compared to 0.442 in the baseline analysis).

Table 6-10 presents the results of the sensitivity analysis scenarios incorporating potential discordance between ETAP and THHA. For the BRDM, taking discordance into account reduces EVISI, EVDSI, ENBS, and ROI for ETAP. This is most apparent in scenarios in which μ_{exp} is high, where $\text{EVDSI}_{\text{ETAP}}$ become negative in Baseline Scenario 7 and 8 (recall that EVDSI was negative in Baseline Scenario 9 in the baseline analysis). However, ETAP still provides superior EVDSI, ENBS, and ROI values in six scenarios, where either ETAP or THHA (or both) provided positive VOI metrics. For the TRDM, THHA produced greater EVDSI and ENBS values in Baseline Scenarios 1, 2 and 3. In Baseline Scenario 1, ETAP produced a negative ROI value while ROI_{THHA} was positive. These sensitivity analysis scenarios indicate that in the presence of greater posterior uncertainty about μ_{tox} , ETAP is not uniformly superior to THHA, even when VOI is measured in terms of ROI. In particular, Baseline Scenario 1 represents a situation where the additional toxicity information provided by ETAP is insufficient to allow the TRDM to make a decision to regulate a chemical, and therefore the COT outweighs the benefits of uncertainty reduction.

Table 6-10. Sensitivity analysis scenarios on incorporating additional source of uncertainty for ETAP due to discordance with traditional bioassay results. (A): BRDM, and (B): TRDM^a.

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			
ORE	0		0		0		52		78		88		100		100		100			
EV/CI (\$B)	35		71		53		187		293		326		683		718		915			
EVIPPI (\$B)	10		24		15		113		154		146		119		122		74			
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI (\$B)	4	8	13	21	7	12	83	105	112	143	106	135	59	101	59	103	27	59		
CoD (\$B)	0.2	5	1	12	0	7	5	85	11	169	12	172	64	876	69	952	99	1,342		
EVDSI (\$B)	4	3	13	9	7	5	78	20	101	-26	94	-36	-5	-775	-10	-849	-72	-1,283		
ENBS (\$B)	4	3	13	9	7	5	78	20	101	-26	94	-36	-5	-775	-10	-849	-72	-1,283		
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		

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			
EV/CI (\$B)	35		71		53		231		446		492		2,115		2,281		3,205			
EVIPPI (\$B)	0.2		14		17		170		323		342		1,443		1,566		2,086			
	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA	ETAP	THHA
EVISI (\$B)	0.00	0.04	1	7	2	12	85	162	227	314	307	339	1,257	1,425	1,466	1,561	2,014	2,078		
CoD (\$B)	0.00	0.03	0.03	4	0.1	7	4	92	10	180	13	194	54	814	62	892	86	1,187		
EVDSI (\$B)	0.00	0.02	1	3	2	5	82	69	217	135	294	145	1,204	611	1,403	669	1,928	890		
ENBS (\$B)	0.00	0.02	1	3	2	5	82	69	217	135	294	145	1,204	611	1,403	669	1,928	890		
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		

^a EVDSI, ENBS, and ROI are shown with color gradation (*min* → *zero* → *max*, with darker shades of red and blue indicating larger **negative** and larger **positive** values, respectively, of the VOI metric).

7. SUMMARY AND CONCLUSIONS

A series of VOI analyses were conducted using the analytic framework previously developed by EPA ORD to compare alternative toxicity testing methods ([Hagiwara et al. 2022](#)). The present report applies the framework in a case study comparing ETAP and THHA, with a goal of evaluating the contexts under which the less costly and timelier ETAP – despite being subject to greater uncertainty – may offer a viable alternative to THHA. The VOI analysis examines the trade-offs between timeliness of decision-making, cost of toxicity testing, and the amount of uncertainty reduced by these tests in order to determine which of the two tests provides the most ‘value’, and which test affords the greatest public health protection from the potential toxic effects of exposure to chemicals present in the human environment.

To conduct VOI analyses, the decision-making criteria are specified to determine whether or not regulatory action is required on the basis of results of toxicity testing and human health assessment. It is assumed that the chemical is or was in commerce with continued human exposure. Two types of decision makers are considered, specifically the BRDM and the TRDM. The BRDM seeks to minimize the TSC associated with chemical exposure. When the economic value of health benefits realized through the exposure mitigation action outweighs the cost of such action, the BRDM would decide to regulate the chemical of interest. In contrast, the TRDM focuses on the average population risk associated with the chemical exposure, without consideration of the cost of risk mitigation, and chooses to reduce exposure whenever that risk is greater than the target risk level. Although neither of these decision-making contexts fully emulates real-world decision-making practices, they do correspond to two of the ten decision-making principles discussed by [Krewski et al. \(2022\)](#).

Parameterization of the decision-making scenarios in the VOI analysis is informed by realistic data on toxicity and exposure. Specifically, the 1,522 chemicals and endpoints considered by [Chiu et al. \(2018\)](#) formed the foundation for gauging uncertainty in toxic potency prior to testing. The conversion of the animal-based toxicity testing results to an HED requires the application of a series of adjustment factors reflecting different sources of uncertainty and variability. Within-study variability for the THHA is estimated using 584 previously evaluated bioassays ([Sand et al. 2011](#)). The animal-to-human scaling factors²⁴ are based on recommendations from the IPCS ([WHO 2017](#)), which conducted an extensive evaluation of empirical data on factors affecting uncertainty in converting the results of animal toxicity tests to humans. Within-study variability for ETAP is taken from experimental data on 14 chemicals ([EPA 2024c](#)). Finally, exposure estimates from SHEDS-HT

²⁴ Specifically, the uncertainty associated with allometric scaling and differences in toxicokinetics and toxicodynamics between animals and humans was examined.

are used to construct the nine baseline exposure scenarios corresponding to a 3 × 3 grid defined by low, medium, and high average exposures and by low, medium, and high variation in population exposure.

As with the choice of parameters for toxicity and exposure, the health costs and control costs are also based on realistic data. The valuation of adverse health effects, ranging from short-term transient toxic responses to longer-term irreversible toxic effects to mortality, is based on examination of values applied by health economists to such effects. As discussed in Section 5.3.1, annualized per case health costs of \$1K and \$10K are used for non-fatal outcomes of lesser and greater severity, along with \$110K for fatal outcomes. For the control costs, a maximum annualized cost of exposure mitigation is set to \$23.1B in the baseline scenarios, based on estimated actual cost of major air pollution emission programs ([EPA 2011b](#)), extrapolated to the case of complete elimination of emissions. For the sensitivity analysis scenarios, this maximum annualized cost is modified to \$578M, based on an examination of the cost of 33 chemical risk management programs implemented or proposed under the European Union's REACH program ([ECHA 2021](#)). The wide-range of annualized control costs examined in the baseline (\$23.1B) and sensitivity analysis scenarios (\$578M) was intended to capture the diversity in potential chemicals to which ETAP may be applied. In comparison, the recent total annualized control cost estimates from the final national primary drinking water rule for six PFAS was \$1.55B ([EPA 2024a](#)) which falls within the range in control costs used in the case study and supports the use of the range for more generalizable conclusions. However, the relationship between the cost of exposure mitigation and its effectiveness was assumed to be continuous in this case study. In practice, there may be a finite number of control measures available, which translates to a stepwise relationship. Nonetheless, this option was not evaluated due to the complexity of pairing the cost and effectiveness of various control measures that is generalizable as well as owing to a lack of data to inform a stepwise function.

This report presents VOI analyses for a total of 360 scenarios under benefit-risk and target-risk decision-making contexts including 18 baseline scenarios (9 for BRDM and 9 for TRDM), and 342 sensitivity analysis scenarios (171 scenarios each for BRDM and TRDM). These sensitivity analysis scenarios investigate the impacts across a broad range of varying parameters including: the degree of uncertainty in exposure information, economic valuation of both adverse health effects and the cost of mitigation action, the time frame associated with the toxicity testing and assessment process, the study cost of the toxicity test, and the time horizon to realize potential health benefits, the size of the exposed population, the choice of the target risk level, and consideration of discordance with traditional toxicity testing results based on the chronic bioassay as an additional source of uncertainty for ETAP.

For the BRDM, the results from the baseline scenarios suggest that, when the ORE (based on the prior information) is over 78%, the cost associated with the 8-year delay in decision-making for the THHA leads to negative EVDSI values (along with negative ENBS and ROI values), indicating that timeliness is an important determinant of the value of information. In contrast, ETAP produces a

positive ROI in all but one baseline scenario, with the benefit realized by collecting additional toxicity information via ETAP outweighing both the delay and the COT. In Baseline Scenarios 1 to 8, where either ETAP or THHA produced positive EVDSI values, ETAP produced greater EVDSI, ENBS, and ROI values as compared to THHA. Similar results are observed for the TRDM, where ROI_{ETAP} is at least 12-fold greater than ROI_{THHA} across the nine baseline scenarios included in the VOI analysis.

For the BRDM, **Table 7-1** summarizes the number of scenarios where ETAP is preferred over THHA based on three key VOI metrics – EVDSI, ENBS, and ROI – across all 180 baseline and additional scenarios considered in the sensitivity analysis. Of these, 31 (17%) scenarios result in negative EVDSI values for both ETAP and THHA (resulting in negative ENBS and ROI values as well). These scenarios represent situations in which the ORE is 100%, either because μ_{exp} or AHC-to-ACC ratio is high. ETAP produces positive EVDSI, ENBS, and ROI values in the remaining 149 (83%) scenarios, whereas THHA produces positive ENBS values in 92 (51%) scenarios. In these 149 scenarios, ETAP always produced greater ENBS values than THHA, with the differences $ENBS_{Diff} = ENBS_{ETAP} - ENBS_{THHA}$ ranging from as low as \$4M to as high as \$1T, with a median difference of \$44B. **Figure 7-1** shows boxplots of $ENBS_{Diff}$ grouped by the baseline scenarios and the scenarios considered under the various sensitivity analyses for the BRDM. From **Figure 7-1**, it is apparent that the choice of the time horizon and the direct cost of testing do not result in notable changes in ENBS. On the other hand, the quality of the exposure information (in particular, the mean exposure level μ_{exp}), associated health and control costs, duration of the toxicity testing and assessment processes, size of the affected population, and the amount of uncertainty reduction all have an impact on the magnitude of the VOI. Nonetheless, the median differences favor ETAP over THHA within each of these six sensitivity analyses. Since ETAP would lead to earlier regulatory decisions than THHA in all scenarios, the results presented in this report underscore the importance of timeliness in toxicity testing and the associated human health risk assessment.

For the TRDM, **Table 7-2** summarizes the number of scenarios where ETAP is preferred over THHA for the same set of VOI metrics and across all 180 baseline and sensitivity analysis scenarios. Of the 180 scenarios considered, 13 (7%) require no further toxicity testing. Of the 13 scenarios that required no additional toxicity testing, 12 of these can be explained by the smaller prior uncertainty in μ_{exp} and σ_{exp} compared to the baseline, with the remaining sensitivity scenario occurring because the TRL is increased to 10^{-4} compared to the baseline value of 10^{-6} . Among the remaining 166 scenarios, ETAP produces greater ENBS values than THHA in 148 (89%) scenarios. In 14 scenarios where $ENBS_{THHA} > ENBS_{ETAP}$, ETAP has difficulty concluding that exposure mitigation action is required because the average population risk is low. Since ETAP is subject to greater uncertainty than traditional bioassay, obtaining accurate estimates of risk is more difficult with ETAP. This is particularly true when additional potential discordance between ETAP and THHA is taken into consideration. Despite these differences, when VOI is measured using ROI, THHA is superior only in Baseline Scenario 1 when discordance is included as additional source of uncertainty for ETAP. Overall, $ENBS_{Diff}$ ranges from -\$3B to as high as \$12T (this maximum value is the extreme outlying

value in the boxplots shown in **Figure 7-2**), with a median value of \$81B. As with the BRDM, extending the time horizon beyond 20 years or changing the study cost did not markedly alter the difference in VOI between ETAP and THHA for the TRDM; changes in values of the remaining parameters did lead to some differences in the numerical values of the VOI metrics for ETAP and THHA, although ETAP generally remained preferable to THHA for both the BRDM and the TRDM across the spectrum of sensitivity analyses conducted in this report.

Table 7-1. Summary of baseline and sensitivity analysis scenarios in which ETAP is preferred for BRDM.

Description (Section)	Number of scenarios				
	All	No testing preferred	ETAP preferred (EVDSI)	ETAP preferred (ENBS)	ETAP preferred (ROI)
Baseline analysis (6.1.1)	9	1	8	8	8
Exposure sensitivity analysis (6.2.1)	81	10	71	71	71
Health and control cost sensitivity analysis (6.2.2)	27	12	15	15	15
Duration sensitivity analysis (6.2.3) ^a	27	5	22	22	22
Assessment cost sensitivity analysis (6.2.4)	9	1	8	8	8
Population size sensitivity analysis (6.2.5)	18	0	18	18	18
Discordance sensitivity analysis (6.2.7)	9	3	6	6	6
All scenarios	180	32 (17.8%)	149 (82.2%)	149 (82.2%)	149 (82.2%)

^a For the assessment duration sensitivity analyses performed in Section 6.2.3, the preference is determined using a 2-year timeframe for ETAP and 6-year timeframe for THHA.

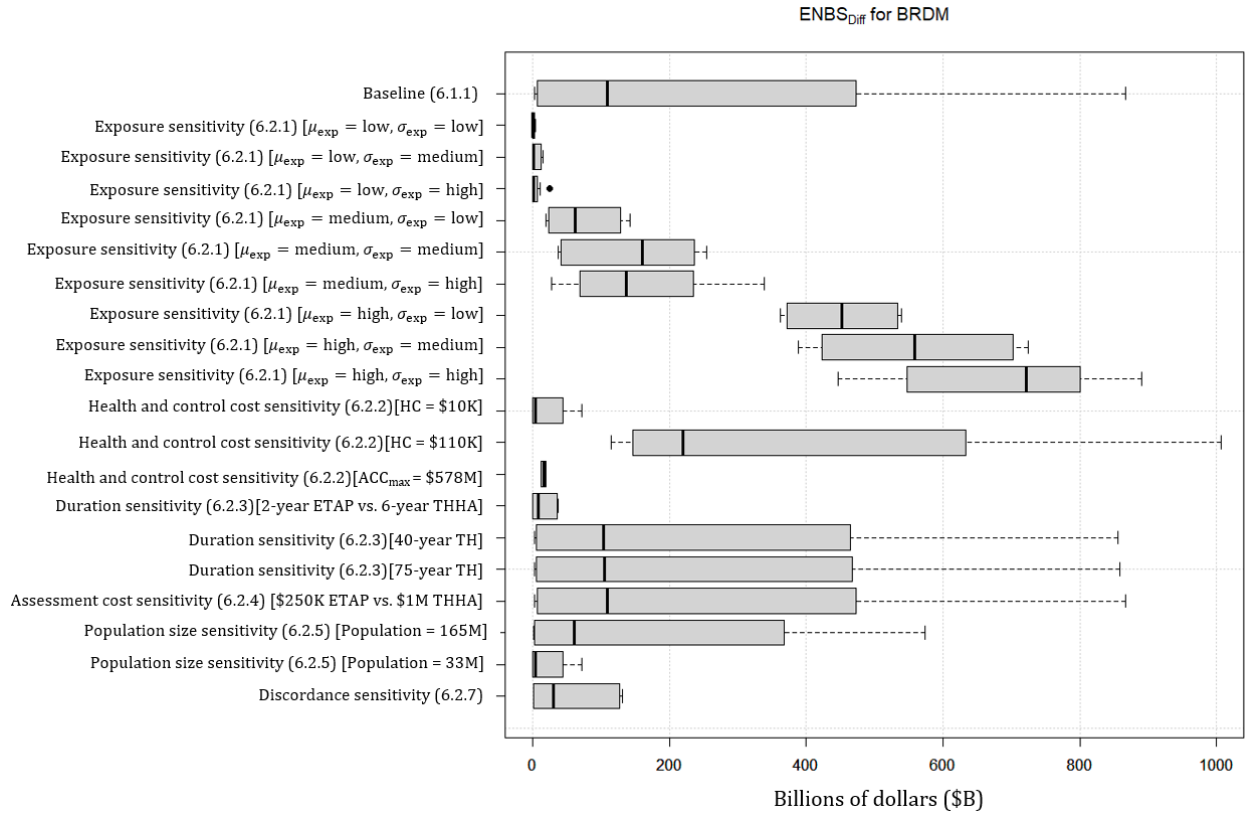


Figure 7-1. Boxplots of $ENBS_{Diff} = ENBS_{ETAP} - ENBS_{THHA}$ for BRDM. Of 180 scenarios considered, 31 scenarios in which both ETAP and THHA produced negative ENBS values are excluded.

Table 7-2. Summary of baseline and sensitivity analysis scenarios in which ETAP is preferred for TRDM.

Description	Number of scenarios				
	All	No testing required	ETAP preferred (EVDSI)	ETAP preferred (ENBS)	ETAP preferred (ROI)
Baseline analysis (6.1.1)	9	0	8	8	9
Exposure sensitivity analysis (6.2.1)	81	12	66	66	69
Health and control cost sensitivity analysis (6.2.2)	18	0	16	17	18
Duration sensitivity analysis (6.2.3) ^a	27	0	20	20	27
Assessment cost sensitivity analysis (6.2.4)	9	0	8	8	9
Population size sensitivity analysis (6.2.5)	18	0	16	17	18
TRL sensitivity analysis (6.2.6)	9	1	6	6	8
Discordance sensitivity analysis (6.2.7)	9	0	6	6	8
All scenarios	180	13 (7.2%)	146 (87.4%)^b	148 (88.6%)^b	166 (99.4%)^b

^a For the assessment duration sensitivity analyses performed in Section 6.2.3, the preference is determined using a 2-year timeframe for ETAP and 6-year timeframe for THHA.

^b Percentages shown against 180-13=167 scenarios in which TRDM requires additional information to make a decision.

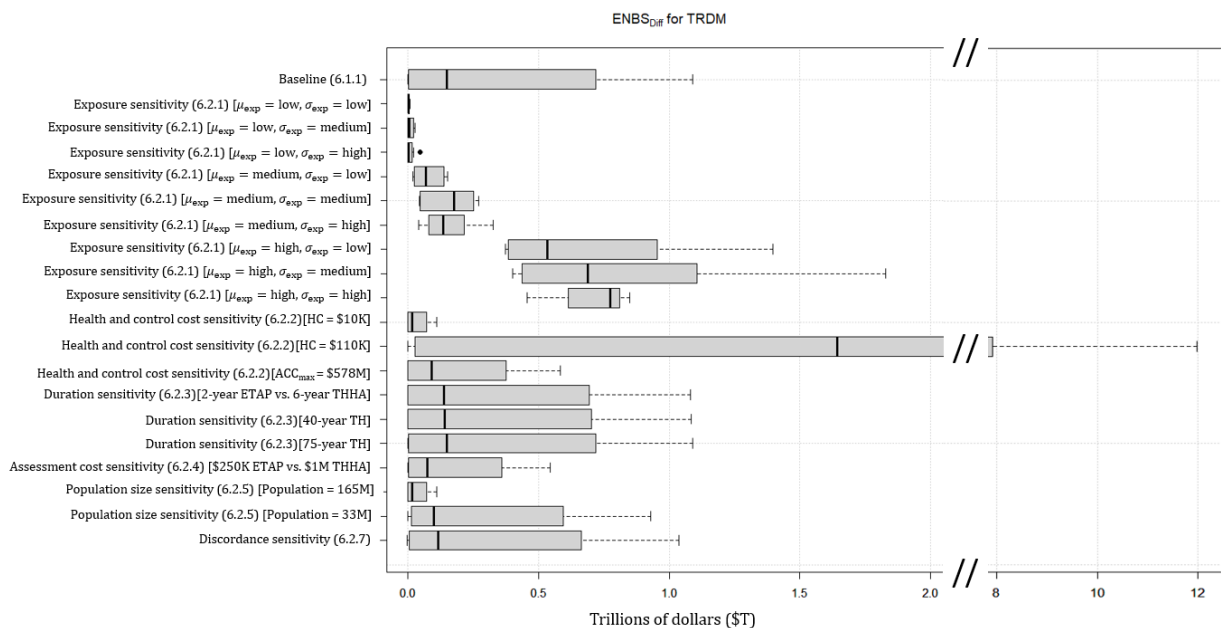


Figure 7-2. Boxplots of ENBS_{Diff} = ENBS_{ETAP} - ENBS_{THHA} for TRDM. Of 180 scenarios considered, 13 scenarios where no additional toxicity testing was required are excluded.

Although additional exposure data may reduce uncertainty about exposure to the chemical of interest in the general population, assessment of the benefits of improved exposure data was outside of the scope of the case study. In order to determine whether additional toxicity testing or additional efforts to reduce the uncertainty about population exposure using more refined exposure ascertainment methods would be more valuable, the cost of specific exposure assessment approaches and the concomitant reduction in uncertainty would need to be incorporated into the VOI analytic framework. Since the overarching goal of this present case study was to evaluate the relative VOI provided by ETAP and THHA, the benefits of improved exposure assessment were not considered. However, assuming that the prior uncertainty distributions for toxicity and exposure are similar, a proportionate reduction in either source of uncertainty would be expected to result in a similar benefit in terms of VOI.

In the scenarios considered in this report, the ETAP was generally preferred over the THHA in terms of cost, timeliness, 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. The robustness of this finding is further supported by the extensive series of sensitivity analyses examining the impact of changes in quality of the exposure information, associated health and control costs, timeliness of the toxicity testing and assessment processes, time horizon to realize potential health benefits, study cost of toxicity testing, size of the affected population, and amount of uncertainty reduction. However, there are several potential caveats to these conclusions. First, the experimental data used to inform some of the parameters for ETAP are limited (e.g., intra-study variability). The continued generation and application of ETAP data will serve to refine these parameter estimates and provide a more accurate VOI comparison. Second, the

ETAP provides a reference value that is not linked to a specific hazard, whereas the traditional toxicity testing process identifies specific hazards that may be relevant to human health. The potential overall economic value of identifying specific hazards has not been incorporated into the analysis. Third, within the context of present VOI framework, 'value' is only realized when the collection of additional toxicity testing information results in a decision based on this additional information that is different from the decision that would be made in the absence of this information. An exception to this assertion that 'value' is only realized when decisions are altered would occur in an extended VOI framework which places value on knowing a chemical does not pose an appreciable population health risk. In this case, knowing that a chemical is safe with less uncertainty would have some value. Although economists have suggested approaches to valuing additional assurances of safety ([Hanemann 1989](#)), the current analysis has not attempted to incorporate such 'option values', in the absence of consensus on the methodological approach to assigning option values or consensus that such valuations should be included in VOI analysis.

VOI analysis provides a set of methods for organizing and evaluating efforts to collect and apply new information to regulatory decisions. However, application of VOI methods in chemical safety decisions in regulatory agencies, such as the EPA, has been underutilized ([NASEM 2009](#); [Yokota and Thompson 2004](#)). To both support application of VOI to decision making and evaluate a draft new human health assessment product, a case study was conducted to evaluate the human health and economic trade-offs associated with the timeliness, uncertainty, and costs of the new toxicity testing and human health assessment process. Collectively, the VOI analyses conducted in the case study demonstrated that under the exposure scenarios and assumptions considered, the ETAP is the more frequently preferred approach for more rapidly and cost effectively evaluating chemicals with no existing toxicity testing or human health data. If applied to a significant number of chemicals lacking toxicity testing and human health assessments, the public health benefits of ETAP would become multiplicative. In addition, ETAP could be combined with other data gap filling methods by strategically selecting chemicals with structural and other characteristics that could serve as analogs for a broader collection of substances or anchor a chemical category. These considerations could be incorporated into the candidate identification step in the ETAP process, which could further enhance the public health benefits. Application of the VOI framework to other case studies and decision contexts should build further confidence in its broad utility and importance for policy and decision makers.

8. SUPPLEMENTAL MATERIAL

The supplemental material includes VOI sensitivity results described via eight tables. Supplemental material can be accessed at <https://doi.org/10.23645/epacomptox.26093572.v1> as an Excel spreadsheet with individual tables delimited via tabs. The 'Read Me' tab in the spreadsheet includes a copy of the table below.

Table / Tab	Content
S 6.2.1 BRDM	Results of VOI sensitivity analysis evaluating the effect of quality of exposure information for BRDM
S 6.2.1 TRDM	Results of VOI sensitivity analysis evaluating the effect of quality of exposure information for TRDM
S 6.2.2	Results of VOI sensitivity analysis evaluating the effect of adverse health outcome and cost of control for BRDM and TRDM
S 6.2.3 A	Results of VOI sensitivity analysis evaluating the effect of assessment duration for BRDM and TRDM
S 6.2.3 B	Results of VOI sensitivity analysis evaluating the effect of time horizon for BRDM and TRDM
S 6.2.3 C	Calculation of total benefits realized within a pre-specified time horizon
S 6.2.5 BRDM	BRDM Results of VOI sensitivity analysis evaluating the effect of affected population size for BRDM
S 6.2.5 TRDM	Results of VOI sensitivity analysis evaluating the effect of affected population size for TRDM

9. REFERENCES

- Belova A, Fann N, Haskell J, Hubbell B, Narayan T. 2020. Estimating Lifetime Cost of Illness. An Application to Asthma. *Ann Am Thorac Soc* 17:1558-1569.
- Biryol D, Nicolas CI, Wambaugh J, Phillips K, Isaacs K. 2017. High-throughput dietary exposure predictions for chemical migrants from food contact substances for use in chemical prioritization. *Environ Int* 108:185-194.
- Bottini AA, Hartung T. 2009. Food for thought... on the economics of animal testing. *ALTEX* 26:3-16.
- Bucher JR. 2002. The National Toxicology Program rodent bioassay: designs, interpretations, and scientific contributions. *Ann N Y Acad Sci* 982:198-207.
- Buescher AV, Cidav Z, Knapp M, Mandell DS. 2014. Costs of autism spectrum disorders in the United Kingdom and the United States. *JAMA Pediatr* 168:721-728.
- Chiu WA, Slob W. 2015. A Unified Probabilistic Framework for Dose-Response Assessment of Human Health Effects. *Environ Health Perspect* 123:1241-1254.
- Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, et al. 2018. Beyond the RfD: Broad Application of a Probabilistic Approach to Improve Chemical Dose-Response Assessments for Noncancer Effects. *Environ Health Perspect* 126:067009.
- Cote I, Anastas PT, Birnbaum LS, Clark RM, Dix DJ, Edwards SW, et al. 2012. Advancing the next generation of health risk assessment. *Environ Health Perspect* 120:1499-1502.
- ECHA. 2021. Costs and benefits of REACH restrictions proposed between 2016-2020. ECHA-21-R-02-EN. Helsinki, Finland:European Chemicals Agency.
- EEA. 2018. Chemicals for a Sustainable Future – Report of the EEA Scientific Committee Seminar. 978-92-9213-936-0. Luxembourg:European Environment Agency.
- EPA. 2002. A Review of the Reference Dose and Reference Concentration Processes. EPA/630/P-02/002F. Washington, DC:US Environmental Protection Agency.
- EPA. 2004. Review of the revised analytical plan for EPA's Second Prospective Analysis—Benefits and Costs of the Clean Air Act 1990—2020, An Advisory by a Special Panel of the Advisory Council on Clean Air Compliance Analysis. EPA-SAB-COUNCIL-ADV-04-004.
- EPA. 2009. Risk Assessment Guidance for Superfund. EPA-540-R-070-002. Washington, DC:U.S. Environmental Protection Agency.
- EPA. 2010. Guidelines for Preparing Economic Analyses. EPA 240-R-10-001. Washington, DC:National Center for Environmental Economics.

- EPA. 2011a. Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose. EPA/100/R-11/0001. Washington, DC:U.S. Environmental Protection Agency.
- EPA. 2011b. Emission Factor Supporting Documentation for the Final Mercury and Air Toxics Standards. EPA-454/R-11-012. Washington, DC:U.S. Environmental Protection Agency.
- EPA. 2011c. Exposure Factors Handbook. EPA/600/R-09/052F. Washington, DC:U.S. Environmental Protection Agency.
- EPA. 2013. Regulatory impact analysis for the final revisions to the National Ambient Air Quality Standards for particulate matter. EPA-452/R-12-005. Research Triangle Park, NC:U.S Environmental Protection Agency, Office of Air Quality Planning and Standards, Health and Environmental Impacts Division.
- EPA. 2014. Framework for Human Health Risk Assessment to Inform Decision Making. EPA/100/R-14/001. Washington, DC:U.S. Environmental Protection Agency.
- EPA. 2021. Estimating PM_{2.5}- and Ozone-Attributable Health Benefits. EPA-HQ-OAR-2020-0272. EPA:US Environmental Protection Agency.
- EPA. 2022a. Our nation's air: status and trends through 2021. Available: <https://gispub.epa.gov/air/trendsreport/2022/#home> [accessed 01/14/2023].
- EPA. 2022b. Mortality Risk Valuation. Available: <https://www.epa.gov/environmental-economics/mortality-risk-valuation> [accessed 1/19/2023].
- EPA. 2022c. ORD Staff Handook for Developing IRIS Assessments. EPA 600/R-22/268. Research Triangle Park, NC:U.S. Environmental Protection Agency.
- EPA. 2024a. Economic Analysis for the Final Per- and Polyfluoroalkyl Substances National Primary Drinking Water Regulation. EPA-815-R-24-001. Washington, DC:U.S. Environmental Protection Agency.
- EPA. 2024b. Standard Methods for Development of EPA Transcriptomic Assessment Products (ETAPs). EPA/600/X-23/083. Research Triangle Park, NC:U.S. Environmental Protection Agency.
- EPA. 2024c. Scientific Studies Supporting Development of Transcriptomic Points of Departure for EPA Transcriptomic Assessment Products (ETAPs). EPA/600/X-23/084. Research Triangle Park, NC:U.S. Environmental Protection Agency.
- Faustman EM, Omenn GS. 2015. Risk Assessment. In: Casarett and Doull's Essentials of Toxicology, Part Third (Klaassen CD, Watkins III JB, eds). New York:McGraw-Hill.
- Finkel AM, Evans JS. 1987. Evaluating the benefits of uncertainty reduction in environmental health risk management. JAPCA 37:1164-1171.

- Ganz ML. 2007. The lifetime distribution of the incremental societal costs of autism. *Arch Pediatr Adolesc Med* 161:343-349.
- Gwinn WM, Auerbach SS, Parham F, Stout MD, Waidyanatha S, Mutlu E, et al. 2020. Evaluation of 5-day In Vivo Rat Liver and Kidney With High-throughput Transcriptomics for Estimating Benchmark Doses of Apical Outcomes. *Toxicol Sci* 176:343-354.
- Hagiwara S, Paoli GM, Price PS, Gwinn MR, Guiseppi-Elie A, Farrell PJ, et al. 2022. A value of information framework for assessing the trade-offs associated with uncertainty, duration, and cost of chemical toxicity testing. *Risk Anal* 43:498-515.
- Hanemann WM. 1989. Information and the concept of option value. *Journal of Environmental Economics and Management* 16:23-37.
- Howard RA. 1966. Information value theory. *IEEE Transactions on Systems Science and Cybernetics* SSC2:22-26.
- Huff J, Jacobson MF, Davis DL. 2008. The limits of two-year bioassay exposure regimens for identifying chemical carcinogens. *Environ Health Perspect* 116:1439-1442.
- Isaacs KK, Glen WG, Egeghy P, Goldsmith MR, Smith L, Vallero D, et al. 2014. SHEDS-HT: an integrated probabilistic exposure model for prioritizing exposures to chemicals with near-field and dietary sources. *Environ Sci Technol* 48:12750-12759.
- Kavlock RJ, Bahadori T, Barton-Maclaren TS, Gwinn MR, Rasenberg M, Thomas RS. 2018. Accelerating the Pace of Chemical Risk Assessment. *Chem Res Toxicol* 31:287-290.
- Krewski D, Gaylor DW, Soms AP, Szyszkowicz M. 1993. An overview of the report: correlation between carcinogenic potency and the maximum tolerated dose: implications for risk assessment. *Risk Anal* 13:383-398.
- Krewski D, Westphal M, Andersen ME, Paoli GM, Chiu WA, Al-Zoughool M, et al. 2014. A framework for the next generation of risk science. *Environ Health Perspect* 122:796-805.
- Krewski D, Andersen ME, Tyshenko MG, Krishnan K, Hartung T, Boekelheide K, et al. 2020. Toxicity testing in the 21st century: progress in the past decade and future perspectives. *Arch Toxicol* 94:1-58.
- Krewski D, Saunders-Hastings P, Larkin P, Westphal M, Tyshenko MG, Leiss W, et al. 2022. Principles of risk decision-making. *J Toxicol Environ Health B Crit Rev* 25:250-278.
- Lave LB, Omenn GS. 1986. Cost-effectiveness of short-term tests for carcinogenicity. *Nature* 324:29-34.
- Lave LB, Ennever FK, Rosenkranz HS, Omenn GS. 1988. Information value of the rodent bioassay. *Nature* 336:631-633.

- Leontaridou M, Gabbert S, Van Ierland EC, Worth AP, Landsiedel R. 2016. Evaluation of non-animal methods for assessing skin sensitisation hazard: A Bayesian Value-of-Information analysis. *Altern Lab Anim* 44:255-269.
- NASEM. 2009. *Science and Decisions: Advancing Risk Assessment*. Washington, DC:National Academies of Sciences, Engineering, and Medicine.
- NASEM. 2021. *The use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations*. Washington, DC:National Academies of Sciences, Engineering, and Medicine.
- NASEM. 2022. *The Importance of Chemical Research to the U.S. Economy*. Washington, DC:National Academies of Sciences, Engineering, and Medicine.
- NTP. 1996. *National Toxicology Program Fiscal Year 1996 Annual Plan*. 96-4168. Research Triangle Park, NC:National Toxicology Program.
- NTP. 2018. *NTP Research Report on National Toxicology Program Approach to Genomic Dose-Response Modeling*. NTP-RR-5. Research Triangle Park, NC:National Toxicology Program, U.S. Department of Health and Human Services.
- Pastoor T, Stevens J. 2005. Historical perspective of the cancer bioassay. *Scand J Work Environ Health* 31 Suppl 1:129-140; discussion 119-122.
- Peng CZ, Hatlestad P, Klug MG, Kerbeshian J, Burd L. 2009. Health care costs and utilization rates for children with pervasive developmental disorders in North Dakota from 1998 to 2004: impact on Medicaid. *J Child Neurol* 24:140-147.
- Raiffa H. 1968. *Decision Analysis: Introductory Lectures on Choices under Uncertainty*. New York, NY:Random House.
- Ring CL, Arnot JA, Bennett DH, Egeghy PP, Fantke P, Huang L, et al. 2019. Consensus Modeling of Median Chemical Intake for the U.S. Population Based on Predictions of Exposure Pathways. *Environ Sci Technol* 53:719-732.
- Sand S, Portier CJ, Krewski D. 2011. A signal-to-noise crossover dose as the point of departure for health risk assessment. *Environ Health Perspect* 119:1766-1774.
- Shahat ARS, Greco G. 2021. The Economic Costs of Childhood Disability: A Literature Review. *Int J Environ Res Public Health* 18:3531.
- Taylor AC, Evans JS, McKone TE. 1993. The value of animal test information in environmental control decisions. *Risk Anal* 13:403-412.
- Thayer KA, Angrish M, Arzuaga X, Carlson LM, Davis A, Dishaw L, et al. 2022a. Systematic evidence map (SEM) template: Report format and methods used for the US EPA Integrated Risk Information System (IRIS) program, Provisional Peer Reviewed Toxicity

- Value (PPRTV) program, and other "fit for purpose" literature-based human health analyses. *Environ Int* 169:107468.
- Thayer KA, Shaffer RM, Angrish M, Arzuaga X, Carlson LM, Davis A, et al. 2022b. Use of systematic evidence maps within the US environmental protection agency (EPA) integrated risk information system (IRIS) program: Advancements to date and looking ahead. *Environ Int* 169:107363.
- Thomas RS, Allen BC, Nong A, Yang L, Bermudez E, Clewell HJ, 3rd, et al. 2007. A method to integrate benchmark dose estimates with genomic data to assess the functional effects of chemical exposure. *Toxicol Sci* 98:240-248.
- Thompson KM, Evans JS. 1997. The value of improved national exposure information for perchloroethylene (Perc): a case study for dry cleaners. *Risk Anal* 17:253-271.
- Wang Z, Walker GW, Muir DCG, Nagatani-Yoshida K. 2020. Toward a Global Understanding of Chemical Pollution: A First Comprehensive Analysis of National and Regional Chemical Inventories. *Environ Sci Technol* 54:2575-2584.
- Whaley P, Aiassa E, Beausoleil C, Beronius A, Bilotta G, Boobis A, et al. 2020. Recommendations for the conduct of systematic reviews in toxicology and environmental health research (COSTER). *Environ Int* 143:105926.
- WHO. 2017. Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization Project Document 11 – 2nd edition. Geneva, Switzerland:World Health Organization, International Programme on Chemical Safety.
- Yokota F, Gray G, Hammitt JK, Thompson KM. 2004. Tiered chemical testing: a value of information approach. *Risk Anal* 24:1625-1639.
- Yokota F, Thompson KM. 2004. Value of information analysis in environmental health risk management decisions: past, present, and future. *Risk Anal* 24:635-650.
- Zabeo A, Keisler JM, Hristozov D, Marcomini A, Linkov I. 2019. Value of information analysis for assessing risks and benefits of nanotechnology innovation. *Environmental Sciences Europe* 31:11.