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Report of the U.S. Environmental Protection Agency Board of Scientific Counselors Value of Information (VOI) Panel

RESPONSES TO CHARGE QUESTIONS

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A Federal Advisory Committee for the U.S. Environmental Protection Agency's Office of Research and Development

BOSC Value of Information Panel

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Tom Tracy, Designated Federal Officer

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CONTENTS

LIST OF ACRONYMS

AI	Artificial Intelligence
AOP	Adverse Outcome Pathways
API	Application Programming Interface
BOSC	Board of Scientific Counselors
CBI	Confidential Business Information
ECHA	The European Chemicals Agency
EPA	Environmental Protection Agency
eSTAR	Emerging Systems Toxicology for Assessment of Risk
FACA	Federal Advisory Committee Act
ETAP	EPA Transcriptomic Assessment Product
FDA	Food and Drug Administration
GIVIMP	Good *In Vitro* Method Practices
HTTK	High-Throughput Toxicokinetics
HTTr	High-Throughput Transcriptomics
HTPP	High-Throughput Phenotypic Profiling
IATA	Integrated Approaches to Testing and Assessment
ICE	Integrated Chemical Environment
ITRC	Interstate Technology and Regulatory Council
IUCLID	International Uniform Chemical Information Database
IVIVE	*in vitro* to *in vivo* extrapolation
LC	Liquid Chromatography
MS	Mass Spectrometry
NAM	New Approach Methods
NAS	National Academy of Sciences
NCCRP	New Chemicals Collaborative Research Program
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
NIH	National Institute for Health
NSF	National Science Foundation
OECD	Organization for Economic Cooperation and Development
OPPT	Office of Pollution Prevention and Toxics
ORD	Office of Research and Development
PFAS	Per- and polyfluoroalkyl substances
QSAR	Quantitative structure-activity relationship
(Q)SAR	A collective term signifying QSARs and SARs collectively
QSUR	Quantitative Structure Use Relationships
RACT	Research Area Coordination Teams
SAR	Structure-activity relationship
SMARTS	Simplified Molecular-input line-entry system Arbitrary Target specification
TSCA	Toxic Substances Control Act
UVCB	Unknown or variable composition, complex reaction products, or biological materials

INTRODUCTION

The EPA Office of Research and Development (ORD) is seeking a scientific peer review of the documents supporting the development of transcriptomic-based reference values (TRVs) and the implementation of a new EPA Transcriptomic Assessment Product (ETAP). The ETAP is a proposed ORD assessment product that utilizes a standardized short-term in vivo study design and data analysis procedures to develop TRVs for data poor chemicals. EPA has a need to develop TRVs, defined as estimates of daily oral doses likely to be without appreciable risk of adverse effects following chronic exposure. The TRV is intended to protect both the individual and population from adverse effects. While a TRV is expressly defined as a chronic value in an ETAP, it may also be applicable across other exposure durations of interest including short-term and subchronic exposures. This generalization has been previously used by EPA in certain risk assessment applications [e.g., Provisional Peer-Reviewed Toxicity Value (PPRTV) assessments] where a chronic non-cancer reference value has been adopted as a conservative estimate for a subchronic non-cancer reference value when data quality and/or lack of duration-relevant hazard and dose-response data preclude direct derivation.

ORD recently developed a framework to compare toxicity testing methodologies. The Value of Information (VOI) framework endeavors to quantitatively compare the human health and economic benefits of various approaches, including the ETAP. In June 2023, ORD conducted a VOI case study to compare the short-term in vivo transcriptomic assay approach and ETAP with the traditional chronic rodent bioassay and human health assessment process. The BOSC VOI Panel was charged with assessing the scientific rigor of ORD's case study and the resulting conclusions.

The identified strengths, suggestions, and recommendations herein are informed by a review of the EPA's draft report entitled, "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)," the EPA's presentations to the Committee, available scientific literature, and Committee members' experiences using a variety of NAM tools including those developed or used by the EPA.

In this report, Committee members provide specific Recommendations for priority actions by EPA. These Recommendations should be of the highest priority. The Committee also provides numerous Suggestions. The Committee's judgement regarding the priority for these Suggestions and estimates of the level of effort for each Suggestion are also provided to aid decision making. However, these Suggestions are subordinate to the Recommendations. Accordingly, Suggestions should be viewed as information for EPA to take under consideration, whereas Recommendations should be viewed as activities that the Committee agreed reflected the most critical opportunities to improve the VOI framework and ORD case study.

CHARGE QUESTIONS AND CONTEXT

The VOI Panel was charged with four questions as follows:

Q.1: The general VOI framework developed by Hagiwara et al. (2022) for comparing human health and economic benefits of toxicity-testing methodologies was adapted for application to this case study. Please comment on the extent to which the VOI framework and decision model are clearly described and the extent to which it provides sufficient representation of chemical risk assessment and decision making that facilitates a reasonable comparison of toxicity testing and human health assessment processes.

Q.2: Most of the inputs to the decision model used in the case study were drawn from published literature sources, experimental measurements, or peer-reviewed computational models. Please comment on the extent to which the input parameters are clearly described and represent the best available sources for use in the case study.

Q.3: The baseline scenarios and sensitivity analyses were intended to represent the range of chemical characteristics and potential uncertainties that could be encountered in applying the toxicity testing and human health assessment approaches to data poor chemicals under EPA regulatory purview. Please comment on the extent to which the baseline scenarios and sensitivity analyses are clearly described and provide reasonable representation of the range of chemical characteristics and potential uncertainties that could be encountered in this context.

Q.4: Please comment on the overall conclusions of the VOI case study that, under the exposure scenarios and assumptions considered, the ETAP is more frequently preferred over the traditional toxicity testing and human health approach for more rapidly and cost effectively evaluating chemicals with no existing toxicity testing or human health data.

PANEL RESPONSES TO CHARGE QUESTIONS

Charge Question 1

Q.1. The general VOI framework developed by Hagiwara et al. (2022) for comparing human health and economic benefits of toxicity-testing methodologies was adapted for application to this case study. Please comment on the extent to which the VOI framework and decision model are clearly described and the extent to which it provides sufficient representation of chemical risk assessment and decision making that facilitates a reasonable comparison of toxicity testing and human health assessment processes.

Narrative

The case study represents an ambitious and appropriate use of VOI techniques on an important problem, and it showed clear results with relevance to EPA's consideration of ETAP vs. THHA. We evaluated the consistency of the methodology between the case study and Hagiwara et al. (2022) and find that the analysis is consistent, and given the specific assumptions of the case study, it appears ETAP is fairly consistently favored. In addition to our assessment of the methodology, we considered the case study as an application of VOI and have some questions about its assumptions. In general, we see much potential for the VOI approach and offer some suggestions on how it can be leveraged and presented within EPA.

Given the implication of the results of the VOI analysis for ETAP vs. THHA, perhaps the framework can eventually be used to compare or refine additional toxicity testing protocols that, like ETAP, also have shorter times to completion than THHA.

The results of this VOI case study are dependent on the characteristics of the particular chemicals in the database used in this study and assumes no additional prior knowledge about the chemicals. It may be that there are chemicals where prior knowledge would suggest parameter distributions (e.g., as in some of the sensitivity results) where ETAP is not superior to THHA. Those considering the results of this VOI case study should bear in mind that the mostly inferior results from THHA is within the context set by the case study, which compared a method needing less time but with higher uncertainty (ETAP) and one needing more time but with less uncertainty (THHA), in terms of avoiding social costs regarding regulating chemicals with no prior data at all. This should not be viewed as a support of eliminating THHA in other contexts.

Strengths

- The calculations and equations were implemented in a manner that appeared consistent with the mathematical formulation in the Hagiwara et al. (2022) Risk Analysis article.
- The committee appreciates the evaluation of VOI under various scenarios. This is useful in understanding how robust the base case results are and how they may be extrapolated.
- The particular implementation of VOI in the case study represents a novel approach to consider the value of time in assessing alternative options in decision-making. Because this is a critical factor in EPA's processes, this VOI approach is particularly useful. The case study clearly demonstrated that lower-cost, time-efficient studies (*e.g.*, ETAP) can be more valuable when compared to higher-cost, time-consuming animal studies when taking into account the cost of delay.

Suggestions

- It is suggested to better explain the time needed to complete the ETAP and THHA, preferably with a breakdown of time needed to complete major steps involved for each method (chemical acquisition, dose exploration, result analysis, review, etc.).
- It is suggested to provide some indications on the implementation plan of the VOI framework in the future of decision-making processes.
- It is suggested to consider the use of other distribution functions *vs*. the lognormal distribution used currently that could better capture outliers that may potentially exist.
- It is suggested to consider adding additional scenarios where the assumption of 20 years horizon is variable.

Future Considerations

- Consider using the VOI process for exposure assessment for data-poor chemicals.
- Consider additional influences from the cost of contamination clean-up efforts in the cost of control.

Recommendations

The Panel offers the following recommendations:

Recommendation 1.1: The case study and report are rather technical and draw on the prior ETAP BOSC document. In order to make the report more accessible to both technical and lay readers, we recommend several additions to improve its transparency without changing its technical content. Ideally, sufficient detail would be provided about the method to enable a knowledgeable reader with access to the data and tools used in the case study to replicate its results.

Recommendation 1.2: Specifically, it is recommended to make it easy to locate the exact input used for BMDExpress in order for others to replicate that step. The dose-response curves for toxicity that were used in calculations should also be easily locatable within the paper or by reference to the ETAP review. Following this, the case study should provide an illustration of a deterministic calculation of BMDL results for a chemical with known parameter values.

Recommendation 1.3: In addition, the logic of the VOI model is described verbally and mathematically. It is recommended to help readers by including additional graphical representations using technical conventions such as an influence diagram and a decision tree in order to clarify the logic of the model. Specifically, a decision tree can illustrate the temporal order between the decisions and the resolution of uncertainties in the model, while an influence diagram can represent the way in which variables in the model and the dependencies between them result in the endpoint values across possible outcomes.

Recommendation 1.4: For further clarity, it is recommended that they case study include figure 3 in the Hagiwara et al. (2022) paper in the written document of VOI (section 4.2 or 4.3).

Charge Question 2

Q.2. Most of the inputs to the decision model used in the case study were drawn from published literature sources, experimental measurements, or peer-reviewed computational models. Please comment on the extent to which the input parameters are clearly described and represent the best available sources for use in the case study.

Narrative

The Value of Information (VOI) case study organized by the U.S. EPA represents a much-needed comparison of the health and economic values estimated to result from the newly proposed 5-day EPA Transcriptomic Assessment Product (ETAP) versus the traditional 2-year animal bioassay historically used in human health risk assessments (THHA). In terms of model parameter inputs, the overall VOI was informed by global parameters, derived from subsets of data that are currently available across 5-day transcriptomics, two-year toxicity profiles, exposure estimates, population and toxicity response variabilities, and health and economic cost assumptions. Overall, this committee viewed the general approaches as scientifically sound, with suggested methods of further refinement detailed below. Some of the main recommendations include improved recognition and discussion surrounding the variable inputs that largely dictated final VOI values. Interpretation and discussion on these inputs are needed to better understand factors that most heavily influence final VOI decisions, which the committee interpreted as the input variables of cost and time. Because this committee interpreted cost and time as the primary drivers of the VOI, we also suggest additional sensitivity analyses through modifications of these two input parameters. Another important consideration is the difference in uncertainty behind the ETAP vs THHA cases, derived through the evaluation of BMD/BMDL ratios. Further discussion surrounding the importance of this ratio and potential factors that influence it are recommended, in addition to the recommendation to continually update this ratio value as more ETAP case studies are produced.

Strengths

- ORD is to be commended for doing applying a formal VOI approach and conducting rigorous analysis. The committee is enthusiastic about the role VOI can play going forward including evaluating alternative approaches to developing risk related information and in chemical-specific analyses to identify efficient and appropriate ways to analyze risks.
- The VOI study leveraged robust information across diverse data streams, spanning toxicity and human health data, exposure estimate modeling, health and chemical control costs, and variables that influence the uncertainty amongst these measures.
- The VOI case study incorporated various sensitivity analyses, and has evaluated some of the influences of different input variable distributions on final VOI estimates; though additional select sensitivity analyses are still recommended (suggestions below).
- The committee appreciates that, in the EPA's comparison between the use of the ETAP vs THHA, they essentially give the ETAP a disadvantage from the beginning by not just simply looking at cost and time alone to justify use of the ETPA over THHA. Instead, the EPA is integrating different information sources, including components of cost and time, into a sophisticated analysis using the VOI framework.

Suggestions

- Exposure reduction and effect of target risk level values: For the TRDM an assumption is made that a decision to act will result in a 90% reduction in exposure and concomitant reduction in adverse health outcomes. While this may be an appropriate assumption, better justification is suggested along with some evaluation of the plausibility of this assumption. Looking across a range of Agency decisions, from changes in NAAQS standards to Superfund cleanup decisions we see a very wide range in exposure reductions. Depending on the type of decision there may be implementation impediments that make reaching 90% reduction difficult because of heterogeneity of receptors.
- In addition, the committee suggests exploration of the effect of alternative values of the TRDM target risk level (e.g., down to 10^{-8}) on the VOI of the alternative data development technologies.

Future Considerations

- Different NAMs Toxicity Data: This is a stylized example to demonstrate the VOI approach to a comparison of the ETAP technology to traditional chronic testing technologies. It is solid and well done but may not reflect the real-world state of testing decisions. A particularly strong assumption is that chemicals will truly be without any existing data to inform a prior estimate of toxicity. Few chemicals will have absolutely no relevant data even an LD_{50} or estimate of toxicity from a quantitative structure activity relationship (QSAR) model. Information like this would lead to a prior distribution of toxicity that his less uncertain than assumed for this case study. This may influence the relative value of different technologies for gathering toxicity information. Acknowledging the information in LD_{50s} or QSARs, read across techniques or similar may also suggest these tools have a significant VOI.
- Additional Study and Assessment Design Comparisons: There are many different study/assessment comparisons that could be carried out using a VOI approach. Additional comparisons that the committee discussed as having future utility could incorporate other animal bioassay study durations (e.g., 90-day study). Another recommendation would be to compare the ETAP 5-day animal bioassay with pre-defined assessment protocol with something similar in the THHA design, which could still include a traditional 2-year animal bioassay but incorporate a similar pre-defined assessment protocol to decrease the time required for results interpretation and assessment. This type of comparison would allow for a more equal comparison between just the study design elements (5-day transcriptomics vs 2-year animal apical endpoints).
- Individual Chemical-Basis Decisions: The committee encourages ORD to consider the use of VOI for evaluation of individual chemical analyses. This will have challenges including estimating the uncertainty present in the risk estimates for a specific chemical and characterization of the uncertainty reduction that might come from different types of toxicity data. The VOI approach may help speed risk evaluations by identifying when information is certain enough to develop a toxicity value to allow a decision about chemical use.
    - In a similar vein, a quantitative statement of the uncertainty in the ETAP derived TRV for a specific chemical would be important for transparency and would allow the VOI approach to be used to evaluate additional toxicity data development options ranging from *in silico* to *in vivo*.
- Incorporate Beneficial Chemicals, Inert Chemicals, or Consequences from Chemical Replacements/Alternatives: The current VOI case study was not designed to incorporate

beneficial chemicals, inert chemicals, or the potential consequences of replacing the chemical under consideration with an alternative chemical. To provide some examples, chemical disinfectants could be demonstrated as harmful, though if we remove such a chemical from the market, what other risks then exist that should be quantified (e.g., increased risk of infectious disease)? Such future analyses could incorporate substitution of chemical consequences and/or chemical alternatives considerations. It is current recommended to include some discussion of this topic within the report.

- Consideration of Mixtures and/or Multiple Stressors: Future VOI analyses could begin to capture the exposure landscape of mixtures and multiple stressors even outside of the chemical domain that influence disease susceptibility. Given that the ETAP study design is leveraging higher throughput transcriptomics methodologies that are translational to *in vitro* designs, mixtures exposures could feasibly be captured and assessed through this mechanism.
- Further Emphasis on Exposure: The committee views that the importance of exposure estimates could be highlighted further in terms of VOI. It would be informative to evaluate the VOI under future circumstances of obtaining more and better exposure information, which could actually be more cost effective than expanding toxicity testing in many cases, under this paradigm.

Recommendations

The Panel offers the following recommendations:

Recommendation 2.01: Presentation of input data sources: To improve overall readability of the VOI methods, we recommend the inclusion of a flow chart or diagram to summarize the different sources of information/databases/literature that were used, and which specific variables each data source contributed to in the overall VOI calculations. This type of visualization and summary would help guide the audience to better understand what, where, and how each input data source was used.

Recommendation 2.02: Improved clarity surrounding the use of variability measures in deriving uncertainty: In many toxicological contexts, the distinction between “variability” (reflecting underlying true variation of a quantity or parameter) and “uncertainty” (reflecting lack of knowledge of a true unknown parameter value) is clear, even if imprecise language sometimes blurs the distinction. However, in a Bayesian context, the variability in a parameter value (i.e. the prior) represents a hypothetical population from which values may be drawn, and this *is* uncertainty for the single parameter value prior to gathering any information. In the VOI document, we recommend a careful description of these concepts for readers less familiar with Bayesian reasoning. In addition, we recommend that the specific term “uncertainty factor,” which is yet another concept, always be used in full, i.e. never just “uncertainty” when the UF is being discussed.

Recommendation 2.03: Sources of uncertainty in THHA: allometric scaling: The ratio of P95/P50 of body sizes reported by Chiu et al. (2018) is 1.235 represents variability in body sizes. We recommend clarification on why measures of variability are being used here to inform uncertainty (and perhaps this issue is related to the above comment).

Recommendation 2.04: Clarifications on toxicity distribution information from Chiu et a. 2018: It is recommended to clarify the source of the difference between the 1522 human equivalent doses considered in the probability distribution function vs final 600 chemicals from which they were derived. Were just the most sensitive endpoints considered, paralleling the proposed ETAP methodologies, or were multiple estimates calculated for each chemical? How might these potential differences influence the mean and uncertainty? The primary concern here is ensuring that the measures of toxicity for µTox are comparable to most sensitive endpoint as done in ETAP.

Recommendation 2.05: Time as an important consideration in VOI results: The input parameter of time was considered to be critical by the committee, which was incorporated into the VOI analysis through two different mechanisms. First, the overall VOI analysis was conducted on an overall timeframe of 20 years. It is advisable to consider the influences of a different overall timeframe recognizing the diminishing returns on decisions due to discounting. Second, the assumptions surrounding the decision to evaluate THHA as a process that requires eight years to complete were discussed by the committee. In interpreting this decision, it would be informative to see historical distributions of time requirements from previous NTP chronic bioassays and IRIS assessment processes. This information could be used to further justify the specific THHA time requirement used in the VOI analysis. The committee also discussed the overall assumption that four years are required within a THHA after data are generated, for the study review and assessment process. It may be that, in future assessments, processes can be emplaced to make this component more streamlined and take less time, similar to processes that are now being proposed in the ETAP pipeline. The element of time is a very important factor in final VOI calculations, and thus we recommend a sensitivity analysis on the time component assumptions of the THHA. For example, running the same VOI analysis with the THHA requiring two years of an assessment period (totaling six years as opposed to eight) would be extremely informative.

Recommendation 2.06: Cost of Testing (COT) as an important consideration in VOI results: The cost of testing (COT) parameter is very different between ETAP and THHA. This makes it potentially important in determining the VOI of the ETAP approach, although, for example, very large values of ETSC may swamp the difference in cost between ETAP and THHA. The sensitivity of the VOI results to COT should be either explored with an additional sensitivity analysis or, if appropriate, the minor role of this parameter should be explained.

Recommendation 2.07: Control costs as a data input requiring clarification: The Benefit-Risk Decision-Maker (BRDM) criterion considers the cost of exposure mitigation (control costs). Although discussions with the EPA representatives indicated that the TRDM model was in some ways better aligned with regulatory practice, the committee recommends further details on exposure mitigation costs. If warranted, some sensitivity analyses for BRDM on this basis would be helpful (*e.g.* do NAAQS control estimates provide any additional basis). The committee also suggests that control costs are not necessarily smooth, but may be stepwise, as a practical control measure may require a discrete regulatory change.

- As a related comment, several graphs considered exposure control in terms of percent exposure reduction. The committee requests clarity that 0% reduction indeed implies "status quo," i.e. no change in current regulation or practice, until such time as actionable data have been gathered for a data-poor chemical. It was only after repeated conversations with the EPA representatives that it emerged (or so the committee recalls) that the expected total social cost (ETSC) savings associated with ETAP were in fact in comparison to a blanket change in all exposures (of 78%). Some simple introductory material explaining these facts would be extremely helpful. At the same time, the committee recognizes that a blanket reduction may be unachievable as a regulatory action, although it would by our understanding result in an enormous cost savings in ETSC.

Recommendation 2.08: Clarification surrounding BMD/BMDL ratio implications and recommended updates over time: Sources of uncertainty were captured through previous transcriptomic-based BMD/BMDL ratios and animal bioassay-based BMD/BMDL ratios. Narrative surrounding why this ratio captures uncertainty is recommended within the VOI report. For example, it is recommended to describe what the BMD/BMDL measures capture, and the general interpretation that as measures become more certain, BMD/BMDL ratios become smaller. This additional narrative is important, as differences between the ETAP vs THHA BMD/BMDL ratios influence the final VOI values. We also recommend updating the BMD/BMDL ratio as ETAP case studies build, since over time, better estimates of uncertainty inherent within transcriptomics-based assessments may lead to more comparable measures of uncertainty between the two study designs. The mean THHA BMD/BMDL ratio of 1.8 is lower than the mean ETAP BMD/BMDL ratio of 3.47, and the number of chemical evaluations that went into informing each of these may have influenced this difference (n=12 in ETPA and n=600 in THHA).

Recommendation 2.09: Clarification surrounding animal-human TK/TD descriptions: In section 5.1.2 the discussion of the sources of uncertainty in the extrapolation of the two-year bioassay to humans needs further clarification. Specifically, the uncertainty in differences of TK/TD between rodents and humans (3.000 - remarkable precision!) taken from the WHO 2017 report needs to be further explained. The fact that this value is empirically derived and not from the decomposition of the commonly used UF_H uncertainty factor should be emphasized. It is recommended that the US EPA place their approach in the context of the 2011 guidance, particularly surrounding allometric scaling in acute vs. chronic toxicity testing.

Recommendation 2.10: Exposure parameterization and partitioning clarification: When considering the exposure estimates outputted from SHEDS-HT, the EPA partitioned the estimates into tertiles (low/medium/high) based upon μ_{exp}, and further sub-tertiles (low/medium/high) based upon σ_{exp}. Further clarification is recommended to make it very clear that these partitions were based upon equal data distributions, resulting in the same number of chemicals per bin (as opposed to other binning approaches). It is also recommended to clarify the exact source of the exposure estimates data from SHEDS-HT, where it is unlikely that analysts used data produced only from the original paper in 2014; but rather, data likely originated from more updated data dumps and/or the recent SHEDS-HT R package.

Recommendation 2.11: Overall interpretation of findings: The committee interpreted this VOI analysis to include many different input variables. The main drivers of the final VOI values, under our interpretation, were time, study cost, and, to a lesser extent, intra-study variability (though these rankings may change based upon additional requested sensitivity analyses). Other variables, such as cost of exposure mitigation action, did not as heavily influence VOI values, as these costs would be incurred at some time during the 20-year overall study period. Therefore, in reality, only a few parameters are likely to have a significant differential effect on the VOI comparison between ETAP and THHA. The current sensitivity analyses account for some of these variable input considerations, though as the committee has previously detailed, expanded sensitivity analyses surrounding time and cost would be extremely informative as they appear to be primary drivers of VOI values. Additionally, we recommend a dedicated discussion that clarifies the role of each input parameter on final VOI calculations. More specifically, a discussion should be included on what was learned by changing each input parameter, individually and in combination (when applicable), and how each influenced final VOI values, with particular emphasis on cost, time, and uncertainty. Lastly, it is important to quantitatively characterize the remaining uncertainty in the ETAP derived TRV to allow the VOI approach to be used on further data gathering for that specific chemical.

Charge Question 3

Q.3: The baseline scenarios and sensitivity analyses were intended to represent the range of chemical characteristics and potential uncertainties that could be encountered in applying the toxicity testing and human health assessment approaches to data poor chemicals under EPA regulatory purview. Please comment on the extent to which the baseline scenarios and sensitivity analyses are clearly described and provide reasonable representation of the range of chemical characteristics and potential uncertainties that could be encountered in this context.

Narrative

Overall, the VOI report is well written and clear and the baseline scenarios for ETAP and the THHA comparisons are well supported and thorough. While the analysis incorporates a reasonable representation of chemical characteristics, many of the recommendations and suggestions below relate to the sensitivity analyses. Some of these recommendations are new analyses such modifications to the duration of the 8-year THHA scenario. Given the duration of the typical IRIS assessment, it is of interest to examine whether, and to what extent, the duration of the risk assessment phase clearly will impact the VOI analyses, and many of the risk assessments / risk evaluations conducted by the Agency are not IRIS-type of evaluations. This might provide insight into how streamlining the risk assessment might be beneficial (or not). Recommendations related to existing sensitivity analyses, the impact of toxicity value distribution should be investigated without changing the annual health cost estimates.

There is some concern that the VOI report presents as if there are only two comparators (the 9 mo ETAP total duration vs the 8-year THHA total duration). There are other published metanalyses demonstrating how short-term studies and read-across methods can be used to estimate chronic toxicity values. While these may (or may not) be as robust as the relationship between TRV and RfD values, the existence of other options should be mentioned and perhaps investigated in a future VOI analysis.

Strengths

- The VOI report is generally well written, clear and highlights the utility of VOI analysis. This document demonstrates that VOI analysis might be useful for assessing other EPA efforts. However, the ultimate benefit of these types of analyses depends on thorough evaluation of the underlying assumptions and model parameters. In this regard, a more targeted review of each assumption and related input parameters by specialists (e.g., control cost experts) as opposed to general review will be critical.
- The baseline scenarios for ETAP and the THHA comparisons included several plausible exposure cases representing multiple combinations of exposure level and associated uncertainty. The inclusion of two decision contexts (target risk vs benefit-risk) adds additional insight into both the VOI process and the conclusions regarding the favoring of ETAP over THHA.

- The sensitivity analyses were generally informative with assessment of parameters related to exposure, population size, target risk and costs of control and health. However, given the clear importance of time in the VOI analysis, additional exploration of durations (9 months and 8 years) and cost (especially associated with risk assessment) associated with the two approaches would provide additional insight into the value of each assessment type.

Suggestions

- It is suggested to revise the text to acknowledge that other proxies for chronic tox health-based guidance value surrogates such as TTCs, read-across, ToxCast PODs, in vivo MN-derived BMD/BMDLs, etc. can be considered in future VOI analyses, to leverage the power and flexibility of VOI models.
- It is suggested to provide clarity on chemical structure/classes covered. How does the domain of applicability of the compounds used in the analysis relate to the range of chemistries for which the ETAP may be applied?
- Clarification is suggested on Pg 17. The definition of “toxicological concordance uncertainty” is not clearly described. What is meant by “toxicological concordance”... that the transcriptome BMDL is not an accurate estimate of the true apical endpoint BMDL?
- Clarification is suggested on Pg 23-24. Does the $\boldsymbol{\theta}$tox parameter refer to both the toxicity BMDL and having information on the *actual apical endpoint hazard* or just on the BMDL?
- In regards to the nature and severity of effect in the VOI, it is suggested to clarify whether the adverse effect endpoint impacts risk management / remediation?
- Clarification is suggested on Pg 34. In describing how the population exposure estimates were partitioned in 9 quadrants, the EPA wrote “Expecting that some prior information about exposure will be available for most chemicals based on intended use and other information…”. This explanation does not seem to help communicate how this “prior information on exposure” was used to define the quadrants.
- It is suggested to add quadrant numbers for the different exposure scenarios in figure 5.2 (as in Slide 29 in Mr. Paoli’s presentation). Why was Scenario 5 selected? Is it the most likely scenario (i.e., randomly selected chemical is likely to meet Scenario 5 conditions) or selected for other reasons (e.g., Med/Med seems like a simple/logical starting case).

Future Considerations

- Future considerations could incorporate a probabilistic approach instead of point estimates for variables in Table 5-4.
- It is suggested to consider VOI analyses for alternative short and longer-term toxicity testing approaches in the future.
- Future considerations should be given to how one could use the results of the agnostic ETAP omics-derived BMDL to group chemicals. It would seem that developing a sufficient similarity analysis for a TEF/ relative potency approach for a mixture (or simultaneous exposures) would be difficult (or impossible) without analyzing the transcriptome data further (such as pathway analysis and/or PCA).
- Future considerations should explore extending the ETAP approach to other toxicity endpoints like DART (among others). For example, could a one generation reproduction study design with a multi-organ transcriptome BMD analysis of parents and offspring be appropriate to derive a DART-based reference dose?

Recommendations

The Panel offers the following recommendation:

Recommendation 3.1: It is recommended to perform sensitivity analyses on different time durations of the traditional testing/assessment scheme. For example, different durations of the risk assessment process, or different study durations to obtain a chronic BMDL in vivo (1 year vs 2 year animal study; 90-day study with an additional 10X UF; etc.)

Recommendation 3.2: It is recommended to revise the text to include more specific information on the steps and timelines associated with each major task within the THHA approach. This will allow comparison to shorter-duration risk evaluations.

Recommendation 3.3: It is recommended to clarify whether the sensitivity analyses evaluated effects on the toxicology distributions separately from the effects of varying cost distributions. If these analyses evaluated these two parameters combined, then it is recommended to evaluate them separately.

Recommendation 3.4: It is recommended to discuss within the text whether there is a loss of value by not assessing MOA or not collecting apical endpoint data in the ETAP study. Could a dollar value for identifying the apical endpoint in the THHA process be assigned and incorporated into the VOI analyses? Conversely, is there a dollar value that can be assigned for the opportunity cost of not knowing anything about the TRV other than a numerical BMDL? Restated, is the only value/goal of a risk assessment to obtain a BMDL, and there is no cost incurred by the selection of one alterative over another due to potential loss of additional information gained from more informative analyses (e.g., THHA). While we are not recommending any change to the VOI analysis itself at this time, it seems that some discussion/acknowledgment of this issue should be included in the VOI report.

Charge Question 4

Q.4: Please comment on the overall conclusions of the VOI case study that, under the exposure scenarios and assumptions considered, the ETAP is more frequently preferred over the traditional toxicity testing and human health approach for more rapidly and cost effectively evaluating chemicals with no existing toxicity testing or human health data.

Narrative

EPA has conducted VOI evaluations for a wide range of chemicals to test whether ETAP or THHA is preferred. In the majority of cases, the ETAP approach is favored. The findings from the VOI analysis support what would seem to be an obvious conclusion. If the parallel BOSC panel agrees that the ETAP yields reliable results and could be benchmarked to give a TRV that is relatively consistent with the RfD one would get from a 2-year bioassay, then it seems an obvious conclusion that relying on an ETAP (that can be conducted vastly quicker and cheaper than the alternative) would be far more valuable to society than relying on the THHA and delaying decisions for 'data poor' compounds. In addition, it is worth noting that the ETAP would also be favored in circumstances where it may not be possible to realize the

Expected Net Benefit of Sampling (ENBS) that would accrue from developing and acting upon a THHA TRV due to limitations in control technologies and/or measurement methods.

Strengths

- The VOI case study clearly demonstrates that the ETAP was favored over THHA across multiple VOI metrics.
- This result is likely to be a consequence of the correlation, documented in the ETAP Scientific Support Document, between TRVs based on an ETAP and RfDs based on chronic non-cancer bioassays, as thoroughly demonstrated in the ETAP Scientific Support Document.
- Importantly, the conclusions of the VOI case study are highly robust over a number of sensitivity analyses, including the conservative assumption of an additional discordance factor between the ETAP and the THHA that is assumed to be solely due to the ETAP.

Suggestions

- It is suggested that the description of the VOI evaluation consider the point that, in some circumstances, the resulting control measure from acting upon exposure mitigation using an ETAP may not differ substantially or may even be identical to the control measure selected to mitigate exposure to a different level based on a THHA, due to the technical and/or performance capabilities for various control measures. For example, if a ETAP for a chemical would result in implementation of a control technology that achieves a 90% reduction in exposure through implementation of a control technology that is currently the best available in terms of exposure reduction then there is limited value to produce an THHA that would result in a desired exposure reduction that is greater than 90%, but is not achievable due to limitations of the available control technology.

- It is suggested that the report acknowledge that the proposed decision component in the VOI approach used by EPA in this case study could be strengthened in the future by considering the use of multi-criteria decision analysis. VOI analysis often starts with a more developed decision model, often with multiple criteria, followed by analysis to determine how the decision may change if new information is added.

Future Considerations

- EPA should consider in the future whether there is adequate data on shorter-term toxicity tests (*e.g.*, 90-day OECD tox study) that should be evaluated in a VOI analysis. This should be addressed to determine whether the choice of the 2-year bioassay as the benchmark for the VOI analysis biased the results.

Recommendations

The Panel offers the following recommendations:

Recommendation 4.1: It is recommended that the EPA clarify the sentence: "In addition, strategically integrating the ETAP approach with other established methods, such as chemical categorization and read across, could further enhance the public health benefits, enabling the EPA to more rapidly address public health and environmental challenges (e.g., per- and polyfluoroalkyl substances)". Clarify the steps at which chemical groupings and/or read across could be integrated (e.g., potentially during the chemical prioritization step vs others); this would result in reduced ambiguity.

Recommendation 4.2: It is recommended to either clarifying monetary units or using the same monetary units in the results section of the case study. The monetary units in Figures 6.1 and 6.3 are billions ($B) while the monetary units for the corresponding tables (Tables 6.1 and 6.3) are millions ($M).

Recommendation 4.3: It is recommended to investigate alternative sources to establish the Annualized Control Cost (ACC) for the ETAP VOI Case Study, particularly for the ACC_{max}. The current case study uses air pollution control cost from implementation of the National Ambient Air Quality Standards (NAAQS), which are focused on criteria pollutants. The most relevant health endpoints for the NAAAQS would be associated with inhalation and thus, reference concentrations (RfC), but the toxicological parameterization for the ETAP focuses on non-inhalation routes of exposure and thus, reference doses (RfD). The types of pollution control measures for air emissions reductions, and the associated costs, may differ substantially than types of control measures, and associated costs, for water pollution discharge/treatment or site clean-up. A possible source of information on control costs more pertinent to RfDs may be the recent economic analyses supporting the National Primary Drinking Water Regulation for 6 PFAS chemicals.

SUMMARY LIST OF RECOMMENDATIONS

Recommendation 1.1: The case study and report are rather technical and draw on the prior ETAP BOSC document. In order to make the report more accessible to both technical and lay readers, we recommend several additions to improve its transparency without changing its technical content. Ideally, sufficient detail would be provided about the method to enable a knowledgeable reader with access to the data and tools used in the case study to replicate its results.

Recommendation 1.2: Specifically, it is recommended to make it easy to locate the exact input used for BMDExpress in order for others to replicate that step. The dose-response curves for toxicity that were used in calculations should also be easily locatable within the paper or by reference to the ETAP review. Following this, the case study should provide an illustration of a deterministic calculation of BMDL results for a chemical with known parameter values.

Recommendation 1.3: In addition, the logic of the VOI model is described verbally and mathematically. It is recommended to help readers by including additional graphical representations using technical conventions such as an influence diagram and a decision tree in order to clarify the logic of the model. Specifically, a decision tree can illustrate the temporal order between the decisions and the resolution of uncertainties in the model, while an influence diagram can represent the way in which variables in the model and the dependencies between them result in the endpoint values across possible outcomes.

Recommendation 1.4: For further clarity, it is recommended that they case study include figure 3 in the Hagiwara et al. (2022) paper in the written document of VOI (section 4.2 or 4.3).

Recommendation 2.01: Presentation of input data sources: To improve overall readability of the VOI methods, we recommend the inclusion of a flow chart or diagram to summarize the different sources of information/databases/literature that were used, and which specific variables each data source contributed to in the overall VOI calculations. This type of visualization and summary would help guide the audience to better understand what, where, and how each input data source was used.

Recommendation 2.02: Improved clarity surrounding the use of variability measures in deriving uncertainty: In many toxicological contexts, the distinction between "variability" (reflecting underlying true variation of a quantity or parameter) and "uncertainty" (reflecting lack of knowledge of a true unknown parameter value) is clear, even if imprecise language sometimes blurs the distinction. However, in a Bayesian context, the variability in a parameter value (i.e. the prior) represents a hypothetical population from which values may be drawn, and this *is* uncertainty for the single parameter value prior to gathering any information. In the VOI document, we recommend a careful description of these concepts for readers less familiar with Bayesian reasoning. In addition, we recommend that the specific term "uncertainty factor," which is yet another concept, always be used in full, i.e. never just "uncertainty" when the UF is being discussed.

Recommendation 2.03: Sources of uncertainty in THHA: allometric scaling: The ratio of P95/P50 of body sizes reported by Chiu et al. (2018) is 1.235 represents variability in body sizes. We recommend clarification on why measures of variability are being used here to inform uncertainty (and perhaps this issue is related to the above comment).

Recommendation 2.04: Clarifications on toxicity distribution information from Chiu et a. 2018: It is recommended to clarify the source of the difference between the 1522 human equivalent doses considered in the probability distribution function vs final 600 chemicals from which they were derived. Were just the most sensitive endpoints considered, paralleling the proposed ETAP methodologies, or were multiple estimates calculated for each chemical? How might these potential differences influence the mean and uncertainty? The primary concern here is ensuring that the measures of toxicity for μTox are comparable to most sensitive endpoint as done in ETAP.

Recommendation 2.05: Time as an important consideration in VOI results: The input parameter of time was considered to be critical by the committee, which was incorporated into the VOI analysis through two different mechanisms. First, the overall VOI analysis was conducted on an overall timeframe of 20 years. It is advisable to consider the influences of a different overall timeframe recognizing the diminishing returns on decisions due to discounting. Second, the assumptions surrounding the decision to evaluate THHA as a process that requires eight years to complete were discussed by the committee. In interpreting this decision, it would be informative to see historical distributions of time requirements from previous NTP chronic bioassays and IRIS assessment processes. This information could be used to further justify the specific THHA time requirement used in the VOI analysis. The committee also discussed the overall assumption that four years are required within a THHA after data are generated, for the study review and assessment process. It may be that, in future assessments, processes can be emplaced to make this component more streamlined and take less time, similar to processes that are now being proposed in the ETAP pipeline. The element of time is a very important factor in final VOI calculations, and thus we recommend a sensitivity analysis on the time component assumptions of the THHA. For example, running the same VOI analysis with the THHA requiring two years of an assessment period (totaling six years as opposed to eight) would be extremely informative.

Recommendation 2.06: Cost of Testing (COT) as an important consideration in VOI results: The cost of testing (COT) parameter is very different between ETAP and THHA. This makes it potentially important in determining the VOI of the ETAP approach, although, for example, very large values of ETSC may swamp the difference in cost between ETAP and THHA. The sensitivity of the VOI results to COT should be either explored with an additional sensitivity analysis or, if appropriate, the minor role of this parameter should be explained.

Recommendation 2.07: Control costs as a data input requiring clarification: The Benefit-Risk Decision-Maker (BRDM) criterion considers the cost of exposure mitigation (control costs). Although discussions with the EPA representatives indicated that the TRDM model was in some ways better aligned with regulatory practice, the committee recommends further details on exposure mitigation costs. If warranted, some sensitivity analyses for BRDM on this basis would be helpful (*e.g*. do NAAQS control estimates provide any additional basis). The committee also suggests that control costs are not necessarily smooth, but may be stepwise, as a practical control measure may require a discrete regulatory change.

- As a related comment, several graphs considered exposure control in terms of percent exposure reduction. The committee requests clarity that 0% reduction indeed implies "status quo," i.e. no change in current regulation or practice, until such time as actionable data have been gathered for a data-poor chemical. It was only after repeated conversations with the EPA representatives that it emerged (or so the committee recalls) that the expected total social cost (ETSC) savings associated with ETAP were in fact in comparison to a blanket change in all exposures (of 78%). Some simple introductory material explaining these facts would be extremely helpful. At the same time, the committee recognizes that a blanket reduction may be unachievable as a regulatory action, although it would by our understanding result in an enormous cost savings in ETSC.

Recommendation 2.08: Clarification surrounding BMD/BMDL ratio implications and recommended updates over time: Sources of uncertainty were captured through previous transcriptomic-based BMD/BMDL ratios and animal bioassay-based BMD/BMDL ratios. Narrative surrounding why this ratio captures uncertainty is recommended within the VOI report. For example, it is recommended to describe what the BMD/BMDL measures capture, and the general interpretation that as measures become more certain, BMD/BMDL ratios become smaller. This additional narrative is important, as differences between the ETAP vs THHA BMD/BMDL ratios influence the final VOI values. We also recommend updating the BMD/BMDL ratio as ETAP case studies build, since over time, better estimates of uncertainty inherent within transcriptomics-based assessments may lead to more comparable measures of uncertainty between the two study designs. The mean THHA BMD/BMDL ratio of 1.8 is lower than the mean ETAP BMD/BMDL ratio of 3.47, and the number of chemical evaluations that went into informing each of these may have influenced this difference (n=12 in ETPA and n=600 in THHA).

Recommendation 2.09: Clarification surrounding animal-human TK/TD descriptions: In section 5.1.2 the discussion of the sources of uncertainty in the extrapolation of the two-year bioassay to humans needs further clarification. Specifically, the uncertainty in differences of TK/TD between rodents and humans (3.000 - remarkable precision!) taken from the WHO 2017 report needs to be further explained. The fact that this value is empirically derived and not from the decomposition of the commonly used UF_H uncertainty factor should be emphasized. It is recommended that the US EPA place their approach in the context of the 2011 guidance, particularly surrounding allometric scaling in acute vs. chronic toxicity testing.

Recommendation 2.10: Exposure parameterization and partitioning clarification: When considering the exposure estimates outputted from SHEDS-HT, the EPA partitioned the estimates into tertiles (low/medium/high) based upon μ_{exp}, and further sub-tertiles (low/medium/high) based upon σ_{exp}. Further clarification is recommended to make it very clear that these partitions were based upon equal data distributions, resulting in the same number of chemicals per bin (as opposed to other binning approaches). It is also recommended to clarify the exact source of the exposure estimates data from SHEDS-HT, where it is unlikely that analysts used data produced only from the original paper in 2014; but rather, data likely originated from more updated data dumps and/or the recent SHEDS-HT R package.

Recommendation 2.11: Overall interpretation of findings: The committee interpreted this VOI analysis to include many different input variables. The main drivers of the final VOI values, under our interpretation, were time, study cost, and, to a lesser extent, intra-study variability (though these rankings may change based upon additional requested sensitivity analyses). Other variables, such as cost of exposure mitigation action, did not as heavily influence VOI values, as these costs would be incurred at some time during the 20-year overall study period. Therefore, in reality, only a few parameters are likely to have a significant differential effect on the VOI comparison between ETAP and THHA. The current sensitivity analyses account for some of these variable input considerations, though as the committee has previously detailed, expanded sensitivity analyses surrounding time and cost would be extremely informative as they appear to be primary drivers of VOI values. Additionally, we recommend a dedicated discussion that clarifies the role of each input parameter on final VOI calculations. More specifically, a discussion should be included on what was learned by changing each input parameter, individually and in combination (when applicable), and how each influenced final VOI values, with particular emphasis on cost, time, and uncertainty. Lastly, it is important to quantitatively characterize the remaining uncertainty in the ETAP derived TRV to allow the VOI approach to be used on further data gathering for that specific chemical.

Recommendation 3.1: It is recommended to perform sensitivity analyses on different time durations of the traditional testing/assessment scheme. For example, different durations of the risk assessment process, or different study durations to obtain a chronic BMDL in vivo (1 year vs 2 year animal study; 90-day study with an additional 10X UF; etc.)

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APPENDIX A: MEETING AGENDA

Day 1: July 25, 2023

Time	Duration	Topic	Speaker
11:00-11:10 am	10 minutes	Welcome	Maureen Gwinn / Chris Frey
11:10-11:20 am	10 minutes	Introduction of the Panel	Tom Tracy
11:20-11:40 am	20 minutes	Day 1 Agenda, Introduction of VOI Team, and Charge to the Panel (Review Charge Qs)	Rusty Thomas
11:40-12:00 pm	20 minutes	Background on Underlying Toxicity Testing and Human Health Assessment Needs	Alison Harrill
12:00-1:00 pm	60 minutes	Value of Information Analyses and Overview of Published Framework	Risk Sciences International (RSI)
1:00-1:30 pm	30 minutes	Break	
1:30-2:00 pm	30 minutes	Design of the Case Study	Alison Harrill
2:00-2:45 pm	45 minutes	Parameterization of the VOI Models for the Case Study	RSI
2:45-3:00 pm	15 minutes	Break	
3:00- 3:45 pm	45 minutes	Case Study Results	RSI
3:45-4:00 pm	15 minutes	Summary and Conclusions	Alison Harrill
4:00-4:50 pm	50 minutes	Questions from Panel	Co-chair: Julia Rager
4:50-5:00 pm	10 minutes	Wrap Up	Rusty Thomas

Day 2: July 26, 2023

Time	Duration	Topic	Speaker
11:00-11:10 am	10 minutes	Welcome Back	Chris Frey
11:10-12:00 pm	50 minutes	Public Comment Period	Facilitator: Tom Tracy
12:00-12:30 pm	30 minutes	Break	
12:30-1:30 pm	60 minutes	Questions from Panel	Co-chair: George Grey
1:30-3:30 pm	120 minutes	Break up into Charge Question Groups (closed session)	Co-chair: Julia Rager
3:30-3:45 pm	15 minutes	Break	
3:45-4:45 pm	60 minutes	Report out and Charge Question Discussions	Co-chair: George Grey
4:45-5:00 pm	15 minutes	Wrap Up and Close meeting	Annette Guiseppi-Elie

APPENDIX B: MATERIALS

Material Provided in Advance of the Meeting

- Agenda
- Charge questions

Material Provided During or After the Meeting

- PowerPoint presentation slides presented during the meeting
- ORD responses to BOSC follow-up questions