EPA Response to External Peer Review of A Proof-of-Concept Case Study Integrating Publicly Available Information to Screen Candidates for Chemical Pre- Prioritization under TSCA (TSCA POC)

BACKGROUND

The U.S. Environmental Protection Agency's (EPA) Office of Research and Development (ORD) has developed an approach that synthesizes information from traditional and new approach methods (NAMs) to understand the overall degree of potential concern related to human health and the environment as well as the relative coverage of potentially relevant human health and ecological toxicity and exposure information that could inform level of effort and resources that may be needed to evaluate that specific substance. A proof-of-concept case study was performed by applying this approach to a subset of the TSCA active inventory. This document, A Proof-of-Concept Case Study Integrating Publicly Available Information to Screen Candidates for Chemical Prioritization under TSCA (herein called TSCA POC), presents a proof-of-concept approach to organizing large numbers of chemical substances for further evaluation. This document describes an approach to integrate publicly available information on the ~33,000 chemical substances on the non-confidential TSCA active inventory to efficiently select substances for expert review prior to prioritization. Such a peer review process is important in establishing the appropriateness, validity, and robustness of the design, conduct, and interpretation of findings of this case study. Further, although this approach was developed with a focus on the TSCA prioritization process, the peer review process addresses whether this approach could be adapted to other large-scale chemical prioritization processes.

The following are EPA's responses to major peer review comments received during the letter peer review held in November 2020 – January 2021. All peer review comments provided were taken into consideration in developing the final report prior to posting on the EPA website. The complete set of all peer review comments is attached as an appendix to this document.

CHARGE QUESTIONS

While considering the diverse chemistry space among chemicals in the TSCA inventory and the various statutory requirements under amended TSCA, please answer the following questions:

1. **OVERALL QUESTIONS**

Based on your knowledge and understanding of toxicology and/or exposure, chemistry, and risk assessment, please comment on the overall TSCA POC document.

- **1A. Does this document address the purpose and aims as laid out in the introduction?**
- **1B. Are the ideas presented throughout the document clear and presented in a logical manner?**
- **1C. Is the method described in this document appropriate to be scalable to the thousands of chemicals on the TSCA inventory?**
- **1D. Is this approach adaptable to other large-scale chemical prioritization efforts other than for TSCA?**

Summary of reviewer comments:

Most reviewers noted that overall, the document clearly described the purpose and aims to develop an approach to integrate publicly available information to efficiently provide screening and prioritization for

large lists of environmental chemicals in clear and logical manner, and would be adaptable to other large-scale chemical prioritization efforts beyond TSCA. Multiple reviewers also noted an appreciation for the inclusion of the discussion on what this approach is and is not intended to do, as this helped to bound scope of the document. Further, reviewers noted the importance of the novel information availability metric in this approach to help inform the amount of research available and potentially highlight data gaps. Along with these comments, reviewers also noted some areas for further clarification or improvement, including discussion of the selection of the POC238 compounds used and potential impacts on interpretation of the results, as well as recommendations on additional figures or tables to more clearly present the data and results.

EPA response:
EPA would like to thank all of the reviewers for their thoughtful and comprehensive review of the document. We appreciate the comments on the clarity of the description of the purpose and aims of this approach and have expanded this description in the executive summary of the document. We have addressed in the revised document the recommendations to include additional figures for clarity, clarify the chemical space covered by the POC238 as compared to the full TSCA active inventory, discuss the inclusion of read-across in multiple scientific domains, and clarify the adaptability of this approach depending on decision context.

Overarching topics were raised by the reviewers, and these are summarized below.

1. **POC Chemical subset selection.**
   Multiple reviewers commented on the make-up of the POC chemical subset used in the case study and noted that the subset was enriched with compounds with increased information availability as compared to the TSCA Active Inventory, and therefore may not reflect the full TSCA Active inventory.
   EPA response:
   The PICS approach was developed using a small subset of compounds from the TSCA active inventory to represent specific chemical groups (e.g., substances from the TSCA workplan) or with known biological effects to use as a reference for specific scientific domains. Once developed, this approach was carried out on the broader TSCA Active Inventory, and we have included more information in the revised document demonstrating how the POC238 compounds are representative of the TSCA active inventory. We have further included additional figures to show how compounds with less information would perform in the PICS approach.

2. **Incorporation of QSAR and read-across approaches.**
   Multiple reviewers commented on the idea of increasing the use of mechanisms to compare related chemicals, through the application of analogue and category approaches and their associated read-across.
   EPA response:
   EPA appreciates the comments on including the use of both read-across and QSAR throughout the PICS approach. We have incorporated read-across and QSARs in the PICS approach when possible based on the maturity of the research. Additionally, we considered adding a QSAR estimation of *in vivo* PODs as a fourth level in the hazard estimation process (in vivo>IVIVE>QSAR>TTC), but at the time of development, we did not have a published QSAR model.

3. **Scientific domain selection.**

Reviewers commented on some of the scientific domains selected for the case study. Specifically, reviewers were mixed on the decision to separate cancer and genotoxicity domains. One reviewer specifically noted that having separate domains for these two was appropriate for weighting this endpoint, while another reviewer questioned the increased weight on these two endpoints but not including additional endpoints for reproductive or developmental toxicity.

EPA response:

The decision to have separate carcinogenicity and genotoxicity domains was to be inclusive of both genotoxic and nongenotoxic carcinogens in this approach, as well as to capture any potential genotoxic environmental chemicals that may not have been assessed for cancer. In terms of additional domains for other endpoints, like reproductive or developmental toxicity, these were not included in the PICS approach case study as separate domains but incorporated into the human health domain and in calculating in information availability domain value. Depending on decision context, these could be developed into a separate domain if desired.

4. **Mixtures and specific chemical classes.**

Multiple reviewers commented on issues of applying this approach to mixtures, as well as comments highlighting specific classes of chemicals that may need to be handled differently by this approach.

EPA response:

We appreciate the comments and recommendations and agree that prioritization of mixtures would be a good addition to this approach. However, the analysis of this approach for mixtures is a longer-term effort beyond the scope of this effort. Further, the comments related to the need to address specific classes of chemicals (e.g., metals) in a different manner are appreciated. A proposal to consider grouping some chemicals by class as a complementary approach to the PICS approach was presented, and while of possible interest it is beyond the scope of this case study. We have included a discussion in the revised document for overall longer-term efforts, which includes the future need to address mixtures and specific chemical classes. We would note that we have included IG (information gathering) flags for specific chemical categories (e.g., volatiles) and could include additional flags for some chemical classes as needed.

5. **Additional data sources.**

Multiple reviewers recommended additional data types and sources for use in the PICS approach.

EPA response:

We thank the reviewers for sharing potential new data types and sources that we can use for expanding the dataset used in this approach. Given the time and resources needed to evaluate these additional sources, they will not be added to this pilot case study but will be proposed to be added to future use of this approach as appropriate.

6. **Addition of other susceptible populations.**

Multiple reviewers recommended expanding the susceptible population domain beyond children's exposure.

EPA response:

For the purpose of this pilot case study, we focused the susceptible exposure domain only on children's exposure as this was a more mature research effort. However, if data sources are

available, they could be incorporated to include additional populations (e.g., workers, elderly) as appropriate for future applications.

7. **Quality control.**
   One reviewer commented that since we did not review the quality of the data, EPA should reconsider using the term 'quality control' to describe the actions we undertook.

   EPA response:
   EPA has applied the term 'quality control' in this document in reference to quality of the transfer of data from the data sources to the automated system. For the purposes of this work, reviewing accuracy of data from secondary sources and available primary sources is considered quality control. EPA noted that the study quality issues were not considered for reasons of time, cost, and scope (i.e., a prioritization tool rather than a regulatory decision). The level of data quality control described by the reviewer is more in line with the expert-driven process that would follow this screening approach.

2. SCIENTIFIC DOMAINS

Based on your knowledge of toxicology, chemistry, risk assessment, and/or exposure science, please comment on the evaluation, workflow, and metrics developed for the individual scientific domains in the TSCA POC.

2A. Were the decisions in each of the domain-specific evaluations logical and based on sound science?

2B. Do you see any significant issues with any of the tiered workflows and metrics developed for these scientific domains? If so, please identify and explain those issues.

<u>For each of the scientific domains</u>, there is a discussion of limitations and longer-term options. Based on your knowledge of toxicology, chemistry, and/or exposure science:

2C. Are the appropriate limitations and long-term options included for each domain?

2D. Are there additional long-term options that could be included?

Summary of reviewer comments:
Overall, the reviewers stated that the format for each of the scientific domains was clear and appreciated the sections on limitations and longer-term research ideas for each domain. No significant issues were described for the workflows and metrics, although limitations were acknowledged and the consideration of a percentile-based metric was raised.

EPA response:
EPA appreciates the thorough review of the scientific domains, and the acknowledgement from multiple reviewers as to their expertise and how that guided their comments. EPA has revised the document to address needed clarifications, with the specifics for each domain highlighted below. EPA would like to note two main points in our development and revisions to this document: First, this document was specifically designed to support TSCA decision-making process, so many aspects of the approach (e.g., specific domains, data types) are specific to that context. This approach was specifically designed to be flexible to adapt to other decision contexts, so EPA appreciates the recommendations from reviewers that can strengthen this approach for future regulatory application. Second, this document reflects a proof-of-concept case study as a starting point for this approach, and many of the longer-term research

proposed in the document and by the reviewers may be excellent additions to a future research effort. Finally, the use of a percentile-based metric was discussed in the development of the approach, but the use of absolute values was selected as they have accepted meaning in the context of risk assessments. The use of percentiles (particularly quartiles) would group compounds with potentially artificial cutoff points, unrelated to the risk assessment questions being addressed. This approach would arbitrarily force (with quartiles for instance) 25% of compounds to have the highest value and 25% to have the lowest value for each domain, when an objective survey of the data would not yield anything like this distribution. We will take this into consideration for future research.

Specific comments/responses by domain:

Human Hazard-to-Exposure Ratio (HER)

Summary of reviewer comments:

Reviewers shared insightful comments which reflected many of the discussions held in the development of the PICS approach. Comments related to including additional routes of exposure (dermal, inhalation), biomonitoring data sources beyond NHANES, and addition of LD50 extrapolation to expand available data on compounds in the inventory. One reviewer also noted that the use of Threshold of Toxicological Concern (TTC) values could be enhanced through the use of recent updates in the field. Finally, one reviewer commented on whether this domain should be given more weight due to its relative importance as the only domain that is risk-based.

EPA response:

EPA appreciates the input from all of the reviewers on the HER domain. In terms of including additional routes of exposure and biomonitoring data sources for this domain, EPA has proposed these as longer-term additions to the approach when the data is available. We considered employing acute-to-chronic extrapolation for filling data gaps, but this was not used here based on the rubric specific to this decision context provided by our regulatory partners. Additionally, we considered adding a QSAR estimation of *in vivo* PODs as a fourth level in the hazard estimation process (in vivo>IVIVE>QSAR>TTC), but at the time of development, we did not have a published QSAR model. Finally, we are reviewing the latest TTC. These issues are included in the expanded section on further refinements of the PICS approach. Similarly, recent updates in the use of TTC in the FDA's extended decision tree could be incorporated when this new decision approach is publicly available and adaptable to an automated approach. We agree that as the only risk-based domain in the PICS approach that this domain may be considered as one of the more key areas of focus for decision-makers using this approach. For this decision context, we are not weighting any domain more than any other. However, given the flexibility of this approach it could be adapted to give additional weight to any domain as appropriate for the decision context.

Ecological Hazard Domain

Summary of reviewer comments:

Multiple reviewers commented that the results from the ecotoxicology domain could be impacted by the inclusion of exposure in the analysis. Further, reviewers acknowledged that this domain is consistent with the Globally Harmonized System (GHS) approach by including aquatic ecotoxicity endpoints, but recommended consideration of inclusion of terrestrial organisms as longer-term options. Reviewers also proposed some other long-term options related to assessment of specific pathways (e.g., estrogenic) based on multiple data streams and predictive data streams.

EPA response:

EPA thanks the reviewers for their comments and suggestions. We agree with many of the points on potential long-term additions to this domain and have included a discussion of possible future research that could be developed and would strengthen this domain if implemented. Given the adaptable nature of the PICS approach, additional pathways could be added when available and if appropriate for specific decision contexts.

Persistence/Bioaccumulation Domain
Summary of reviewer comments:
Reviewers noted that EPA could include analysis of partitioning of ionizable compounds, biomagnification and other factors that could impact persistence. One reviewer also noted that EPA could consider the magnitude of use (e.g., pseudo-persistence) and remediation of substances.

EPA response:
EPA appreciates the reviewers' comments on considerations to strengthen this domain. EPA has revised the document to further discuss the partitioning of ionizable compounds for clarification. We did not include further information on remediation of compounds and the impact on persistence as that is beyond the scope of this approach, but something that would be considered as part of a larger expert-driven review of the specific compounds.

Carcinogenicity
Summary of reviewer comments:
Reviewers were mixed on whether or not the cancer and genotoxicity domains should be split, with two reviewers expressing different views on whether or not this led to an appropriate weighting of these endpoints. There was also a comment on requesting further clarification on the determinations made for carcinogenicity. One reviewer noted that the carcinogenicity workflow triggered some thinking about the use of predictive tools for cancer endpoints, with a final conclusion that this would be better used in a weight-of-evidence approach. Finally, reviewers also recommended additional data sources for the cancer domain.

EPA response:
EPA determined that splitting the cancer and genotoxicity into separate domains was appropriate for this decision context in order to be sure to capture nongenotoxic carcinogens, as well as noncarcinogenic genotoxic endpoints. Inclusion of additional data sources is addressed above. In terms of the use of predictive tools for carcinogenicity determinations, EPA agrees with the reviewers that Oncologic would be best utilized in a weight of evidence approach but can also be used for hazard characterization, which is how it is currently applied in the TSCA decision context. We have included further discussion of this clarification in the document. EPA thanks the reviewers for the list of additional profilers or databases, some of which were used in the current approach through the OECD Toolbox, so have been included in the list of data sources.

Genotoxicity
Summary of reviewer comments:
Reviewers were mixed on whether or not the cancer and genotoxicity domains should be split, with two reviewers expressing different views on whether or not this led to an appropriate weighting of these endpoints. Reviewers also commented on why only specific genotoxicity assays were included in the genotoxicity domain, and that the inclusion of genotoxicity data is using a different approach than other domains.

EPA response:
As noted above EPA determined that splitting the cancer and genotoxicity into separate domains was appropriate for this decision context in order to be sure to capture nongenotoxic carcinogens, as well as noncarcinogenic genotoxic endpoints. The selection of a subset of genotoxicity assays used in this approach was based on recent work by Williams et al. 2019[1] which demonstrated that this subset of assays is sufficient to identify 99% of mutagens tested. In response to the comment that this domain used a different approach for inclusion of data, for this domain EPA accepted secondary sources of data given the lack of specific details on much of the available genotoxicity data. An Information Gathering (IG) flag was included to note that this metric was not confirmed to a primary source so that the expert peer reviewers would know that an in-depth review of the primary literature would be needed.

Susceptible Populations
Summary of reviewer comments:
Multiple reviewers commented on including additional susceptible populations beyond children, including occupational, pregnant women and the elderly as well as inclusion of additional factors or behaviors. Further, reviewers noted that the inclusion of inhalation and dermal routes of exposure are relevant but may require the use of different exposure models. One reviewer also noted the potential to use reproductive toxicity points of departure for this domain. One reviewer requested clarification on how the cutoffs were determined for the values to the metric used overall.

EPA response:
EPA agrees that expanding the exposure models to incorporate other routes of exposure and populations will allow for an expanded range of HER values in the HER domain. For the purposes of this case study, the susceptible populations domain was focused on children, but the flexibility of the PICS approach would allow the incorporation of additional populations as needed. EPA has updated the report text to recommend longer-term efforts to further develop exposure models to fully use dermal and inhalation data, as well as expanding to include additional susceptible populations. Finally, the document has been revised to further clarify the cutoffs used to determine the metric used overall in this domain.

Skin Sensitization and Skin/Eye Irritation
Summary of reviewer comments:
Reviewers noted that EPA has developed a scoring system that is aligned with the Globally Harmonized System (GHS) classifications, and that alternative scoring systems would be difficult to implement. However, reviewers noted that this may miss chemicals that do not meet classification criteria. One reviewer further commented on altering the analysis for sensitization in order to align with the highest irritant metric

EPA response:
EPA appreciates the reviewers' comments on the appropriateness of the GHS classification system and have updated the document to note that EPA's Design for the Environment classification system was also incorporated. At this time, EPA did not make a change to the metric but have noted in the longer-term efforts that this may be something to be considered in the future.

3. INFORMATION AVAILABILITY

[1] Williams RV, DM DeMarini, LF Stankowski Jr, PA Escobar, E Zeiger, J Howe, R Elespuru, KP Cross. Are all bacterial strains required by OECD mutagenicity test guideline TG471 needed? Mutat Res 2019 Dec; 848:503081 doi: 10.1016/j.mrgentox.2019.503081

3A. How clearly and concisely are the descriptions of purpose and methodology of the information availability presented? Please identify areas where additional clarity is needed.

Summary of reviewer comments:
In general, the reviewers stated the information availability metric was clearly described, but clarity could be increased with the addition of a flowchart on the calculation for this metric, a limitations and long-term needs section and minor revisions on topics such as the IG flags.

EPA response:
We thank the reviewers for their recommendations to increase clarity on the information availability metric. These comments have been addressed in the revised document in the text and through the development of a flowchart.

4. RESULTS and CONCLUSIONS

4A. Are the results of the TSCA POC clearly described and presented? If no, please identify areas where clarity is needed.

4B. Do the results presented adequately support the conclusions? If so, please identify and explain those issues.

Summary of reviewer comments:
Overall, the reviewers stated that the results were clearly described and presented, but also included some suggestions to increase that clarity through graphical visualization of the results along with making the supporting data file (Appendix E) more user-friendly. One reviewer raised concerns about merging the results from the individual domains and recommended adding histograms to show the distribution across chemicals for each metric. Comments from reviewers related to the POC238 subset, mixtures and data sources are addressed under the overarching topics above.

EPA response:
EPA thanks the reviewers for the comments on how well this document presents the results and conclusions. We further appreciate the recommendations from the reviewers on how to strengthen the readability of the results and conclusions. In response to these recommendations, we have revised the document to include histograms to show the chemical distributions of the active TSCA inventory compounds for each of the metrics in Appendix F.

5. EDITORIAL OR ADDITIONAL COMMENTS

5A. Please provide any editorial or additional comments you would like to make here. These should be any comments that are not in direct response to the technical charge questions above.

Summary of reviewer comments:
Overall, the reviewers agreed that the document was clear and easy to read, while including some specific editorial comments to be addressed.

EPA response:
EPA thanks the reviewers for their attention to detail and have addressed editorial comments in the revised document. This includes updates to the text and figures to improve clarity as well as addressing technical editorial comments.