May 20, 2024

Dr. Nicole Kleinstreuer
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National Institute of Environmental Health Sciences (NIEHS)
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Re: Interagency Coordinating Committee on the Validation of Alternative Methods; Notice of Public Meeting; Request for Public Input. 89 Fed. Reg. 38906 (May 8, 2024).

Dear Dr. Klienstreuer:

The American Chemistry Council (ACC)[1] is pleased to provide public input via written comments, as well as oral public testimony (which is attached as an Appendix), at the May 2024 meeting of the Interagency Coordinating Committee on the Validation of Alternative Methods.

Please contact Jessica Ryman (jessica_ryman@americanchemistry.com) for questions or to request additional information.

Sincerely,

Jessica Ryman, PhD, DABT

[1] The American Chemistry Council (ACC) represents the leading companies engaged in the multibillion-dollar business of chemistry. ACC members apply the science of chemistry to make innovative products, technologies and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health, safety and security performance through Responsible Care®; common sense advocacy addressing major public policy issues; and health and environmental research and product testing. ACC members and chemistry companies are among the largest investors in research and development, and are advancing products, processes and technologies to address climate change, enhance air and water quality, and progress toward a more sustainable, circular economy.

1) **ACC applauds ICCVAM's adoption of a scientific confidence framework (SCF) to operationalize 'fit-for-purpose' "validation" amongst federal agencies. We are optimistic this will accelerate the adoption and evolution of New Approach Methods (NAMs). It is important to note that the regulatory scientific community will probably need training and encouragement to embrace SCFs.**

As ICCVAM is aware, traditional, round-robin "validation" of NAMs is impractical because it is so time- and resource-intensive. Additionally, technology in the NAMs space is evolving so rapidly that traditional validation cannot keep pace. The concept of 'fit-for-purpose' "validation" as an alternative to traditional "validation" emerged about a decade ago, but it was an additional several years before it was operationalized as scientific confidence frameworks (SCFs).

We note that ACC recognized the value of SCFs early on and we have previously presented our SCF to ICCVAM and in other scientific fora. The similarity of ACC's SCF with that published by van der Zalm in 2022[2] that strongly influenced ICCVAM's SCF speaks to the consensus regarding the crucial elements of an SCF.

In our experience, the regulatory scientific community will need training and encouragement to embrace SCFs. Specifically, our community has been conditioned for the last two decades to expect lists of validated studies to be available for specified regulatory uses. In scientific fora on NAMs, ACC has heard more than once that a list of NAMs should be posted somewhere so that people know which ones to use for what purpose. SCFs are a fundamental paradigm shift, as SCFs can technically be applied to any NAM for any purpose. This could mean (and probably will mean) that lists will become less important: lists may one day be "out" once SCFs are fully "in". Training on how to apply SCFs to demonstrate fit-for-purpose for a particular use will likely be necessary, not unlike the trainings that were offered to socialize the idea of Adverse Outcome Pathways. However, we think such training and socialization for SCFs could be valuable because it could help us realize the benefits of rapidly evolving science and technology in the NAMs space much sooner.

[2] van der Zalm AJ, Barroso J, Browne P, Casey W, Gordon J, Henry TR, Kleinstreuer NC, Lowit AB, Perron M, Clippinger AJ. A framework for establishing scientific confidence in new approach methodologies. Arch Toxicol. 2022 Nov;96(11):2865-2879. doi: 10.1007/s00204-022-03365-4. Epub 2022 Aug 20. PMID: 35987941; PMCID: PMC9525335.

2) **Artificial Intelligence (AI) has the potential to be 'the end of the tox as we know it'[3], and ACC is aware that federal agencies are in the early stages of exploring and implementing AI. This anticipated transition will involve the entire regulatory scientific community, and ICCVAM should provide and/or encourage meaningful opportunities for engagement for all stakeholders.**

Recently, Kleinstreuer and Hartung published a paper entitled "Artificial intelligence (AI)-it's the end of the tox as we know it (and I feel fine)" (2024).[3] This article made the case that data-rich toxicology will converge with AI to fundamentally change toxicology and chemical safety assessment. This is plausible because it is already happening, from use of AI in drug discovery and development[4] to the prediction of exposure pathways at EPA[5].

It will be critical that all facets of the regulatory scientific community be involved in the AI transition in toxicology. It a bit ironic (and appropriate) to note that the last time our field went through a change of this magnitude was back in the mid-2000s, with "Toxicology in the 21st Century" (Tox21). Tox21 pushed NAMs forward and was inclusive of everyone in the regulatory scientific community: academia, government, the regulated community and other stakeholders. This was both appropriate and necessary to ensure the Tox21 transition that, in large part, brings us here today. AI in toxicology should be the same way.

ACC is also aware of various AI-related fora in which federal agencies are participating. As stakeholders in the regulatory scientific community, ACC is very interested in opportunities to be involved in, and contribute to, this effort, and we encourage ICCVAM to identify opportunities for meaningful engagement for all stakeholders in the convergence of AI and toxicology.

[3] Kleinstreuer N, Hartung T. Artificial intelligence (AI)-it's the end of the tox as we know it (and I feel fine). Arch Toxicol. 2024 Mar;98(3):735-754. doi: 10.1007/s00204-023-03666-2. Epub 2024 Jan 20. PMID: 38244040; PMCID: PMC10861653.
[4] Inside the nascent industry of AI-designed drugs | Nature Medicine
[5] EPA Artificial Intelligence Inventory | US EPA.

3) ACC is funding NAMs research.

ACC is not merely interested in NAMs, we are also actively engaged by funding NAMs research through ACC's Long Range Research Initiative. A catalogue of all research, including currently funded and past NAMs research can be found at: **https://www.americanchemistry.com/chemistry-in-america/research/long-range-research-initiative-lri**

An example of some NAMs research that ACC is currently funding is below in Figure 1. Please note that this figure does not include *all* NAMs research ACC is funding/has funded.

Figure 1. Example of some NAMs research currently funded by ACC LRI. (Not exhaustive).

4) Value of Information (VOI) analysis should be considered as an additional consideration in the evaluation of utility of adopting NAMs for regulatory use.

Recently, EPA presented an in-depth Value of Information (VOI) analysis comparing a relatively new 5-day *in vivo* rodent exposure EPA Transcriptomic Assessment Product (ETAP) with human health risk assessments (THHA) based on health guidance values derived from traditional chronic / subchronic animal testing results[6,7,8]. This type of VOI framework and analysis can be a key component of scientific and policy considerations for adopting NAMs for regulatory and product stewardship safety evaluations.

To gain experience with the VOI analysis approach, and to extend this method to other NAMs, we recently published a pilot VOI analysis[9] comparing the threshold of toxicological concern (TTC) – a computational NAM that requires no further animal testing to use - to the ETAP and the THHA. The results show the TTC provides equivalent or greater health protection compared to toxicity reference values from the ETAP and THHA, and the "TTC ROI [return on investment] was immensely greater (5,000,000-fold on average) than the ROI for THHA and the ETAP ROI (100,000-fold on average)." For the TTC, we concluded, "these results support the use of the TTC for substances within its domain of applicability to waive requiring certain *in vivo* tests, or at a minimum, as an initial screening step before conducting either the ETAP or THHA *in vivo* studies."

We encourage ICCVAM, and the ICCVAM agencies, to consider how VOI analysis such as these could be included in decisions to incorporate specific NAMs into tiered hierarchal screening and testing frameworks, such as that described in Andersen et al., 2019[10]. In this tiered risk-based framework, the TTC would be used as an initial tier, whereas a tailored *in vivo* study such as the ETAP would be employed at a much higher tier, and such an *in vivo* study would be used only if warranted.

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[6] USEPA. (2023a). Scientific Studies Supporting Development of Transcriptomic Points of Departure for EPA Transcriptomic Assessment Products (ETAPs). https://www.epa.gov/system/files/documents/2023-06/ETAP%20Sci%20Support%20Doc_BOSC%20Report_Draft%20Final_5_31_23_508%20tagged.pdf.

[7] USEPA. (2023b). Standard Methods for Development of EPA Transciptomic Assessment Products (ETAPs). https://www.epa.gov/system/files/documents/2023-06/ETAP%20Standard%20Methods%20Doc_BOSC%20Report_Draft%20Final_5_19_23_508%20Tagged.pdf.

[8] USEPA. (2023c). Value of Information Case Study: Human Health and Economic Tradeoffs Associated with the Timeliness, Uncertainty, and Cost of the Draft EPATranscriptomic Assessment Product (ETAP). https://www.epa.gov/system/files/documents/2023-06/VOI%20Case%20Study_BOSC%20Report_Draft%20Final_6_13_23_508%20Tagged.pdf

[9]Simon at al. 2024. Commentary: Value of information case study strongly supports use of the Threshold of Toxicological Concern (TTC). Regulatory Toxicology and Pharmacology, Volume 149, 2024, 105594. https://doi.org/10.1016/j.yrtph.2024.105594.

[10] Andersen et al. 2019. Developing context appropriate toxicity testing approaches using new alternative methods (NAMs). ALTEX 532–534. https://doi.org/10.14573/altex.1906261.

APPENDIX

American Chemistry Council

May 20-21, 2024

Jessica Ryman PhD, DABT
Rick Becker, PhD, DABT

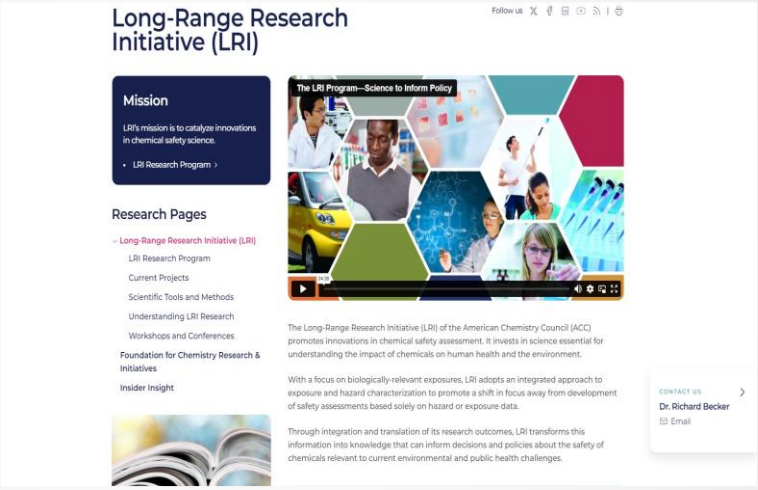
Scientific Confidence Frameworks

- ACC applauds ICCVAM's adoption of a scientific confidence framework (SCF) to operationalize 'fit-for-purpose' "validation" amongst federal agencies.
- This should accelerate the adoption and evolution of New Approach Methods (NAMs).
- It is important to note that the regulatory science community will need training and encouragement to embrace SCFs:
  - Our community is conditioned to expect lists;
  - Lists may one day be "out" as SCFs are phased "in".

AI in Tox & Chemical Safety Evaluation

- The ‘end of the tox as we know it’ (Kleinstreuer &, Hartung 2024):
  - Already happening.
- Convergence of tox and AI:
  - Lesson from Toxicology in the 21st Century: it takes the whole regulatory scientific community.
- We ask ICCVAM to identify opportunities for meaningful engagement for all stakeholders in this transition.

ACC Funds NAMs Research



https://www.americanchemistry.com/chemistry-in-america/research/long-range-research-initiative -lri

Some Examples of Current ACC LRI NAMs Research

Improve Chemical Safety Testing Technologies: Design Fit-for-Purpose Assays and Advance Data Interpretation

Project Title: Omics for Assessing Signatures for Integrated Safety (OASIS) Consortium
Consortium Manager: Chrissy Crute, Ph.D.
Research Institution: Health and Environmental Sciences Institute (HESI)

Project Title: Exploring Tissue Chips for Toxicity Testing: Testing Consortium at Texas A&M University (TEX-VAL)
Principal Investigators: Ivan Rusyn, Ph.D.,; Courtney Sakolish, Ph.D.,; Clifford Stephan Ph.D.
Research Institution: Texas A&M University

Project Title: Development of a Fit-For-Purpose In Vitro Model of Lung Toxicity
Principal Investigator: Les Recio, Ph.D.
Research Institution: ScitoVation

Project Title: Application of Toxicogenomics in Next-Generation Risk Assessment
Principal Investigator: Rasim Barutcu, Ph.D.
Research Institution: ScitoVation

VOI for NAMs Regulatory Use

- **Value of Information (VOI) analysis should be considered as an additional consideration in the evaluation of utility of adopting NAMs for regulatory use:**
  - 2023: EPA published a VOI analysis in 2023 for 5-day ETAP vs traditional human health risk assessment (THHA);
  - 2024: We publish VOI analysis for TTC, ETAP, and THHA (Simon et al.);
  - VOI can be used to inform tiered testing frameworks (e.g. TTC then ETAP then longer duration *in vivo*)