May 17, 2022

Submitted to ICCVAMquestions@niehs.nih.gov via email
Dr. Nicole Kleinstreuer, Acting Director,
NICEATM, email: *nicole.kleinstreuer@nih.gov,* telephone: (984) 287–3150.

Re: Interagency Coordinating Committee on the Validation of Alternative Methods; Notice of Public Webinar; Request for Public Input 87 Fed. Reg. 25649 (May 2, 2022).

Dear Dr. Kleinstreuer:

The American Chemistry Council (ACC)[1] appreciates the opportunity to submit comments to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). Our comments on the following pages provide suggestions for how ICCVAM could encourage greater regulatory acceptance and use of NAMs, well as input on the establishment of scientific comments in NAMs.

Please contact Jessica Ryman-Rasmussen at 202-249-6406 or jessica_ryman-rasmussen@americanchemistry.com if you have any questions.

Sincerely,

(signature redacted)

Jessica Ryman-Rasmussen, PhD, DABT
Senior Director, Chemical Management

[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.

General Comments

1. ICCVAM should consider implementing metrics and goal setting to encourage member federal regulatory agencies toward greater regulatory acceptance and use of new approach methods (NAMs).

The ICCVAM Authorization Act of 2000, Public Law 106-545, is an Act "*To establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness.*"

It has been over two decades since the Act was enacted. While numerous NAMs have been developed and continue to be developed, federal regulatory acceptance and regulatory use of NAMs remains rare. This could change if ICCAAM places greater resources and efforts on encouraging member federal regulatory agencies toward greater acceptance and use of NAMs. ICCVAM should therefore consider implementing metrics and goals for regulatory acceptance and use as well as strategies to realize these goals.

2. Due to mandates under TSCA, EPA is the ICCVAM-member federal regulatory agency that is the most poised to accelerate the regulatory acceptance and use of NAMs.

TSCA Section 4 specifies EPA must facilitate the use of "scientifically valid test methods and strategies that reduce or replace the use of vertebrate animals while providing information of equivalent or better scientific quality and relevance." In 2019, Administrator Wheeler issued a Directive that, among other things, commits to reducing requests for mammal studies by 30% by 2025 and eliminating mammal studies completely (unless approved by the Administrator) by 2035.[2] While there is no reference to this Directive in the 2021 Workplan (that ACC could find), the 2021 Workplan still moves away from animal testing[3]. As such, EPA (particularly OPPT which administers TSCA) is incentivized to reduce animal testing. The reduction requires accelerated regulatory acceptance of NAMs.

3. EPA/OPPT currently does not implement NAMs to the fullest extent possible under TSCA.

EPA/OPPT is issuing test orders under TSCA that include both human exposure studies and vertebrate animal testing. It is not transparent to stakeholders whether EPA/OPPT is applying

[2] https://www.epa.gov/sites/default/files/2019-09/documents/image2019-09-09-231249.pdf
[3] https://www.epa.gov/system/files/documents/2021-11/nams-work-plan_11_15_21_508-tagged.pdf

any tiered testing criteria, except perhaps a cursory consideration of read across, prior to ordering these studies. This contrasts sharply with EPA/OPP, which has transparent and publicly available criteria for bridging and waiving data.[4]

As already mentioned herein, TSCA Section 4(h) requires EPA to reduce and replace the use of vertebrate animals in the testing of chemical substances, to the extent practicable. This includes promoting the development and implementation of alternative test methods and strategies such as tiered testing methods. However, recent test orders issued by EPA/OPPT requested acute and chronic (reproductive) toxicity testing of several TSCA high priority substances using avian species.[5,6,7] EPA/OPP has guidance for waiving sub-acute avian dietary tests[8] based on a retrospective analysis of avian acute and dietary tests for 119 newer pesticides demonstrating avian sub-acute dietary testing typically does not contribute to risk conclusions.[9] The use of similar decision logic by EPA/OPPT could possibly reduce or eliminate unnecessary avian testing, although such an approach may require additional analysis for chemicals that are not as data-rich as pesticides.

In addition, EPA/ORD has conducted pioneering work in cross-species susceptibility to consistently predict chemical susceptibility for hundreds of species through their Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) tool.[10] SeqAPASS allows EPA regulators to extrapolate toxicity information across species when protein targets are known. For example, for some species, such as humans, mice, rats, and zebrafish, large amounts of data are available regarding their toxicological susceptibility to various chemicals. However, the toxicity data for numerous other plants and animals is very limited. SeqAPASS can potentially be used to avoid vertebrate animal testing and potentially other ecotoxicity testing so that EPA can reach better decisions faster.

4. EPA's Collaborative Research Program for New Chemicals provides an opportunity for ICCVAM to encourage greater regulatory acceptance and use of NAMs.

EPA has recently decided to create a collaborative research program to improve and modernize the methods used to review and evaluate new chemicals.[11] We recommended that EPA create opportunities for broad collaborations with scientific experts across the breadth of the regulatory

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[4] https://www.epa.gov/pesticide-registration/bridging-or-waiving-data-requirements
[5] https://www.epa.gov/system/files/documents/2022-03/9544-01_testorder-112-tca_aa_signature.pdf
[6] https://www.epa.gov/system/files/documents/2022-03/9544-01_testorder-12_dcp_aa_signature.pdf
[7] https://www.epa.gov/system/files/documents/2022-03/9544-01_testorder-tpp_aa_signature.pdf
[8] https://www.epa.gov/newsreleases/epa-takes-important-step-reduce-unnecessary-animal-testing
[9] Hilton, G.M., Odenkirchen, E., Panger, M., Waleko, G., Lowit, A. and Clippinger, A.J. 2019. Evaluation of the avian acute oral and sub-acute dietary toxicity test for pesticide registration. *Regul. Toxicol. Pharmacol.*, 105, pp.30-35.
[10] https://www.epa.gov/chemical-research/sequence-alignment-predict-across-species-susceptibility
[11] https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca/new-chemicals-collaborative

science community. This is also an opportunity for ICCVAM participation to encourage greater regulatory acceptance and use of NAMs. Contributions from academia, industry and other scientific experts have been essential to ICCVAM and should also be welcomed by EPA as part of the collective responsibility of the regulatory science community to harness the power of NAMs to improve the scientific basis and efficiency of chemical regulation.

5. A scientific confidence framework should be adopted to ensure that NAMs are 'fit-for-purpose' for specific applications and to accelerate regulatory use of NAMs.

It is well-recognized that traditional (round robin) validation approaches for NAMs are impracticable chiefly because traditional validation is too time- and resource-intensive to keep pace with technological evolution. In the wake of validation, the concept of 'fit-for-purpose' emerged. However, 'fit-for-purpose' was not formally defined or operationalized. Over the last several years, 'fit-for-purpose' has been re-framed as 'scientific confidence' that requires NAMs developers and users to produce analyses sufficient to support use in specific contexts, including regulation. Such a NAM Scientific Confidence Framework (SCF) should include at least 7 components:

1) problem formulation and the hypothesis/proposition statement describing the intended use of the NAM for a specific decision context and the hypothesis for extrapolating from the NAM results (e.g., mechanistic data) to predicted outcomes;
2) the biological relevance & plausibility of the NAM;
3) assay performance (documentation of sensitivity, specificity, reliability, and domain of applicability of the NAM assay);
4) documentation of the performance of the inference (prediction) model imbedded in the NAM (the relationship of the NAM response to the outcome response);
5) dissemination of the data, inference models, etc. to support independent replication;
6) a narrative rationale of whether there is sufficient scientific confidence in the NAM to support the specific application for the chemistry domain of interest; and
7) verification through independent scientific peer review.

To this end, ICCVAM and member agencies (to include EPA) should adopt and use a uniform, yet flexible, framework to develop, document, and communicate the scientific confidence in specific NAMs for distinct uses. Such a scientific confidence framework is needed before using them to meet requirements of TSCA that NAMs must "provide information of equivalent or better scientific quality and relevance for assessing risks of injury to health or the environment" as well as other statutes.

5. Federal Agencies should better share and curate toxicity information in order to promote the development and use of NAMs.

It is reasonable to presume that federal agencies have toxicity information from regulatory-required studies and other sources that could be pooled into databases to facilitate the development and assessment of scientific confidence for NAMs. Expansion of chemical toxicity databases in this case would likely extend the applicability domain of various NAMs. This database could also provide both test chemicals and validation chemicals, thus allowing for assessment of fit-for-purpose for particular NAMs. While there may be challenges involved in accessing and using confidential or proprietary data, approaches such as MELLODDY[12] should be explored.

[12] https://www.melloddy.eu/faqs