Humane World for Animals
Humane World Action Fund

Formerly called the Humane Society of the
United States and Humane Society Legislative Fund

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Mary S. Wolfe, PhD
Director, Office of Policy, Review, and Outreach
Division of Translational Toxicology, NIEHS
P.O. Box 12233
Research Triangle Park, NC 27709

RE: National Institute of Environmental Health Sciences; Notification of Meeting

Dear Dr. Wolfe,

On behalf of Humane World for Animals, formerly called the Humane Society of the United States, and Humane World Action Fund, formerly called Humane Society Legislative Fund, and our members and supporters, we appreciate the opportunity to provide comments in response to the July 3, 2025 Federal Register notice "National Institute of Environmental Health Sciences; Notification of Meeting" 90 FR 29572. The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) meeting agenda outlines a few main topics for discussion, which we address individually here.

Session IA: Updates

Humane World for Animals and Humane World Action Fund continue to be supportive of the efforts of the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) member agencies to advance new approach methodologies (NAMs) and communicate with stakeholders about efforts to replace traditional animal tests across federal agencies. With recent announcements from the National Institutes of Health (NIH),[1] the Food and Drug Administration (FDA),[2] and the Environmental Protection

[1] National Institutes of Health. (2025, April 29). NIH to prioritize human-based research technologies. Retrieved from: https://www.nih.gov/news-events/news-releases/nih-prioritize-human-based-research-technologies
[2] Food and Drug Administration. (2025, April 10). FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs. Retrieved from: https://www.fda.gov/news-events/press-announcements/fda-announces-plan-phase-out-animal-testing-requirement-monoclonal-antibodies-and-other-drugs

Agency (EPA)[3] to prioritize human-based research and phase out animal use, NICEATM and ICCVAM agencies, with the scientific guidance of SACATM, have an important role to play to ensure the successful implementation of these forward-thinking goals.

All ICCVAM member agencies must prioritize agency resources, including the need for dedicated staff, to make the shift to NAMs a reality. Staff must be given the time and resources necessary to invest in NAMs work occurring within their own agencies and to become active participants in ICCVAM workgroups. It will be important to ensure that staff are granted enough time to update guidance and other policy documents to communicate about both acceptance and preferred use of non-animal data and remove outdated references to animal tests that can be replaced. Additionally, reviewers will require dedicated resources for training on various non-animal methods including complex in vitro models, computational tools and artificial intelligence. As described in the March 2024 report from the ICCVAM Validation Workgroup, "education and familiarity with NAMs among all stakeholders are necessary to build sufficient confidence for NAM adoption."[4] In particular, agency staff must learn how data from these emerging technologies could be used for regulatory decision making.

In April of this year, NIH announced its plan to prioritize human-based research and create the Office of Research Innovation, Validation and Application (ORIVA). We support the prompt creation of this office so that it can fulfill its charge to coordinate "NIH-wide efforts to develop, validate and scale the use of non-animal approaches across the agency's biomedical research portfolio and serve as a hub for interagency coordination and regulatory translation for public health protection."[5] As the largest biomedical research funder in the world, NIH's commitment to moving toward non-animal science will have an enormous impact on research.

Session IB: Roadmaps and Collaboration

The April 2025 release of the *FDA Roadmap for Reducing Animal Testing in Preclinical Safety Studies* (FDA Roadmap) set out ambitious timelines for the agency to phase out animal use for drugs. "In the long-term (3-5 years), FDA will aim to make animal studies the *exception* rather than the norm for pre-clinical safety/toxicity testing."[6] The agency laid out a strategy and list of scientific and policy objectives to ensure that "a comprehensive integrated NAM toolbox

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[3] Dinan, Stephen. (2025, April 10). Zeldin to pursue new ban on animal testing at EPA. Retrieved from: https://www.washingtontimes.com/news/2025/apr/10/epa-chief-lee-zeldin-eyes-ban-animal-testing

[4] ICCVAM Validation Workgroup. (2024). Validation, Qualification, and Regulatory Acceptance on New Approach Methodologies. Retrieved from: https://ntp.niehs.nih.gov/sites/default/files/2024-03/VWG_Report_27Feb2024_FD_508.pdf

[5] National Institutes of Health. (2025). NIH To Prioritize Human-based Research Technologies. Retrieved from: https://nihrecord.nih.gov/2025/07/04/nih-prioritize-human-based-research-technologies

[6] Food and Drug Administration. (2025). FDA Roadmap for Reducing Animal Testing in Preclinical Safety Studies. Retrieved from: roadmap_to_reducing_animal_testing_in_preclinical_safety_studies.pdf

(human cell models + computational models) will be the new standard."[7] Humane World for Animals and Humane World Action Fund strongly believe that all ICCVAM agencies should create similar strategies to help drive the changes that are needed. However, as discussed in these comments, these timelines must be accompanied by dedicated agency resources, comprehensive training programs, and international harmonization efforts to be successful.

In the 2021 *EPA New Approach Methods Workplan*, the agency identified "tangible steps to pursuing and achieving a reduction in the use of vertebrate animals for toxicity testing and related research"[8] with specific goals ending in 2024. Humane World for Animals and Humane World Action Fund encourage EPA to recommit to this work and release a new work plan covering the next four to five years.

Session II: Data Standards, Validation, and Qualification

One of the clearest barriers to uptake of NAMs by regulated industries is the lack of international harmonization. While U.S. agencies are clearly prioritizing the development and acceptance of new approaches, companies are likely to continue to conduct animal studies until all international regulators have followed suit. NICEATM and ICCVAM member agencies must increase their involvement in, and leadership within, international organizations such as the Organisation for Economic Co-operation and Development (OECD), International Cooperation on Alternative Test Methods and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), whenever possible. In the FDA Roadmap, one of the policy recommendations was to work with international groups on "joint workshops or qualification projects (perhaps an international validation of a particular organ chip)."[9] It is through this type of work toward global harmonization that we will see the largest impact on reducing animal use.

The Foundation for the National Institutes of Health's (FNIH) Validation and Qualification Network has intentions to validate several NAMs over the next three to four years, and is making progress in defining readiness criteria, identifying common data elements and, importantly, has early engagement with regulators to ensure that models and data are fully fit for purpose. Humane World for Animals is proud to be part of this FNIH project and appreciates the contributions of FDA, EPA, NIH and the National Institute of Standards and Technology, and ICCVAM itself to this effort. However, to ensure global harmonization, there needs to be

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[7] Food and Drug Administration. (2025). FDA Roadmap for Reducing Animal Testing in Preclinical Safety Studies. Retrieved from: roadmap_to_reducing_animal_testing_in_preclinical_safety_studies.pdf

[8] Environmental Protection Agency. (2021). New Approach Methods Workplan. Retrieved from: https://www.epa.gov/system/files/documents/2021-11/nams-work-plan_11_15_21_508-tagged.pdf

[9] Food and Drug Administration. (2025). FDA Roadmap for Reducing Animal Testing in Preclinical Safety Studies. Retrieved from: roadmap_to_reducing_animal_testing_in_preclinical_safety_studies.pdf

greater engagement of the relevant ICCVAM members with OECD and ICH, to raise awareness of, and confidence in, the use of NAMs data for decision making. This international work should be prioritized within ICCVAM.

Session III: Computational Resources

Our organizations strongly support the use of available computational tools and encourage NICEATM and ICCVAM agencies to continue to develop and improve upon them in collaboration with all stakeholders. In particular, we are interested to see how the Collection of Alternative Methods for Regulatory Application (CAMERA) system can be incorporated into all ICCVAM agencies' plans to communicate acceptance of NAMs with regulated industries. In the FDA Roadmap, CAMERA was referenced as a helpful tool that would enable cross-agency data sharing. In addition, it mentioned that the considerable amount of data from investigational new drug submissions could be combined with NIH research data to become "a treasure trove for training AI models or doing retrospective NAM analyses."[10]

As new computational resources are developed, ICCVAM agencies will need to consider how they can be used in a regulatory context and monitor how their use can be expanded to cover a broader area of the chemical or product space. In a joint effort between Humane World for Animals, EPA and NICEATM, the Collaborative Acute Toxicity Modeling Suite (CATMoS) was shown to reliably predict EPA hazard categories III and IV of pesticide active ingredients when compared to in vivo data from rat studies and also performed well in predicting discrete LD_{50} values of >2000 mg/kg for use in wild mammal risk assessment.[11] It is now vital for EPA to clearly communicate its intent to accept data from CATMoS for pesticide ingredients by expediting development of a notice of availability. We also urge NICEATM and ICCVAM member agencies to work together to broaden the context of use for this important in silico tool.

During the 2024 SACATM meeting, Dr. Mansouri presented on the Collaborative Modeling Project for Acute Inhalation Toxicity (CoMPAIT).[12] Similar to CATMoS, CoMPAIT intends to accurately predict rat acute inhalation toxicity doses based on chemical structure to eliminate the need for live animal studies. We hope the work was successfully completed this past year

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[10] Food and Drug Administration. (2025). *FDA Roadmap to Reducing Animal Testing in Preclinical Safety Studies.* Retrieved from: roadmap_to_reducing_animal_testing_in_preclinical_safety_studies.pdf

[11] Bishop, P. L., Mansouri, K., Eckel, W. P., Lowit, M. B., Allen, D., Blankinship, A., Lowit, A. B., Harwood, D. E., Johnson, T., & Kleinstreuer, N. C. (2024). Evaluation of in silico model predictions for mammalian acute oral toxicity and regulatory application in pesticide hazard and risk assessment. Regul Toxicol Pharmacol, 149, 105614. https://doi.org/10.1016/j.yrtph.2024.105614

[12] Mansouri, K. (2024) Collaborative Modeling Project for Acute Inhalation Toxicity (CoMPAIT). SACATM Presentation. Retrieved from: https://ntp.niehs.nih.gov/sites/default/files/2024-10/4-2_Mansouri_SACATM2024_508.pdf

and that a manuscript will soon be published, with the results presented to all stakeholders. As with CATMoS, it will be essential to ensure that, as new computational models are developed, their ability to satisfy regulatory needs is demonstrated. These tools could be accepted on their own or as part of integrated testing strategies that can serve as replacements for new animal tests.

Session IV: ICCVAM Public Outreach and Education

As ICCVAM agencies transition away from animal studies, the public needs to understand that at the heart of this change is the desire to have research and testing methods that provide greater safety for humans and the environment. Therefore, ICCVAM agencies should educate the public about the shortcomings of animal tests that have never received the same level of scrutiny or formal validation that NAMs have been subjected to. SACATM members can serve an important role in helping to provide additional credibility to the work that is being done by NICEATM and ICCVAM agencies. The recent announcements align with public opinion.[13] ICCVAM agencies should adopt messaging to ensure that the public understand that this transition is about better, more human-relevant science while simultaneously preventing unnecessary animal testing.

While the ICCVAM public forum and communities of practice webinars are important ways to communicate the work NICEATM and ICCVAM agencies are doing, they are not accessible to the public at large. NICEATM and ICCVAM agencies should consider how to communicate the highlights of these events using plain language. In addition, policymakers should be a part of the discussion so that they can better understand how to support the continued advancement of the work NICEATM and ICCVAM agencies are doing in this space. Humane World for Animals and Humane World Action Fund stand ready to assist with this communication to the public at large and legislators to help ensure continued support.

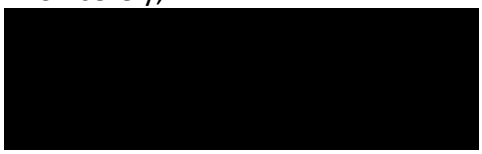
Additionally, all stakeholders should be able to obtain current information from NICEATM and ICCVAM agencies on accepted NAMs both in these forums but also on the agency websites to support the early adoption of NAMs. Discussions of ways to avoid unnecessary animal testing and incorporate NAMs into testing plans should become a regular part of agency interactions with regulated industries. In August 2024, ICCVAM launched its first ever Method Developers Forum (MDF) on carcinogenicity bringing together scientists developing alternative approaches

[13] Physician's Committee for Responsible Medicine. (2024). Physicians Committee Survey Finds Most Americans Favor Ending Animal Research. Retrieved from: https://www.pcrm.org/news/good-science-digest/physicians-committee-survey-finds-most-americans-favor-ending-animal

and how they may be used in a regulatory context.[14] We hope that ICCVAM is planning its next MDF as this was a unique way for agencies and NAMs developers to focus on a specific endpoint with an eye to the regulatory needs of the different agencies. In future MDFs additional time should be added to the schedule for discussion and collaboration. We recommend that ICCVAM member agencies organize follow-up activities where more specific uses for the individual methods can be explored. In addition, since many NAMs are not stand-alone replacements for traditional animal tests, it would be beneficial for the method developers to work together with regulators to build testing strategies that incorporate the best approaches. We look forward to future ICCVAM Method Developers Forums and encourage the agencies to take additional steps to ensure these meetings ultimately lead to regulatory acceptance of NAMs.

Humane World for Animals and Humane World Action Fund welcome the opportunity to work with NICEATM or any ICCVAM agency to replace the use of animals with scientifically sound testing strategies. Thank you for the consideration of our comments.

Sincerely,



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[14]National Toxicology Program. (2024). Method Developers Forum: New Approaches for Carcinogenicity Testing. https://ntp.niehs.nih.gov/whatwestudy/niceatm/resources-for-test-method-developers/method-developers-forums