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

October 23, 2026

Kelly Chandler, Ph.D.
Designated Federal Officer
National Institute of Environmental Health Sciences
6707 Democracy Boulevard
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RE: National Institute of Environmental Health Sciences; Notice of Meeting; Request for Public Input

Dear Dr. Chandler,

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 September 22, 2026, Federal Register notice "National Institute of Environmental Health Sciences; Notice of Meeting; Request for Public Input" 91 FR 60140. The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) meeting agenda outlines a few main topics for discussion, which we address individually here.

Session I: International Harmonization Around Validation

Humane World for Animals and Humane World Action Fund have long stressed the importance of international harmonization in order for efforts to replace animal tests with non-animal new approach methodologies (NAMs) to have the greatest impact and are pleased to see that this topic will be a focus of the 2026 SACATM meeting. While U.S. agency review and approval of new approaches is vital, it does not necessarily ensure immediate industry adoption as companies will continue to test on animals as long as government authorities require them to do so to enter international markets. Whenever possible, Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) member agencies' work to validate non-animal methods should be done in conjunction with and with support from international bodies

such as the Organisation for Economic Co-operation and Development (OECD), the International Cooperation on Alternative Test Methods (ICATM), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH). U.S. agencies should continue to actively participate in and lead these international efforts and coordinate with international scientific organizations such as the Health and Environmental Sciences Institute (HESI). It is also important to ensure that all OECD member countries are operating under the multilateral agreement of mutual acceptance of data to ensure that animal tests are not unnecessarily repeated in other countries and to build industry confidence in adopting OECD test methods that eliminate animal use.

We are looking forward to the finalization of the updates to OECD Guidance Document 34 on Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment that is anticipated in 2027. We encourage ICCVAM member agencies to incorporate this guidance into their own validation documents when appropriate and applicable to help ensure greater consistency among U.S. agencies and internationally.

We also encourage ICCVAM member agencies to adopt OECD Harmonised Template 201 (OHT 201) to support the structured reporting, sharing and reuse of mechanistic data generated by non-animal methods. Building on existing National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), Environmental Protection Agency (EPA) and international collaboration to format high-throughput screening data using OHT 201, agencies should explore opportunities to embed harmonized reporting into their data systems and regulatory workflows. Practical case studies demonstrating how mechanistic evidence can inform hazard and risk assessment would further support consistent implementation across agencies and jurisdictions, helping to ensure that harmonization facilitates not only data sharing but also meaningful integration of non-animal evidence into regulatory decision-making.

Session II: Federal Efforts Addressing Method Development Challenges

In 2018, ICCVAM finalized its *Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States*, which correctly identified some of the challenges with the validation model that was currently being used. Specifically, it called out the fact that the process was “lengthy, inefficient, and resource-intensive” and that it was not necessarily compatible with modern approaches that place “more emphasis on NAMs that incorporate batteries of assays, in silico approaches, and computational models.”¹ In 2024,

¹ ICCVAM (Interagency Coordinating Committee on the Validation of Alternative Methods). 2018. A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United

the ICCVAM Validation Workgroup published *Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies* that encouraged “implementation of flexible, fit-for-purpose validation strategies that consider the intended application” and described how NAMs could be evaluated through consideration of “concepts such as context of use, biological relevance, and technical characterization.”² While these changes are positive and reflective of the global commitment to harmonization of validation principles, challenges remain. Specifically: 1) the lack of agency resources of both time and funds dedicated to pursuing validation or qualification of new approaches and training in those methods; 2) the slow speed at which these evaluations can be completed and clearly communicated to industry; 3) the continued concern that NAMs are being held to a higher standard than the animal models that have known scientific limitations; and 4) the reticence to change that persists among some agency reviewers. ICCVAM member agencies must proactively address these continued obstacles and SACATM could be helpful in providing recommendations to do so.

While international harmonization is important for industry uptake, there is also a need for greater coordination and collaboration among U.S. agencies to advance NAMs. Humane World for Animals and Humane World Action Fund would like to bring a few opportunities to your attention.

We urge SACATM to increase its advice, consultations and recommendations to ICCVAM member agencies, the Department of Defense (DoD) and the National Institutes of Health (NIH) with respect to medical countermeasures (MCM). At the 2026 Society of Toxicology meeting, we were disappointed by the research using live animals to model sulfur mustard exposure. MCM research is important for the protection of military and civilian populations. However, exposing live animals to highly toxic agents when more human-relevant, non-animal approaches are often available underscores an important methodological transition that ICCVAM and SACATM should be pursuing. There is a growing suite of ex vivo and human-relevant models offering valid and valuable replacement strategies for live animals.

Continuing research using in vivo approaches, particularly for such harmful studies where sophisticated ex vivo and other non-animal platforms are now available, contradicts the research direction that federal agencies have increasingly prioritized, the adoption of human-relevant methods. For example, the same meeting hosted mustard agent research using human lung epithelial cells, perfused human skin equivalents, human corneal epithelial cells and

States. Available: <https://ntp.niehs.nih.gov/go/iccvam-rdmp>. <https://dx.doi.org/10.22427/NTP-ICCVAM-ROADMAP2018>

² ICCVAM Validation Workgroup. 2024. *Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies*. Available: <https://ntp.niehs.nih.gov/whatwestudy/niceatm/resources-for-test-method-developers/submissions>. <https://doi.org/10.22427/NICEATM-2>

human oral mucosal tissue models. SACATM could offer valuable feedback on this work and identify and recommend more human-relevant, non-animal approaches for MCM research.

On the other hand, we were pleased to see that the Food and Drug Administration's (FDA) Human Foods Program (HFP) will be cohosting a workshop for advancing NAMs with NIH's new Office of Research innovation, Validation, and Application (ORIVA) in spring 2027.³ This is an excellent collaboration and a strong follow-up to HFP's pilot program ENTRÉE – Engaging NAMs for Toxicant Regulation and Effects. According to the ICCVAM Authorization Act, one of ICCVAM's purposes is to “optimize utilization of scientific expertise outside the U.S. federal government.”⁴ The uniquely American Generally Recognized as Safe (GRAS) process for assessing the safety of food substances is well suited to this purpose because many companies and academics are developing NAMs for use in safety assessments of food substances. We look forward to seeing their NAMs reviewed in ENTRÉE and at the HFP-ORIVA workshop.

We would like to see SACATM have the opportunity to review NAMs work occurring within additional ICCVAM member agencies and centers such as DoD, FDA's HFP, the Department of Veterans Affairs and FDA's Center for Veterinary Medicine.

We recognize the potential value of initiatives such as the Complement Animal Research in Experimentation (Complement-ARIE) program and the Foundation for the National Institutes of Health (FNIH) Validation and Qualification Network (VQN) in bringing stakeholders together to advance the development and evaluation of non-animal methods and we are pleased to have participated in some of the steering committees related to the VQN. A key consideration is the extent to which regulatory engagement informs the definition of the context of use from the outset, so that methods are developed and evaluated against clearly defined regulatory needs and evidentiary requirements. We encourage SACATM to consider what lessons these initiatives offer in this respect, and how they can help bridge the gap between identifying promising methods, establishing fitness for purpose and achieving prompt regulatory uptake that supports the replacement of animal testing.

ICCVAM member agencies should not only focus efforts and attention on development and acceptance of new non-animal methods but also consider ways to eliminate unnecessary animal testing. To this end, agencies should prioritize efforts to conduct and complete retrospective analyses of animal test data obtained for regulatory purposes and evaluate whether those data, or what portion of those data, were actually used in agency decision-making, until such time when they can be replaced with non-animal tests. Also, where specific

³ ORIVA. (2026). Workshop: Advancing New Approach Methods (NAMs) for Chemical Risk Assessment in the Human Foods Program. Retrieved from: <https://dpcpsi.nih.gov/oriva/events/workshop-advancing-nams-chemical-risk-assessment-human-foods-program>

⁴ ICCVAM Authorization Act of 2000, Pub. L. No. 106-545, 114 Stat. 2721 (2000).

types of animal data were never or rarely used, agencies should remove the requirement or publicize acceptance of waivers as quickly as possible. In 2023, Humane World for Animals scientist, Patricia Bishop and her former EPA-scientist coauthors released the results of their analysis of EPA's use of the 90-day dog study currently required under the Federal Insecticide, Fungicide, and Rodenticide Act regulations for new pesticide registrations. They found that in most cases the dog study did not add value to the risk assessment beyond what was already obtained from other studies.⁵ EPA's Office of Pesticide Programs must now work quickly to complete their follow-up retrospective analysis of the dog study and publish waiver guidance that allows pesticide companies to forgo this unnecessary test.

Session III: IATA Case Studies

Humane World for Animals and Humane World Action Fund appreciate work being done to proactively share case studies demonstrating the way that NAMs can and should be used in Integrated Approaches to Testing and Assessment (IATA). These frameworks will be particularly important for addressing more complex and systemic endpoints, where a single test may not be sufficient to address regulatory needs. However, while case studies are important for demonstrating the steps taken to make a regulatory decision under a particular set of circumstances, more needs to be done to move toward defined approaches and IATAs that can be used consistently in regulatory decision making. NICEATM and EPA have collaborated on developing several defined approaches including for skin sensitization, eye irritation and endocrine disruption.⁶

We encourage consideration of how federal initiatives to advance NAMs can be better connected to accelerate their regulatory implementation and replacement of animal testing. For example, the outcomes and lessons from FDA's Center for Drug Evaluation and Research's NAMs Integrated Review Team pilot could be shared with ICCVAM to inform cross-agency learning. More broadly, it would be useful to understand how the effectiveness of these coordination initiatives will be evaluated and how successful approaches will be translated into wider practice across ICCVAM member agencies.

We also encourage greater coordination across related federal and international teams to identify opportunities to build on existing work, share findings and avoid duplication, particularly across systemic toxicity, developmental neurotoxicity and respiratory endpoints. Where projects address complementary scientific or regulatory questions, sharing data, methods, reference chemicals and lessons from case studies could help avoid duplication, identify gaps and accelerate the development of integrated approaches that support regulatory

⁵ Bishop, P.L, V.L Dellarco, and D.C. Wolf. 2023. Is the 90-day dog study necessary for pesticide toxicity testing? *Critical Reviews in Toxicology* 53(4): 207-228. <https://doi.org/10.1080/10408444.2023.2221987>

⁶ National Toxicology Program. (2026). Integrated Approaches to Testing and Assessment. Retrieved from: <https://ntp.niehs.nih.gov/whatwestudy/niceatm/comptox/ct-its/its>

decisions using non-animal evidence. We were pleased to see the ICCVAM Communities of Practice webinar earlier this month that focused on how NAMs could be “incorporated into regulatory decision-making through defined approaches, weight-of-evidence frameworks, and integrated approaches to testing and assessment.”⁷ We would welcome additional consideration of how this coordination can be strengthened across ICCVAM member agencies, with progress assessed in terms of regulatory applicability and the extent to which animal testing can be replaced.

Session IV: Computational Tools and Databases

Computational tools include fast-advancing methods that increase efficiency in toxicity testing and can create opportunities to share data between U.S. agencies and internationally. Humane World for Animals and Humane World Action Fund appreciate learning about the ways that these resources are developing and advancing during SACATM and other meetings, but without clear guidance about how they can be used in a regulatory context, their full potential may not be realized. These computational tools should be incorporated into IATAs and defined approaches when applicable. It is also important that once these computational tools have been evaluated and found to be suitable replacements for an animal test, that agencies move quickly to communicate acceptance to regulated industries.

For example, the Collaborative Acute Toxicity Modeling Suite (CATMoS), has been shown via a collaborative effort between Humane World for Animals, EPA and NICETAM 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 LD₅₀ values of >2000 mg/kg for use in wild mammal risk assessment.⁸ As CATMoS has been proven reliable for predicting pesticide toxicity, it is now vital for EPA to clearly communicate its intent to accept data from this model for pesticide active 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 valuable in silico tool. Research has shown that in combination with expert judgment, CATMoS can reliably predict acute oral toxicity of many industrial chemicals as well.⁹

⁷ National Toxicology Program. (2026, October 7). ICCVAM Communities of Practice Webinar 2026: Integration of NAMs Data into Regulatory Decision-making. Retrieved from: <https://ntp.niehs.nih.gov/whatwestudy/niceatm/3rs-meetings/commprac-2026>

⁸ 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>

⁹ Weyrich et al. 2025. Can acute oral in vivo toxicity testing for EU REACH be fully replaced by a QSAR method? Evaluation of the CATMoS model using chemical industry data. *Reg Toxicol Pharm* 2025 Nov:162:105861. doi: 10.1016/j.yrtph.2025.105861.

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

Sincerely,



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