



**THE HUMANE SOCIETY
OF THE UNITED STATES**



HUMANE SOCIETY
LEGISLATIVE FUND™

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Dr. Elizabeth Maull
Designated Federal Official for SACATM
Office of Liaison, Policy and Review
Division of NTP, NIEHS
P.O. Box 12233, K2-17
Research Triangle Park, NC 27709

RE: Scientific Advisory Committee on Alternative Toxicological Methods; Announcement of Meeting; Request for Comments

Dear Dr. Maull,

On behalf of the Humane Society of the United States (HSUS), Humane Society Legislative Fund (HSLF), and our members and supporters, we appreciate the opportunity to provide comments in response to the August 13, 2019 notice “Scientific Advisory Committee on Alternative Toxicological Methods; Announcement of Meeting; Request for Comments” 84 Fed. Reg. 40072. The meeting agenda outlines topic areas for public comments, which we address here.

US Strategic Roadmap: New Approaches to Validation

HSUS and HSLF commend the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) on its continued implementation of plans outlined in the January 2018 publication, *A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States*. The “Roadmap” has served as an important catalyst for federal agencies to adopt more human-relevant, predictive, and economical approaches to chemical safety evaluation, while also reducing animal use.

HSUS and HSLF are pleased that the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) continues to demonstrate leadership in providing stakeholders with information about new approach methodologies (NAMs). We encourage NICEATM and ICCVAM member agencies to continue to grant opportunities to regulators, industry, and other stakeholders to share news and discuss innovative approaches in risk assessment and safety testing.

NICEATM has made great strides in implementing the Roadmap and ensuring that validation becomes a proactive and collaborative effort rather than a linear event. HSUS and HSLF urge ICCVAM and NICEATM to continue to focus on a few overarching needs within NAMs development and acceptance:

1. **Increase agency engagement and communication on NAMs:** The federal agencies that comprise ICCVAM have an important role to play in realizing the goals of the Roadmap. The May 23, 2019 ICCVAM public forum highlighted the work agencies are doing to reduce animal testing and encourage the development and acceptance of NAMs. It is vital that they also inform their respective regulated industries about these efforts to ensure uptake and acceptance. For example, during the public forum, the Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition (CFSAN) presented about a recent analysis of the use of dog studies to conduct safety assessments of food and color additives and found that there were no unique toxicities that were seen only in the dog and concluded that rodent studies combined with ADME data could be sufficient to evaluate the safe use of food and color additives.¹ HSUS and HSLF are pleased that the agency took the initiative to conduct such an analysis, and we now look forward to CFSAN taking concrete steps to share the results and proactively communicate the conclusions to the regulated community so no unnecessary dog testing is performed for such products.

In addition, communication efforts regarding NAMs should be directed toward the public to promote acceptance of these approaches and maintain confidence that human and environmental safety is not being compromised with their use. In his September 20, 2019 memorandum, Environmental Protection Agency (EPA) Administrator Andrew Wheeler put forth a public commitment by EPA to “reduce its requests for, and [its] funding of, mammal studies by 30 percent by 2025 and eliminate all mammal study requests and funding by 2035.”² Other agencies should be encouraged to release similar forward-thinking plans to reduce animal use and reliance.

2. **Ensure international harmonization:** HSUS and HSLF are excited about the progress agencies in the United States are making in NAMs acceptance, but in order to make a true impact on industry uptake and thus animal lives, global acceptance and harmonization of testing methods and requirements will ultimately be needed. We

¹ Fitzpatrick, Suzanne. (2019). FDA activities: ICCVAM public meeting [PowerPoint slides]. Retrieved from: https://ntp.niehs.nih.gov/iccvam/meetings/iccvam-forum-2019/05-fitzpatrick-fda_update_508.pdf

² Wheeler, Andrew. (2019, September 10). Directive to Prioritize Efforts to Reduce Animal Testing [Memorandum]. Washington, DC: Environmental Protection Agency. Retrieved from: <https://www.epa.gov/sites/production/files/2019-09/documents/image2019-09-09-231249.pdf>

strongly encourage ICCVAM and its federal member agencies to increase involvement with the International Cooperation on Alternative Test Methods (ICATM), which was instrumental in fostering global acceptance of non-animal skin sensitization testing methods. Moreover, ICCVAM agencies should become active participants in Organisation for Economic Cooperation and Development (OECD) working and expert groups to accelerate international acceptance of NAMs. This summer, OECD issued new and updated test guidelines that forgo the use of animals for eye irritation, skin sensitization, and skin irritation/corrosion categorization.³ NAMs implementation would benefit from the committed participation of all ICCVAM members in these international efforts.

3. **Invest in NAMs development:** In order to speed the expansion of NAMs, significant time and money will need to be invested in their development by both industry and government. As the Roadmap points out, one way to facilitate funding of NAMs is to modify grant review criteria. An Additional Review Criterion that specifically considers the development and use of NAMs would be appropriate and timely and would help to promote consideration of these methods by the grant reviewers. As ICCVAM is housed within the National Institutes of Health (NIH), it could also encourage the issuance of specific grant opportunities for development of NAMs as it does through National Institute of Environmental Health Sciences (NIEHS) Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs. For example, a 2018 Funding Opportunity Announcement from NIEHS requested proposals for Novel Approaches for Characterizing Exposure and Response to Engineered Nanomaterials.⁴ NICEATM should not only encourage this sort of targeted funding to address specific agency data needs, but also encourage a corresponding shift toward NAMs reflected in NIH disease-related funding.

New Approach Methodologies: Computational Tools

HSUS and HSLF strongly support the development, use and regulatory acceptance of computational tools in risk assessment. As these tools are created, collaborative development will be important to ensure that the data produced will be accepted by regulators and incorporated into industry chemical assessment processes. An excellent example of success is the approach used by NICEATM to address acute systemic toxicity, where curated sets of rat oral acute toxicity data were made available to modelers to develop and evaluate predictive

³ Organisation for Economic Cooperation and Development. (2019). OECD Test Guidelines for the Chemicals. Retrieved from: <http://www.oecd.org/env/ehs/testing/oecdguidelinesforthetestingofchemicals.htm>

⁴ National Institutes of Health. (2018). Funding Opportunity Announcement: Novel Approaches for Characterizing Exposure and Response to Engineered Nanomaterials. Retrieved from: <https://grants.nih.gov/grants/guide/rfa-files/rfa-es-18-008.html>

models for this endpoint, culminating in the now publicly available Collaborative Acute Toxicity Modeling Suite (CATMoS).⁵ The intentional process that NICEATM used to facilitate exchange of knowledge and information needs among federal agencies, industry, academia, and other stakeholders allowed for the successful development of computational tools in which all stakeholders can have confidence. While each agency will likely conduct its own evaluation of CATMoS before fully accepting model acute toxicity predictions in lieu of animal tests for new chemical substances, we believe this kind of early exchange is critical for faster adoption and hope this will be a model for future endeavors to develop and implement computational tools in a regulatory context.

HSUS and HSLF also encourage an increased focus on exposure when developing NAMs for risk assessment. Since even the most toxic chemicals do not present a public health concern without exposure, the use of high-throughput exposure prediction models that can rapidly and accurately estimate exposure potential for thousands of chemicals is an important part of prioritizing chemical safety evaluations. Consideration of exposure contributes to reduction of animal use, as only priority chemicals, those with higher likelihoods of both toxicity and exposure, may require further hazard testing. The Environmental Protection Agency's ExpoCast can evaluate exposure to chemicals that are released into the environment as well as those used in consumer products.⁶ All agencies should be incorporating exposure considerations into their product safety assessments to help determine potential routes of exposure and make real-world risk assessments. However, a serious impediment to reduction of animal use through incorporation of exposure will be the continued focus of other countries on chemical hazard without regard for exposure. The U.S. should work through available international forums whenever possible to demonstrate its leadership in this area and encourage harmonization, without which significant impacts on animal use reduction will be difficult.

New Approach Methodologies: Translational Impact and Human Relevance of Microphysiological Systems

The Human Microphysiological Systems: Organs-on-Chips for Drug Safety and Efficacy Testing Program initiated between the National Center for Advancing Translational Sciences (NCATS), the Defense Advanced Research Projects Agency (DARPA), and the Food and Drug Administration (FDA), has been a resounding success in the rapid development and commercialization of several organ-on-a-chip systems that are currently in different phases of implementation. The use of dynamic, physiologically accurate microphysiological systems is proving revolutionary for drug discovery- and for disease modeling. The NIH have confirmed their commitment to the development of organs-on-chips with over 72 million dollars devoted

⁵ National Toxicology Program. (2019). Predictive Models for Acute Oral Systemic Toxicity. Retrieved from: <https://ntp.niehs.nih.gov/pubhealth/evalatm/test-method-evaluations/acute-systemic-tox/models/index.html>

⁶ Environmental Protection Agency. (n.d.). Rapid Chemical Exposure and Dose Research. Retrieved from: <https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research>

to the advancement of these human-based systems.⁷ Organ-on-a-chip models of every human organ either exist already or are under development, with many at very advanced stages, including platforms that mimic the complexity of human immune responses.^{8,9,10} With 90% of drugs failing to make it to market¹¹ due to either adverse events not predicted in animal models or lack of efficacy, the development and regulatory acceptance of human-relevant chip technology will be revolutionary in the drug discovery process and will ultimately lead to a notable decrease in unnecessary animal testing. In addition, advances in chip technology will enable drugs to come to market more quickly and at less cost than the current drug discovery process.

ICCVAM should help facilitate the continued development and regulatory acceptance of chip technology to reduce and eventually replace animal testing in the drug discovery process. In addition, we recognize efforts of ICCVAM agencies in the use of chip technology employing animal cells to assess the predictive capacity of these systems for chemical safety assessment and urge that this work continues. Demonstrating the utility of chips in cross species comparison of toxicity profiles allows vital confidence building in these new technologies and is necessary for the phase-out of animal use, and ICCVAM is ideally situated to facilitate this process.

HSUS and HSLF welcome an opportunity to assist ICCVAM agencies in further dissemination and uptake of NAMs in the United States, whether in the form of webinars, agency trainings, outreach to international partners, or in organizing further workshops.

Sincerely,



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⁷ National Center for Advancing Translational Sciences. (2018). Tissue Chips for Disease Modeling and Efficacy Testing. Retrieved from: <https://ncats.nih.gov/tissuechip/projects/modeling>

⁸ Oleaga, C., et al. (2018). Investigation of the effect of hepatic metabolism on off-target cardiotoxicity in a multi-organ human-on-a-chip system. *Biomaterials* 182: 176-190.

⁹ Edington et al. (2018). Interconnected Microphysiological Systems for Quantitative Biology and Pharmacology Studies. *Sci Rep.* 2018 Mar 14;8(1):4530. doi: 10.1038/s41598-018-22749-0.

¹⁰ Sharifi, F., et al. (2019). A Foreign Body Response-on-a-Chip Platform. *Adv Healthc Mater*: e1801425. doi: 10.1002/adhm.20180142.

¹¹ Lee, Bo Yeon. (2019). The NIH Microphysiological Systems Program: Tissue-on-chips for Safety and Efficacy Studies in Drug Development [PowerPoint slides]. Retrieved from: https://ntp.niehs.nih.gov/iccvam/meetings/iccvam-forum-2019/06-lee-ncats_508.pdf