THE HUMANE SOCIETY
OF THE UNITED STATES

August 29, 2018

Mary Wolfe
Designated Federal Official for the SACATM
Office of Liaison, Policy and Review Division of NTP
NIEHS, P.O. Box 12233, K2–03,
Research Triangle Park, NC 27709

Dear Dr. Wolfe:

In response to the August 7, 2018 Federal Register Notice by the National Institutes of Health (NIH), "Scientific Advisory Committee on Alternative Toxicological Methods; Announcement of Meeting; Request for Comments, the following is submitted on behalf of the Humane Society of the United States, its members and supporters, who share the common goal of promoting the use of reliable and relevant regulatory chemical testing methods and strategies that protect human health and the environment while reducing, and ultimately eliminating, the use of animal testing to assess chemical toxicity." The meeting agenda outlines topic areas for public comments, which we address here.

Overview of US Strategic Roadmap and Goal: Connect End users with the Developers of New Approach Methodologies (NAMs)

We are encouraged by the publication in January 2018 of the Interagency Coordinating Committee for the Validation of Alternative Method's (ICCVAM's) Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States. We are also pleased by the National Toxicology Project (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods' (NICEATM's) recent activities, including those to reduce the use of animals in acute toxicity testing and vaccine testing. Overall, ICCVAM's strategic plan outlines a way forward that is likely to produce effective results to reduce animal use in toxicity testing in a timely fashion. Our comments are intended to generally support and facilitate ICCVAM's outlined plans.

<u>Identify anticipated testing requirements</u>

As the strategic roadmap explains, in order to encourage widespread uptake of NAMs, it is essential that end users have input early in the discussion. Allowing end users to participate in the development of new technologies ensures that the technologies are designed to fit the desired purpose. In addition, early engagement and participation will provide a stake for end users in the final application and use of the new method. End users include both the regulated community and agency

staff reviewing submissions. Soliciting input can be accomplished through a variety of approaches including surveys, information exchange sessions between regulators and industry, establishment of stakeholder workgroups, webinars, and workshops. An excellent model for success is the approach used recently by NICEATM in addressing acute systemic toxicity, where the groundwork was laid by a workshop co-sponsored by the National Institute for Environmental and Health Services (NIEHS) and stakeholders, with recommendations from the workshop followed up by stakeholder groups, and a series of publications (e.g., Hamm et al. 2017[1]; Strickland et al. 2018[2]). NICEATM then progressed by creating a challenge for development of an *in silico* approach to predict acute systemic toxicity. Agencies that could potentially use the model were surveyed on their needs and uses of acute data, a list of desired model outputs was developed (e.g., point estimates, categories, etc.), and curated datasets were provided as both training and validation data subsets. This approach ensured that submitted models would meet the needs of agencies anticipated to use them. A similar approach could be used to encourage development of NAMs targeted toward other specific regulatory needs.

Industry often uses their own NAMs to predict toxicity early in the development of new chemicals. With further development and validation, some of these NAMs may have the potential to meet the needs of agencies. Therefore, regulatory agencies could host information exchange sessions with their regulated communities to share ideas and afford industry the opportunity to discuss technologies they have developed or are developing to gauge regulators' openness to acceptance of these approaches, once adequate performance has been demonstrated.

Encourage establishment of grant review criteria tailored to development of alternative methods

The vast majority of grant funding from federal sources like NIH goes to animal-based research. As the strategic plan mentions, ensuring a meaningful portion of these funds is devoted to promoting non-animal testing approaches could significantly speed the development and uptake of these methods. Although NICEATM is limited in the recommendations it can make to other NIH institutes, we are encouraged by the example NIEHS is setting by issuing specific granting opportunities for the development of NAMs, such as the Novel Assays for Screening the Effects of Chemical Toxicants on Cell Differentiation (SBIR R44)[3] and NIEHS SBIR Phase IIB Awards for Validation and Commercialization of Approaches to Reduce Animal Use in Toxicology Testing (U44)[4]. It may also be possible that NIEHS could stimulate cross-institute activities – for example, several NIH institutes have programs that focus on human-relevant, biological pathway or systems biology approaches, such as the National Cancer Institute's Cancer Systems Biology Consortium or the National Institutes of Mental Health, which is moving research focus away from disease categories toward basic research on biological pathways of mental illness. NICEATM could organize workshops that identify scientific/knowledge gaps and facilitate the development of tools to address cross-cutting needs for these types of activities. In addition, agencies could allocate funding to identified priority areas, which ICCVAM could facilitate.

[1] Hamm et al. 2017. Alternative approaches for identifying acute systemic toxicity: Moving from research to regulatory testing. Tox In Vitro 41: 245-253.
[2] Strickland et al. 2018. Status of acute systemic toxicity testing requirements and data uses by U.S. regulatory agencies. Reg Tox Pharma 94: 183-196.
[3] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-17-007.html
[4] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-15-016.html

Recommendations from agencies addressing the need for more practical, applied research could also stimulate funding for NAMs.

Develop mechanisms to improve communication between end users and researchers

As mentioned above, bringing in end users early in the process will likely improve the chances of NAM understanding and use. NICEATM could work through ICCVAM agencies to solicit feedback from the regulated community and their own staff, as well as hold information exchange sessions, and form stakeholder workgroups. EPA's Office of Pesticide Programs (OPP) has set an example for developing a transparent forum for the agency and its stakeholders when it created the Acute Toxicity Alternatives Stakeholder Group. In collaboration with its stakeholders, OPP has established goals for adopting alternatives to acute toxicity testing and has been giving regular updates to the stakeholder group. The forum provides a feedback mechanism for industry and NGOs to provide comments, give advice, and participate in workgroups that deal with specific issues. We recommend that this stakeholder group serve as a model for other agencies seeking to coordinate and interact with their stakeholder end users in developing and adopting alternative methods.

Workshops can play an important role in bringing together researchers and end-users. The recent webinars and workshops on acute toxicity resulted in publication of several papers outlining agencies' needs and uses of acute toxicity data, a discussion of the state of the science, and a set of recommendations for moving forward. These workshops can serve as a model for addressing NAMs for other toxicities.

NGOs can support agency efforts by sponsoring and organizing sessions that bring end users and developers together. HSUS is willing to work with agencies and the regulated community to foster collaboration whenever possible.

Anticipated Science and Technology – Microphysiological Systems

The partnership between the National Center for Advancing Translational Sciences (NCATS), the Defense Advanced Research Projects Agency (DARPA), and the Food and Drug Administration (FDA) that initiated the Human Microphysiological Systems: Organs-on-Chips for Drug Safety and Efficacy Testing Program, has met and even surpassed expectations in the rapid development and commercialization of several organ-on-a-chip systems that are currently in different phases of implementation and commercialization. This type of interagency collaboration should serve as a model for other technology development projects, and also for projects that address common information needs. Next steps in this program include FDA's public-private partnership with Emulate to qualify microphysiological systems for implementation in the FDA's Office of Foods and Veterinary Medicine risk assessment process[5]. In addition, in 2017/2018, NCATS partnered with several other NIH institutes in Tissue Chips 2.0, allocating more than $15 million to fund 14 awards for the Tissue Chips for Disease Modeling and Efficacy Testing initiative. NCATS is also coordinating the development of several NextGen Tissue Chip Testing Centers for the validation of microphysiological systems.[6]

[5] https://blogs.fda.gov/fdavoice/index.php/2017/04/organs-on-chips-technology-fda-testing-groundbreaking-science/
[66] https://ncats.nih.gov/tissuechip/projects/modeling

This is exactly the type of multi-institute approach that can facilitate pooling of resources and accelerate the development of cross-cutting technologies, and could serve as a model for development of NAMs to address additional information needs (e.g. developmental toxicity).

US Strategic Roadmap Goal: Foster the Use of Efficient, Flexible, and Robust Practices to Establish Confidence in New Methods

As NAMs are developed it is important that certain basic properties are established, i.e., that reproducibility, variability, applicability and limitations be sufficiently described. Also critical to uptake and acceptance is that the NAMs be fit-for-purpose. One approach would be the establishment of a set of performance standards, ideally based on a well-characterized set of reference chemicals. NAM performance relative to the context of use should also be determined, e.g. for a particular application or within a specific decision context or Integrated Approaches to Testing and Assessment (IATA), as described by the Organisation for Economic Cooperation and Development (OECD)[7]. NICEATM could facilitate a broader understanding of this approach to assay characterization by development of select case studies relevant for US regulatory agencies.

Moving Beyond Animal Data as the Gold Standard

A major step toward moving beyond animal data is an increased understanding of mechanisms of toxicity. Formal articulation of biological pathways involved in toxicity, such as the Adverse Outcome Pathways (AOP) framework, are important in the design of integrated approaches to testing and assessment that facilitate the implementation of NAMs. As AOPs are developed to cover more biological space critical to predicting toxicological endpoints, and as understanding of human biology increases (e.g. from biomarkers of chemical exposure or disease), NAMs will increasingly be assessed via internal consistency of biological hypotheses, rather than empirical comparison to historical animal tests. Increased allocation of resources toward capturing human biological pathway information will greatly facilitate the development and evaluation of relevant NAMs.

In addition, the continued evaluation of the reproducibility and variability of animal data through retrospective analyses is critical for defining the performance standards that NAMs must meet to perform similarly or better than historical methods. Retrospective analyses that NICEATM has already performed, of the local lymph node assay (LLNA) for skin sensitization[8], the rat uterotrophic assay[9], and the rat oral lethality test[10], have demonstrated that animal tests are in the neighborhood of 60 – 80% reproducible and can be quite variable. As an example, the work on acute toxicity showed that 234 chemicals for which there were three or more rat LD_{50}s values had at least one study with a value falling outside 1.5 times the interquartile range of the LD_{50} distribution for that chemical, while 30 chemicals had LD_{50} values ranging across at least two

[7] http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm
[8] Kleinstreurer et al. 2018. Non-animal methods to predict skin sensitization (II): an assessment of defined approaches. Crit Rev Tox 48(5): 359-374.
[9] Browne et al. 2015. Screening Chemicals for Estrogen Receptor Bioactivity Using a Computational Model. Environ Sci Tech 49: 8804-8814.
[10] https://ntp.niehs.nih.gov/iccvam/meetings/iccvam-forum.../03a-atimplementation.pdf

orders of magnitude, with seven of these chemicals having LD_{50} values ranging across at least three orders of magnitude[11]. With respect to predictivity, Kleinstreuer et al. (2018) demonstrated that the LLNA for human outcomes was "74% for hazard prediction (sensitizer versus non-sensitizer), 59% for potency prediction using three classes (strong, weak, and non-sensitizer) and only 45% for potency prediction using five classes."[12] These analyses are essential to understand the limitations of animal tests and the acceptable limits of NAMs.

US Strategic Roadmap Goal: Encourage the Use and Adoption of New Methods and Approaches by Federal Agencies and Regulated Industry

Encouraging use and adoption of NAMs by agencies and industry is a final step along the development process from soliciting input early on from end users, communicating through workgroups and other forums, and establishing confidence in the method through to having certainty that it will be accepted by the agency. Agencies should issue policy statements clearly outlining parameters regarding acceptance of NAMs and communicate via a webpage specifically devoted to acceptable NAMs and how they should be used. Articles in news sources like *ChemWatch* and *InsideEPA* could also facilitate dissemination of this information. NGOs, including ourselves, could assist by organizing webinars, training and demonstrations of NAMs. In addition, agencies could create incentives for industry to use new methods and establish a preferred list of 3Rs best practices that encourages use of methods that eliminate or reduce animal use.

Gaining Access to Large Quantities of Standardized Animal Testing Data: Considerations, Challenges, and Are There Truly Insurmountable Barriers?

Publically accessible, curated animal test data is necessary to best leverage existing information for conducting retrospective analyses, developing predictive models, and comparing results of non-animal to animal approaches. NICEATM has been a successful intermediary for data sharing on several recent projects and should continue in this capacity. It was also instrumental in developing several curated data sets including the one used to develop the acute toxicity consensus model by mining and manual review of multiple available databases. NICEATM also collaborated with EPA OPP to include large quantities of FIFRA acute toxicity data, from which confidential business information was removed. In addition, NICEATM has gathered and curated data from public sources to develop databases for work carried out under the Endocrine Disruptor Screening Program.

Across different NIH institutes there are several projects to collect, curate, and integrate many types of chemical (including drug) safety information – for example LINCS and NCATS Biomedical Data Translator.[13] In addition, industry, both as individual companies and through collaborations, has a number of such activities in progress (e.g. Integrative Medicine Initiative's

[11] Variability of LD50 Values from Rat Oral Acute Toxicity Studies: Implications for Alternative Model Development. Available: https://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=340317

[12] Kleinstreurer et al. 2018. Non-animal methods to predict skin sensitization (II): an assessment of defined approaches. Crit Rev Tox 48(5): 359-374.

[13] http://www.lincsproject.org; https://ncats.nih.gov/translator

eTox project).[14] It may be possible that NICEATM could facilitate, via workshops or working groups, sharing of information, databases and best practices of these different information gathering activities. In addition, by identifying cross-cutting priorities, it may be possible to allocate funding more sustainably to these data curation efforts. Development and application of data mining efforts such as that being developed by the NTP Office of Health Assessment and Translation (OHAT) to automate systematic reviews, are likely, over time, to make data mining and curation more efficient.

Effective implementation of ICCVAM's strategic roadmap will require significant resources, collaboration, and input from a wide variety of stakeholders. HSUS has successfully partnered with NICEATM and ICCVAM member agencies in the past and we hope to continue this type of collaboration in the future. We would also like to offer our assistance in implementing any of the above suggestions whenever possible. Please feel free to contact us with any thoughts or questions.

Thank you.

Sincerely,

Catherine Willett, PhD
Senior Director, Science and Regulatory Affairs
Humane Society of the United States

Patricia L. Bishop, MSc
Regulatory Science Advisor
Research and Technology Department
Humane Society International

[14] http://www.etoxproject.eu