THE HUMANE SOCIETY OF THE UNITED STATES

HUMANE SOCIETY LEGISLATIVE FUND™

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Nicole Kleinstreuer, PhD
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RE: Interagency Coordinating Committee on the Validation of Alternative Methods; Notice of Public Webcast; Request for Public Input

Dear Dr. Kleinstreuer,

On behalf of the Humane Society of the United States (HSUS), Humane Society Legislative Fund (HSLF), and our members and supporters, thank you for the opportunity to comment on the important ongoing work by Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and its member agencies. HSUS and HSLF commend ICCVAM on the great strides it has made implementing plans to move toward more human-relevant testing as described 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 made it clear that a shift away from linear validation models will be necessary for ICCVAM and its member agencies to achieve progress toward greater development, use and acceptance of new approach methodologies (NAMs) in chemical safety assessment.

The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) has demonstrated strong leadership in providing current and relevant information about NAMs development. We encourage NICEATM to continue to engage with regulators, industry, and all stakeholders on the latest information about conducting safety assessments while also minimizing the need for animal testing such as those listed below:

- The April 2020 town hall meeting, *Development of New Approach Methodologies to Reduce Animal Use in Toxicity Testing*, held in conjunction with National Institute of Environmental Health Sciences (NIEHS) Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) program, which sought to connect NAMs

developers with agency representatives to ensure that new methods are meeting current regulatory needs.

- The January 2020 ICCVAM Communities of Practice Webinar about the use of animal-free affinity reagents.
- The October 2019 workshop, *Mind the Gaps: Prioritizing Activities to Meet Regulatory Needs for Acute Systemic Lethality,* which brought together experts to discuss how to assess acute lethality of chemicals and mixtures while minimizing reliance on new animal testing.

While HSUS and HSLF are excited to see the enormous amount of activity surrounding NAM development, acceptance, and use, we encourage ICCVAM to focus on a few specific areas to ensure successful implementation of Roadmap goals.

Critical evaluation of traditional animal models

HSUS and HSLF encourage NICEATM to continue its work comparing results from animal data and non-animal testing strategies such as those published on skin sensitization[1] and acute oral toxicity[2]. This work is important in building confidence in NAMs and we ask NICEATM and ICCVAM agencies to continue this type of comparative analysis. In addition, we urge NICEATM to engage with agencies on conducting retrospective analyses of data obtained for regulatory purposes to investigate whether the data were used in making risk assessments. For those instances where specific types of animal data were never or rarely used by the agency in regulatory decision-making, agencies should be encouraged to remove the requirement or publicize acceptance of waivers. Careful consideration of the value of animal data will enable regulators to allow weight of evidence decisions, without compromising human or environmental safety.

Develop metrics for tracking uptake of NAMs

HSUS and HSLF were pleased to see that NIEHS accepted the recommendation from the 2019 Government Accountability Office Report, *Animal use in Research: Federal Agencies Should Assess and Report on Their Efforts to Develop and Promote Alternatives,* to create a workgroup "to develop metrics that the agencies could use to assess the progress they have individually or collectively made toward reducing, refining, or replacing animal use in testing."[3] These metrics will be useful for determining agency success in NAMs uptake, but will also point to areas where uptake is lacking, and identify barriers to that uptake. As each agency and center collects

[1] Kleinstreuer, Nicole et.al (2018): Non-animal methods to predict skin sensitization (II): an assessment of defined approaches, Critical Reviews in Toxicology, DOI: 10.1080/10408444.2018.1429386

[2] Kleinstreuer, Nicole et.al (2018): Predictive models for acute oral systemic toxicity: A workshop to bridge the gap from research to regulation, Computational Toxicology, DOI: 10.1016/j.comtox.2018.08.002

[3] GAO. (2019 September). Animal use in Research: Federal Agencies Should Assess and Report on Their Efforts to Develop and Promote Alternatives. https://www.gao.gov/assets/710/701635.pdf

different information, metrics should be tailored to each office/center to accurately ascertain successes and failures in the use and implementation of NAMs. For example, the Environmental Protection Agency (EPA) collects standard submissions from pesticide manufactures where test methods (whether animal or NAMs) could be clearly identified as could the use of any data bridging or waivers. In contrast, cosmetics companies are not required to register with the Food and Drug Administration (FDA) so there is a lack of information about the types of tests that are being done. In cases such as these, industry could be encouraged to volunteer information about the endpoints being assessed and any use of animals, NAMs, or data waiving.

Focus on regulatory acceptance

While the increase in NAMs development has been a story of success over the last several years, barriers to regulatory acceptance and industry use persist. We encourage all ICCVAM agencies to engage in dialogues with industry and NAM developers to ensure that new approaches are satisfying regulatory data needs and enabling reduction in animal use. The recent virtual townhall meeting with SBIR and STTR was a good example of how this type of communication can occur. ICCVAM agencies should continue to engage with all stakeholders in this manner to ensure new test methods and strategies are fit for purpose. When NAMs reliability and relevance have been shown, their use should be immediately incorporated into tiered testing strategies to reduce the need for additional animal testing wherever possible. When NAMs enable elimination of an animal test entirely, this information needs to be publicly communicated and its preferred use encouraged by the agency.

We were pleased to see that FDA has recently created an Alternative Methods Working Group and look forward to the agency making progress on adopting new approaches that can "support decision-making in regulatory toxicology."[4] In his September 20, 2019 memorandum, EPA Administrator Andrew Wheeler put forth a public commitment by the agency 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."[5] Other agencies should be encouraged to release similar forward-thinking plans to reduce animal use and reliance and provide the incentive needed to ensure NAMs are incorporated into regulatory decision-making.

Increase international harmonization

HSUS and HSLF are excited about the progress United States agencies are making in NAMs acceptance, but global harmonization will need to be prioritized to make a true impact on reduction of animal use. We strongly encourage ICCVAM and its member agencies to increase

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[4] FDA. (2020, April 20). Advancing Alternative Methods at FDA. Retrieved from: https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda

[5] 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

involvement and leadership with the Organisation for Economic Co-operation and Development (OECD), International Cooperation on Alternative Test Methods (ICATM), and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), whenever possible. NAMs implementation would benefit from the committed participation of all ICCVAM members in these international regulatory bodies.

NAMs funding

In order to speed the expansion of NAMs, stakeholders need to invest significant time and money into their development. HSUS and HSLF encourage agencies to shift funding to NAMs development as these offer the promise of providing more human-relevant data often at a lower cost than traditional animal methods. For example, the National Center for Advancing Translational Science (NCATS) recently issued a notice allowing awardees to apply for competitive revisions to their research grants in order to maximize tissue chips for COVID-19 modeling, advancement of diagnostic tools, and rapid development and assessment of new therapeutics.[3] What the pandemic has made clear is the need to rapidly develop and test new therapeutics and utilization of NAMs will be critical for this and any future health emergencies. We also support modifying National Institutes of Health (NIH) grant review criteria to identify and specifically fund NAMs development as the Roadmap points out. NICEATM might also play a larger role in influencing approaches taken by NTP more generally, which could, when successful, influence the investment in NAMs by other institutes. ICCVAM agencies should explore additional opportunities for prioritizing funding of non-animal approaches.

Thank you for the opportunity to comment and for all the work that NICEATM has done to encourage NAMs development and uptake. HSUS and HSLF would be pleased to help ICCVAM and its member agencies to further NAMs development, use and acceptance in the United States and around the globe, whether in the form of webinars, agency trainings, outreach to international partners, or in organizing future workshops.

Sincerely,

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