THE HUMANE SOCIETY OF THE UNITED STATES

HUMANE SOCIETY LEGISLATIVE FUND™

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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 the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and its member agencies. Since the release of 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), ICCVAM has made great progress in moving toward more human-relevant testing. HSUS and HSLF continue to offer our full support of efforts by ICCVAM and member agencies on the development, acceptance, and use of new approach methodologies (NAMs) in chemical safety assessment.

With strong leadership at the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), NAMs development, awareness, and acceptance continues to increase. Through regular engagement with regulators, industry, and other stakeholders on the latest testing methods and strategies, NICEATM provides valuable information about modernizing safety assessments and minimizing animal use. For example:

- The January 2021 ICCVAM Communities of Practice Webinar about the use of non-animal approaches for assessing mixtures.
- The September 2020 webinar symposium, *Opportunities and Challenges in Using the Kinetically Derived Maximum Dose (KMD) Concept to Refine Risk Assessment*, held in conjunction with the Environmental Protection Agency (EPA) Office of Pesticide

Programs, and the Health and Environmental Sciences Institute, which brought together experts to discuss how to support the use of KMD as an approach to select appropriate doses in toxicology studies or interpret dose-response study results in chemical risk assessments.

- The 2020 webinar series on the benefits and applications of animal-free recombinant antibodies.

To successfully implement the goals laid out in the Roadmap and further reduce reliance on animal test methods, HSUS and HSLF urge ICCVAM and its member agencies to focus on a few specific areas highlighted below.

**Critical evaluation of data from animal models**

As NICEATM and ICCVAM member agencies evaluate NAMs to determine when their use should be promoted, HSUS and HSLF encourage looking critically at the reliability of data from animal models. NICEATM should continue this work comparing results from animal data and non-animal testing strategies such as those published on skin sensitization[1] and acute oral toxicity[2] to build confidence in NAMs. The inherent problems with variability and uncertainty in animal data need to be clearly recognized when evaluating NAMs against this standard. Careful consideration of the value of animal data will enable regulators to minimize animal use without compromising human or environmental safety.

NICEATM should also engage with ICCVAM member agencies to conduct retrospective analyses of data obtained for regulatory purposes, to evaluate whether those data were necessary for agency decision-making. In instances where specific types of animal data were never or rarely used, agencies should be encouraged to remove the requirement or publicize acceptance of waivers as EPA has done with the release in December 2020 of its *Guidance for Waiving Acute Dermal Toxicity Tests for Pesticide Technical Chemicals & Supporting Retrospective Analysis*.[3] There also needs to be a commitment from agencies to clearly communicate expectations to industry to avoid continued submission of animal data, when it is no longer deemed necessary. In a 2020 article, *Acute toxicity "six-pack" studies supporting approved new drug applications in the U.S.,* it was revealed that despite the existence of updated guidance documents stating that lethal dose studies were no longer needed, pharmaceutical companies continued to submit these animal data to the Food and Drug Administration (FDA) Center for Drug Evaluation and

[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] Environmental Protection Agency (2020, December). Guidance for Waiving Acute Dermal Toxicity Tests for Pesticide Technical Chemicals & Supporting Retrospective Analysis. Retrieved from: https://www.epa.gov/sites/production/files/2021-01/documents/guidance-for-waiving-acute-dermal-toxicity.pdf

Research (CDER).[4] In addition, FDA guidance has allowed for the use of NAMs to assess skin and eye irritation for reformulated topical drug products since 2015.[5] However, drug companies continue to submit the animal studies for these tests in new drug applications.[6] There needs to be clear communication between agencies and their regulated industries to avoid the continued collection of animal test data that are no longer deemed necessary and ultimately prevent needless animal use.

**Focus on regulatory acceptance**

NAMs continue to be developed at a rapid pace. These innovative technologies offer promise to immediately reduce and eventually eliminate the use of animals in regulatory testing. However, barriers to regulatory acceptance and industry use persist. ICCVAM agencies must regularly engage with industry and NAMs developers to ensure that new approaches are satisfying regulatory data needs. Through direct communication and collaboration with all stakeholders, ICCVAM member agencies can ensure that new test methods and strategies are designed to address the proper applicability domain and are fit for purpose. As soon as the reliability and relevance of NAMs has been established, their use should be immediately incorporated into tiered testing strategies, enabling a rapid reduction in animal use. When NAMs provide an opportunity to completely eliminate the need for animal testing, the acceptance of data from these new methods must be clearly communicated to stakeholders. Given their remit to reduce reliance on animal tests, the preferred use of the NAMs, rather than the traditional animal tests, should be strongly encouraged by ICCVAM member agencies.

HSUS and HSLF urge all ICCVAM member agencies to provide clear plans to move away from reliance on animal test methods. In his September 20, 2019 memorandum, former 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."[7] In a 2020 National Academies of Sciences, Engineering and Medicine report, *Necessity, use, and care of laboratory dogs at the U.S. Department of Veterans Affairs (VA)*, the committee urged the agency to "establish a strategic

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[4] Manuppello J, Sullivan K, Baker E. Acute toxicity "six-pack" studies supporting approved new drug applications in the U.S., 2015-2018. Regul Toxicol Pharmacol. 2020 Jul;114:104666. doi: 10.1016/j.yrtph.2020.104666. Epub 2020 Apr 23. PMID: 32335206.

[5] Food and Drug Administration. (2015, October). Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route. Retrieved from: https://www.fda.gov/files/drugs/published/Nonclinical-Safety-Evaluation-of-Reformulated-Drug-Products-and-Products-Intended-for-Administration-by-an-Alternate-Route.pdf

[6] Manuppello J, Sullivan K, Baker E. Acute toxicity "six-pack" studies supporting approved new drug applications in the U.S., 2015-2018. Regul Toxicol Pharmacol. 2020 Jul;114:104666. doi: 10.1016/j.yrtph.2020.104666. Epub 2020 Apr 23. PMID: 32335206.

[7] 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

roadmap and accompanying framework to promote the development and incorporation of NAMs to replace, reduce, or refine the use of dogs and all other laboratory animals in VA research."[8] As a new member agency of ICCVAM, we hope that the VA is working toward developing such a roadmap. Through its creation of the Alternative Methods Working Group, FDA has also prioritized adoption of new approaches that can "support decision-making in regulatory toxicology."[9] All ICCVAM member agencies should release or update strategic plans to reduce animal use and reliance, create timelines for progress, and provide the incentive needed to ensure NAMs are fully incorporated into regulatory decision-making.

**Increase international harmonization**

One of the clearest barriers to uptake of NAMs by regulated industries is the lack of international harmonization. While U.S. agencies may be prioritizing the development and acceptance of new approaches, companies will continue to conduct animal studies until all international regulators have done the same. 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 (ICATM), and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), whenever possible. While the global pandemic has made collaboration more challenging in some ways, there are also additional opportunities for representatives from ICCVAM member agencies to participate in work being done at international regulatory bodies. It is through this work toward global harmonization that we will see the largest impact on reducing animal use.

**ICCVAM member agencies must develop clear metrics for tracking uptake of NAMs**

The 2019 Government Accountability Office Report, *Animal use in Research: Federal Agencies Should Assess and Report on Their Efforts to Develop and Promote Alternatives,* led to the creation of an ICCVAM metrics workgroup (MWG) tasked with the goal of developing "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."[10] The MWG released its February 2021 report, *Measuring U.S. Federal Agency Progress Toward Implementation of Alternative Methods in Toxicity Testing,* leaving the task of developing metrics to the individual agencies and suggesting agencies may rely on qualitative metrics such as "the provision of educational opportunities that raise awareness regarding alternatives…training, publications, and

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[8] National Academies of Sciences, Engineering, and Medicine. 2020. *Necessity, Use, and Care of Laboratory Dogs at the U.S. Department of Veterans Affairs*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25772.

[9] 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

[10] 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

presentations given by agency scientists."[11] While we agree with the MWG's conclusion that "no one set of metrics can be used by all ICCVAM member agencies,"[12] the MWG report was a missed opportunity to provide clarity and best practices to individual agencies. This may consist of a combination of quantitative and qualitative data to determine agency success in NAMs uptake, identification of areas where NAMs use may be lacking, and addressing potential barriers to successful implementation of NAMs. It is now incumbent upon the ICCVAM member agencies to take steps to develop such metrics, clearly communicate them to the public, and develop plans to overcome obstacles that prevent full implementation of NAMs.

**NAMs funding**

All ICCVAM agencies must work to shift funding from traditional animal models to NAMs development and use. These new, non-animal technologies provide more human-relevant information often at a lower cost, increasing the impact of agency funds. For example, the National Institutes of Health (NIH) recently issued a Funding Opportunity Announcement for the development of approaches to study neurogenesis, including human induced pluripotent stem cell (iPSC) and organoid models.[13] All agencies funding research should similarly encourage the use of NAMs to meet their scientific objectives. As part of the Roadmap, ICCVAM also stressed the importance of increased funding for NAMs development. It recommended "the establishment of grant review criteria tailored to the development of alternative methods."[14] Currently, NIH grant applications are awarded scores for five review criteria (significance, investigator, innovation, approach, and environment). There are additional criteria that are considered, but not scored, including use of vertebrate animals.[15] Unfortunately, this criterion is focused more on refinement than replacement of animal use. HSUS and HSLF agree with the ICCVAM roadmap that adding a criterion that specifically considers the development and use of NAMs would have a significant impact on how funds are distributed and how researchers approach their work. Defining, and importantly, scoring, the development and use of NAMs sends a clear signal to the researchers that NAMs must be seriously considered and will form a crucial component of grant evaluation. We also support the recommendation from the 2020 National Academies of Sciences, Engineering and Medicine

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[11] ICCVAM. (2021, February). Measuring U.S. Federal Agency Progress Toward Implementation of Alternative Methods in Toxicity Testing. Retrieved from: https://ntp.niehs.nih.gov/iccvam/docs/about_docs/iccvam-measuringprogress-feb2021-fd-508.pdf

[12] ICCVAM. (2021, February). Measuring U.S. Federal Agency Progress Toward Implementation of Alternative Methods in Toxicity Testing. Retrieved from: https://ntp.niehs.nih.gov/iccvam/docs/about_docs/iccvam-measuringprogress-feb2021-fd-508.pdf

[13] NIH. (2021, January 4). New Approaches to Identify Neurogenesis and Study its Dynamics in Brain Aging and AD/ADRD. Retrieved from: https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-22-006.html

[14] ICCVAM. (2018, January). A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States. Retrieved from: https://ntp.niehs.nih.gov/iccvam/docs/roadmap/iccvam_strategicroadmap_january2018_document_508.pdf

[15] NIH. (2016). Definitions of Criteria and Considerations for Research Project Grant (RPG/R01/R03/R15/R21/R34) Critiques. Retrieved from: https://grants.nih.gov/grants/peer/critiques/rpg.htm

report that the VA provide "grant opportunities to promote the development of NAMs that meet the unique needs of VA researchers, including the use of human tissues and organs, *in vitro*, *in silico*, and computational approaches."[16] All ICCVAM agencies should explore additional opportunities for prioritizing funding of non-animal approaches, as well as opportunities to work together to more efficiently develop and approve NAMs.

**Conclusion**

HSUS and HSLF welcome the opportunity to work with NICEATM or any ICCVAM agency to help achieve the common goal of replacing animals with human relevant test methods and strategies. Thank you for the consideration of our comments.

Sincerely,

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[16] National Academies of Sciences, Engineering, and Medicine. 2020. *Necessity, Use, and Care of Laboratory Dogs at the U.S. Department of Veterans Affairs*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25772.