THE HUMANE SOCIETY OF THE UNITED STATES

HUMANE SOCIETY LEGISLATIVE FUND™

May 20, 2022

Nicole Kleinstreuer, PhD
Acting Director, NICEATM
National Institute of Environmental Health Sciences
P.O. Box 12233, K2–17
Durham, NC USA 27709

RE: Interagency Coordinating Committee on the Validation of Alternative Methods; Notice of Public Webinar; Request for Public Input (87 FR 25649)

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. HSUS and HSLF offer our full support of efforts from ICCVAM and the member agencies in moving toward greater development, acceptance, and use of new approach methodologies (NAMs) in chemical safety assessment as articulated in its 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).

The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods' (NICEATM) leadership and regular engagement with regulators, industry, and other stakeholders, has helped raise the profile of NAMs and encourages the continued development, awareness, and acceptance of these modern test methods. NICEATM provides valuable information about modernizing safety assessments and minimizing animal use. For example:

- The January 2022 ICCVAM Communities of Practice Webinar on Developmental Neurotoxicity and the NAMs that are being considered or developed for assessing potential effects of chemicals on the nervous system.
- The 2021/2022 webinar series on Quantitative Risk Assessment for Skin Sensitization organized with the Swiss Centre for Applied Human Toxicology and the Swiss State

Secretariat for Economic Affairs. These webinars provided important information on the available NAMs that can be used to provide quantitative risk assessment of skin sensitizing chemicals.

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

HSUS and HSLF encourage NICEATM and ICCVAM member agencies to address the reliability of data from animal models as they evaluate NAMs. In 2018, NICEATM scientists published articles comparing the results from animal data and non-animal testing strategies on skin sensitization[1] and acute oral toxicity.[2] These studies not only help to build confidence in NAMs but point out some of the flaws with the traditional animal models. At the request of the Environmental Protection Agency (EPA), an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine was established, *Variability and Relevance of Current Laboratory Mammalian Toxicity Tests and Expectations for New Approach Methods for use in Human Health Risk Assessment*[3]. HSUS and HSLF appreciate this forward-thinking approach to address the inherent problems with variability and uncertainty of data from animal toxicity tests for human health risk assessment. These factors are important when evaluating NAMs against this standard and we look forward to seeing recommendations from the committee on the best way to incorporate their findings into an evidence-based scientific confidence framework to facilitate the use of NAMs in human health risk assessment.

Confidence frameworks have recently been proposed for Adverse Outcome Pathways (AOP) specifically[4] and for NAMs more generally.[5] These offer a relatively defined structure with which to evaluate the suitability of the different non-animal methods for regulatory applications. Developing and publishing case studies for the utility of NAMs, based on the structured frameworks, could be valuable for increasing confidence, which is needed to accelerate development of new NAMs and encourage the use of existing NAMs. Additionally,

---

[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] https://www.nationalacademies.org/our-work/variability-and-relevance-of-current-laboratory-mammalian-toxicity-tests-and-expectations-for-new-approach-methods--nams--for-use-in-human-health-risk-assessment

[4] Patlewicz, Grace at al. (2015). Proposing a scientific confidence framework to help support the application of adverse outcome pathways for regulatory purposes. Regulatory Toxicology and Pharmacology. doi.org/10.1016/j.yrtph.2015.02.011

[5] Parish, Stanley et al. (2020). An evaluation framework for new approach methodologies (NAMs) for human health safety assessment. doi.org/10.1016/j.yrtph.2020.104592

understanding the variability (and therefore inherent limitations) of animal-test based data will allow the regulators to rationalize the potential value of animal data, and could encourage increased reliance on NAMs data, minimizing animal use, without compromising human or environmental safety.

NICEATM should also engage with ICCVAM member agencies to conduct retrospective analyses of animal test data obtained for regulatory purposes, to evaluate whether those data or what portion of those data were actually used in agency decision-making. In a 2021 article, *Retrospective analysis of dermal absorption triple pack data,* scientists from NICEATM and EPA presented the results of their analysis of determining the human dermal absorption factor (DAF) for agrochemicals using the traditional "triple pack," which includes rat *in vivo*, rat *in vitro*, and human *in vitro* studies and comparing it to the DAF found by using each study individually. The retrospective analysis concluded that "for most of the formulations, the human *in vitro* method provided a similar or higher estimate of dermal absorption than the triple pack approach" and was supportive of "potentially using *in vitro* data alone for DAF derivation for human health risk assessment of pesticides."[6] This retrospective analysis not only demonstrated the value of NAMs data, but also highlighted when additional animal data does not provide additional value. Retrospective analyses should be carried out to define which tests, in what species, actually provide the data needed for decision making. Also, 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*.[7]

Along with retrospective analyses, there are additional opportunities to reduce animal use. For example, taking a stepwise approach to testing with an emphasis on eliminating redundant tests until such time that NAMs are available that can fully replace animals. The current paradigm of a pesticide registrant or drug company doing multiple tests on multiple species, usually at non-human-relevant exposure doses, before submitting the data package to the regulatory agency, in many cases is a waste of animal lives as typically only one or a few tests are used for actual decision-making. We have seen cases of pesticide human health risk assessments where there was no measurable toxicity in any animal species to the point where a quantitative risk assessment was not even conducted, yet thousands of animals were used to reach the same conclusion before the data package was even submitted to EPA. There should

[6] Allen, D. G., Rooney, J., Kleinstreuer, N., Lowit, A. and Perron, M. (2021) "Retrospective analysis of dermal absorption triple pack data", *ALTEX - Alternatives to animal experimentation*, 38(3), pp. 463–476. doi: 10.14573/altex.2101121.

[7] 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

be an opportunity to consult with the regulatory agency with respect to evidence of toxicity and real-world exposure levels before all animal tests are completed to avoid redundant and unnecessary testing.

Clear communication with stakeholders

HSUS and HSLF urge ICCVAM and all member agencies to clearly communicate with stakeholders about the acceptance of NAMs data, ways to eliminate unnecessary animal testing, and appropriate processes to ensure consideration of new technologies in the regulation of chemical substances. ICCVAM's public forum provides a unique opportunity for member agencies to provide information about the work they are doing to develop, accept, and implement NAMs. However, to realize the goal of reducing animal testing, ongoing and open communication between regulators, industry, NAMs developers, and nongovernmental organizations is necessary and should include workshops, webinars, meetings, and website updates. Discussion of ways to avoid unnecessary animal testing and incorporate NAMs into testing plans should become a regular part of agency interactions with regulated industries. We also encourage ICCVAM member agencies to consider opportunities for incentivizing NAMs use and data submission for their regulated industries.

NAMs developers

To ensure acceptance of NAMs, it is important that the developers are granted an opportunity to present their new technologies to relevant regulatory agencies. Several ICCVAM member agencies have recently tried to address this need. In 2020, the Food and Drug Administration (FDA) announced the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program with the stated goal of supporting "the development of novel approaches to drug development that may be acceptable for regulatory use." HSUS and HSLF strongly support the implementation of this program and encourage FDA to devote additional funding and staff support to ensuring its success. Earlier this year, the Consumer Product Safety Commission (CPSC) released *Guidance for Industry and Test Method Developers: CPSC Staff Evaluation of Alternative Test Methods and Integrated Testing Approaches and Data Generated from Such Methods to Support FHSA Labeling Requirements,* with the aim of providing a procedure for the consideration of NAMs since the agency previously relied upon ICCVAM's formal validation process.[8] While HSUS and HSLF expressed concerns that the CPSC guidance may be unnecessarily repetitive and complicated, we encourage all ICCVAM member agencies to figure out how best to proactively and efficiently evaluate NAMs to prevent delays in uptake of the new methods.

[8] Consumer Product Safety Commission. (2022, January). Guidance for Industry and Test Method Developers: CPSC Staff Evaluation of Alternative Test Methods and Integrated Testing Approaches and Data Generated from Such Methods to Support FHSA Labeling Requirements. Retrieved from: https://www.regulations.gov/document/CPSC-2021-0006-0010

Avoiding unnecessary animal testing

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 FDA Center for Drug Evaluation and Research (CDER).[9] In addition, FDA guidance has allowed for the use of NAMs to assess skin and eye irritation for reformulated topical drug products since 2015.[10] However, drug companies continue to submit the animal studies for these tests in new drug applications.[11] 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.

Updating guidance documents and public communication

HSUS and HSLF urge all member agencies to proactively update their websites, removing outdated guidance and regularly updating available lists of NAMs and guidance documents to ensure the latest scientific developments are adequately addressed and to avoid confusion about testing requirements. NAMs continue to be developed at a rapid pace and it is important that agency documents and websites are regularly updated to reflect these changes. 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 eliminate the need for an animal test, the acceptance of data from these new methods must be clearly communicated to stakeholders and posted on the agency website. 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 all ICCVAM member agencies.

Setting clear timelines and roadmaps for the replacement of animal testing

HSUS and HSLF urge all ICCVAM member agencies to develop strategic plans to move away from reliance on animal test methods. In December 2021, EPA released its updated *New*

---

[9] 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.

[10] 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

[11] 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.

Approach Methods Workplan. This important document sets out the agency's plan to replace animal testing with NAMs with clear deliverables and timelines. EPA "identifies tangible steps to pursuing and achieving a reduction in the use of vertebrate animals for toxicity testing and related research while ensuring that the Agency's regulatory, compliance, and enforcement activities, including chemical and pesticide approvals and Agency research, remain fully protective of human health and the environment."[12] All ICCVAM member agencies should release or update strategic plans to reduce animal use and reliance, create timelines for progress, produce metrics for tracking adoption, and provide the incentive needed to ensure NAMs are fully incorporated into regulatory decision-making. These plans communicate agency priorities while also offering opportunities for input and collaboration among all stakeholders.

Increase international harmonization

International harmonization continues to be a barrier to widespread uptake of NAMs by regulated industries. 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. HSUS and HSLF encourage the continued participation and leadership by NICEATM and ICCVAM member agencies in 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). It is through this work toward global harmonization that we will see the largest impact on reducing animal use.

NAMs funding

HSUS and HSLF encourage all ICCVAM member agencies to proactively shift funding away from animal models toward NAMs development and use. Because these new, non-animal technologies provide more human-relevant information often at a lower cost, shifting funding will increase the impact of agency dollars, without compromising human or environmental safety. As part of the Roadmap, ICCVAM also stressed the importance of increased funding for NAMs development and specifically recommended "the establishment of grant review criteria tailored to the development of alternative methods."[13] Currently, National Institutes of Health 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.[14] Unfortunately, this criterion is focused more

---

[12] USEPA 2021. New Approach Methods Work Plan (v2). U.S. Environmental Protection Agency, Washington, DC. EPA/600/X-21/209.

[13] 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

[14] 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

on refinement than replacement of animal use. 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.

HSUS and HSLF were pleased to see that FDA, as part of the FY23 President's Budget Request asked for $5 million in new funding "to support a new, FDA-wide *New Alternative Methods Program* to reduce animal testing through the development of qualified alternative methods and spur the adoption of methods for regulatory use that can replace, reduce and refine animal testing."[15] We support agency efforts to receive dedicated funding for NAMs work and we will continue to urge Congress to provide appropriations for the prioritization of these agency efforts. 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,

(signature redacted)

(signature redacted)

Vicki Katrinak
Director, Animal Research and Testing
Animal Research Issues
The Humane Society of the United States

Gillian Lyons
Director, Regulatory Affairs
Federal Affairs
Humane Society Legislative Fund

[15] U.S. Food and Drug Administration. (2022, March 28). *FDA Seeks $8.4 Billion to Further Investments in Critical Public Health Modernization, Core Food and Medical Product Safety Programs* [Press Release]. https://www.fda.gov/news-events/press-announcements/fda-seeks-84-billion-further-investments-critical-public-health-modernization-core-food-and-medical