AN INTERNATIONAL ORGANIZATION DEDICATED TO PROTECTING THE RIGHTS OF ALL ANIMALS

PETA

PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

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Dr. Nicole Kleinstreuer
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Via e-mail: ICCVAMquestions@niehs.nih.gov

Dear Dr. Kleinstreuer:

We are submitting the following comments on behalf of People for the Ethical Treatment of Animals (PETA) in response to the National Institutes of Health (NIH) request for public input for the 2022 Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Public Forum published in the Federal Register on May 2, 2022 (87 FR 25649).

We would like to thank ICCVAM for its continued commitment to the development and application of new approach methodologies (NAMs). ICCVAM member agencies and ICCVAM Workgroups are addressing both new technical strategies as well as overarching topics to advance animal-free methods that will better predict human and environmental health outcomes. We commend this multifaceted approach and look forward to progress, particularly in the areas identified below.

Gaining Confidence in NAMs

ICCVAM member agencies must adopt a streamlined process for gaining confidence in, and increasing the uptake of, NAMs that demonstrate technical reliability, are biologically relevant, and are fit for purpose. The processes often used to demonstrate inter-laboratory reproducibility of NAMs are lengthy and expensive, and the predictive capacity of NAMs has usually been determined through comparison to results from traditional test methods using animals, for which reproducibility and human biological relevance are often assumed rather than empirically demonstrated. We are pleased that ICCVAM's Validation Workgroup is drafting criteria and processes for gaining confidence in NAMs.

It is important to recognize the lack of reproducibility of many test methods using animals[1,2,3,4] and that NAMs may have the ability to provide more

[1]Luechtefeld T, Maertens A, Russo DP, Rovida C, Zhu H, Hartung T. Analysis of Draize eye irritation testing and its prediction by mining publicly available 2008–2014 REACH data. ALTEX. 2016;33(2):123-134. https://doi.org/10.14573/altex.1510053
[2]Rooney JP, Choksi NY, Ceger P, Daniel AB, Truax J, Allen D, Kleinstreuer N. Analysis of variability in the rabbit skin irritation assay. Regul Toxicol Pharmacol. 2021;122:104920. https://doi.org/10.1016/j.yrtph.2021.104920
[3]Pham LL, Watford SM, Pradeep P et al. Variability in *in vivo* studies: Defining the upper limit of performance for predictions of systemic effect levels. Comput Toxicol. 2020;15:100126. https://doi.org/10.1016/j.comtox.2020.100126
[4]Paparella M, Colacci A, Jacobs MN. Uncertainties of testing methods: What do we (want to) know about carcinogenicity? ALTEX. 2017;34:235–252. https://doi.org/10.14573/altex.1608281

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biologically relevant information and mechanistic insights. The results of NAMs should not be expected to directly replicate the results of the traditional tests on animals. Instead of relying on direct comparisons between animal-derived and non-animal data, agencies should ensure that NAMs fulfill their intended purposes and provide technically reliable information that is relevant to the understanding of human biology and also health protective for the endpoint of concern.

Since demonstrating scientific confidence and regulatory acceptance of a NAM does not necessarily translate to that method's adoption in practice, ICCVAM member agencies should address resources and incentives for application of NAMs. We are pleased that ICCVAM has assembled the 'Consideration of Alternative Methods' Workgroup, and we look forward to the white paper it will develop on approaches to foster the use of NAMs in organizations currently using animals for testing.[5] As one avenue to address NAMs uptake, we suggest that ICCVAM member agencies collaborate with the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and organizations such as PETA Science Consortium International and the European Union Reference Laboratory for alternatives to animal testing (EURL ECVAM) to update ICCVAM member agency educational resources (e.g., ToxTutor and the Animal Welfare Informational Center training program). A good example of NAMs training information made publicly available is the U.S. Environmental Protection Agency's (EPA) NAMs catalog of training materials.[6] We also encourage this workgroup to consider multiple techniques to incentivize the use of NAMs, such as increased funding, collaborative opportunities, and research exposure.

Clear and Timely Communication

Increasing communication among ICCVAM member agencies and stakeholders can increase the uptake of reliable and relevant NAMs while a lack of communication can stall their implementation. For example, in the anticaries final monograph published in 1995, the U.S. Food and Drug Administration (FDA) stated that the agency would consider alternatives to the animal caries reduction test when proposed alternative testing procedures were submitted as a petition. In the almost three decades since then, data demonstrating the validity of non-animal models have been submitted, but the FDA has yet to respond to petitions for acceptance of data from non-animal methods submitted by companies in 2009,[7] 2015,[8] 2020,[9] and 2021.[10] This long response time is a clear hurdle to using NAMs.

In some instances, ICCVAM member agencies have carried out significant work to implement non-animal methods, but similarly long periods without follow-up on these projects leaves their

[5]National Toxicology Program. ICCVAM Workgroups. Accessed May 9, 2022. Available at https://ntp.niehs.nih.gov/whatwestudy/niceatm/iccvam/wg/index.html
[6]US EPA. New Approach Methods (NAMs) Training. Accessed May 19, 2022. Available at https://www.epa.gov/chemical-research/new-approach-methods-nams-training
[7]Docket FDA-1980-N-0074. Accessed May 17, 2022. Available at https://www.regulations.gov/docket/FDA-1980-N-0074
[8]Docket FDA-2015-P-0464. Accessed May 17, 2022. Available at https://www.regulations.gov/docket/FDA-2015-P-0464
[9]Docket FDA-2020-P-0983 Accessed May 17, 2022. Available at https://www.regulations.gov/docket/FDA-2020-P-0983
[10]Docket FDA-2021-P-0581. Accessed May 17, 2022. Available at https://www.regulations.gov/docket/FDA-2021-P-0581

resolution unclear. PETA Science Consortium International recently analyzed the progress of an *in vitro* method to replace the use of hamsters for *in vivo* leptospirosis potency testing in a manuscript that has been submitted for publication. In 2012, the U.S. Department of Agriculture (USDA) co-sponsored a workshop that was also co-organized by ICCVAM to identify opportunities to replace the use of hamsters to evaluate veterinary leptospirosis vaccines. In the ten years since this workshop, animal use to test these products has been reduced by approximately 55 percent as vaccine manufacturers adopt USDA-led policy changes intended to have this effect. Nevertheless, approximately 15,000 hamsters are still used to assess the potency of these products each year, and it is unclear whether there are plans to revisit the goals established in 2012 to assist industry's adoption of the currently available non-animal tests. We encourage ICCVAM member agencies to communicate their plans regarding long-term projects like these over time, and to establish consistent contacts to work with external stakeholders in order to facilitate the uptake of NAMs.

Additionally, there is a need for clear communication from regulatory agencies to the public on the acceptance of NAMs. ICCVAM member agencies should regularly update their public webpages with information that includes policies and guidance on the use of NAMs and clearly identifies what NAMs will be accepted. Further, any outdated guidance should be taken offline to prevent confusion.

NAMs Application in Regulatory Programs

We appreciate the FDA's efforts to transition towards the use of non-animal methods to enable more efficient and human-relevant pre-clinical development and evaluation of new drugs and devices. Several immunotherapy products have recently reached clinical studies on the basis of strictly *in vitro* safety and efficacy studies, a scenario we expect will become routine and more broadly applied in time.[11,12] A FDA News Release[13] regarding the fiscal year 2023 budget details a funding request for a New Alternative Methods Program aimed at reducing animal testing through the development and adoption of alternative methods, and funds are allocated to the goals of FDA's Predictive Toxicology Roadmap for furthering NAMs. However, funding is included to conduct large-scale testing on animals. We urge the FDA to consult with the ICCVAM Validation Workgroup on strategies to validate NAMs, and we suggest that resources be directed towards comparing data from NAMs with the wide range of existing human clinical data that is readily available to the FDA. Further, to fully maximize the use of existing data, we encourage the development of a database of preclinical data[14] as a counterpart to ClinicalTrials.gov, as suggested by FDA Commissioner Dr. Robert Califf.

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[11]Pink Sheet. Achilles On Getting 'New Wave' Immunotherapy From Concept to Clinic In Three Years. Accessed May 12, 2022. Available at https://pink.pharmaintelligence.informa.com/PS124934/Achilles-On-Getting-New-Wave-Immunotherapy-From-Concept-To-Clinic-In-Three-Years

[12]MedNous. Immunocore pioneers new safety studies. Accessed May 13, 2022. Available at https://www.mednous.com/system/files/Immunocore.Apr%202011%20pdf.pdf

[13]US FDA. FDA Seeks $8.4 Billion to Further Investments in Critical Public Health Modernization, Core Food and Medical Product Safety Programs. Accessed May 9, 2022. Available at https://www.fda.gov/news-events/press-announcements/fda-seeks-84-billion-further-investments-critical-public-health-modernization-core-food-and-medical

[14]Stat News. Califf's big idea: Build a database for research done before clinical trials. Accessed May 9, 2022. Available at https://www.statnews.com/2016/06/10/califf-database-preclinical-trials/

We also support the EPA's efforts to develop and implement NAMs in new chemical evaluations under the Toxic Substances Control Act (TSCA) to better protect human health and the environment. We were happy to hear the presentation given by Dr. Warren Casey at the TSCA Collaborative Research Program Public Meeting on April 20, 2022 showing support for the continued use and development of NAMs for chemical risk assessment under TSCA. In addition to the development and use of NAMs, there are many measures that the EPA can implement to reduce animal use while protecting human health, including providing timely responses to industry on data submissions using NAMs, maintaining an ongoing program to train staff on how to interpret data from NAMs for chemical risk assessment, building case studies demonstrating fit for purpose application of NAMs to fulfill risk management decisions, establishing metrics to monitor progress implementing NAMs, initiating data sharing projects, increasing transparency in deciding and issuing test orders under TSCA Section 4, and allowing public comment on test orders. We look forward to both the upcoming roadmap document with details of the partnership between the NIH and the EPA as well as to the more detailed plan of the TSCA Collaborative Research Program that is due out this fall from the Board of Scientific Counselors.

Metrics Development

The development of metrics to track the use of NAMs and animal use is critical to monitor progress, identify obstacles to the implementation of existing NAMs and areas where NAM development is still needed, and provide accountability for resources spent on NAMs. The ICCVAM Metrics Workgroup's (MWG) 2021 report, "Measuring U.S. Federal Agency Progress Toward Implementation of Alternative Methods in Toxicity Testing,"[15] was published in response to the U.S. Government Accountability Office's (GAO) recommendation for ICCVAM and its member agencies to propose metrics to help them better monitor progress in reducing animal use and to report their progress to the public. The MWG report notes that no one set of metrics can be used by all ICCVAM member agencies and recommends that each agency develop its own metrics that are relevant and practical to its unique situation and to communicate those metrics transparently to the public online. Thus, to address the recommendation of the GAO, agencies must build on this report by developing strategies to compile data on animal use. It appears that some agencies are in the process of doing so, while it is unclear for others (e.g., the U.S. Food and Drug Administration,[16] the U.S. Geological Survey,[17,18] and the U.S. Consumer Product Safety Commission).[19] We congratulate ICCVAM member agencies on their commitment to metrics development, and we encourage agencies to follow through on the GAO recommendation by developing metrics and

[15]ICCVAM. Measuring U.S. Federal Agency Progress Toward Implementation of Alternative Methods in Toxicity Testing. Available at https://ntp.niehs.nih.gov/iccvam/docs/about_docs/iccvam-measuringprogress-feb2021-fd-508.pdf
[16]US FDA. Advancing Alternative Methods at FDA. Accessed May 9, 2022. Available at https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda
[17]USGS. Accessed May 9, 2022. Assessing Contaminant Hazards Without a Critter—Advancements in Alternatives to Animal Toxicity Testing. Available at https://www.usgs.gov/programs/environmental-health-program/science/assessing-contaminant-hazards-without-critter#overview
[18]USGA. Accessed May 9, 2022. Available at https://www.usgs.gov/mission-areas/ecosystems/area-animal-welfare-assurance
[19]CPSC. Recommended Procedures Regarding the CPSC's Policy on Animal Testing. Accessed May 9, 2022. Available at https://www.cpsc.gov/Business--Manufacturing/Testing-Certification/Recommended-Procedures-Regarding-the-CPSCs-Policy-on-Animal-Testing

communicating them to the public. As a starting point, a framework for developing metrics tracking animal use relative to the application of NAMs was published in 2021, which we encourage ICCVAM member agencies to review.[20]

We look forward to continuing to collaborate with ICCVAM and its member agencies to further advance non-animal test methods.

Thank you for considering these comments. If you have any questions, please contact us.

Sincerely,

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[20]Marty MS, Andrus AK, Groff KA. Animal metrics: Tracking contributions of new approach methods to reduced animal use. ALTEX. 2022;39:95–112. https://doi.org/10.14573/ALTEX.2107211