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Dr. Nicole Kleinstreuer
Director, NICEATM
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Dear Dr. Kleinstreuer,

The following comments are submitted on behalf of People for the Ethical Treatment of Animals (PETA) in response to the April 12, 2023 Federal Register notice by the National Institutes of Health (88 FR 22050).

We commend the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) for their continued development and implementation of robust non-animal testing strategies that protect human health and the environment. Our comments specifically address establishing confidence in new methods and ensuring the timely uptake of established methods.

Framework

While the development of robust non-animal testing approaches has accelerated, validation and regulatory acceptance of these methods have not kept pace. There is widespread recognition that—while the principles of validation hold true—the processes need to be updated to allow for timely uptake of the most reliable and relevant scientific tools that will best protect human health and the environment. We congratulate ICCVAM on its effort to develop a framework for transparently and consistently establishing scientific confidence in test methods. The framework will allow for the strengths and limitations of existing and new test methods to be evaluated based on their intended purposes and ability to reliably provide information that is biologically relevant. We look forward to the release of this framework and its swift adoption by ICCVAM agencies to meet the pressing demand for the prompt implementation of non-animal methods to fulfill regulatory data needs.

Stakeholder engagement

To facilitate scientific confidence in new testing approaches, it is essential to engage all stakeholders, including regulators and the regulated community, government, academics, non-government organizations, and the public. Communicating with stakeholders about new test methods and how the data from these methods are interpreted and used in regulatory decision making is important to ensure the timely uptake of scientifically-sound non-animal testing approaches and prevent the spread of misinformation. Many non-animal test methods have been demonstrated to be as or more reliable and relevant than

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tests on animals.[1–11] They also provide an opportunity for higher throughput, allowing for faster removal of potentially dangerous chemicals from the market and preventing potentially toxic chemicals from ever reaching the market in the future. These benefits are essential to ensure the protection of the environment and humans, in particular those disproportionately affected by chemical exposure (e.g., fenceline communities, those with pre-existing conditions, those more sensitive to certain chemicals, and other vulnerable populations, such as pregnant people and children). We encourage ICCVAM agencies to continue to engage the stakeholder community.

Coordination

It is essential that ICCVAM continues to coordinate nationally and internationally across sectors. Industry and regulatory agency uptake of non-animal methods that are as good as or better than traditional animal tests could be expedited with improved coordination and communication within and across agencies. In particular, when a test method undergoes an extensive validation process and gains acceptance at an international standards-making organization, it should not be necessary for each agency to extensively re-validate this method. For example, in 2010, the Organisation for Economic Co-operation and Development (OECD) published test guideline (TG) 439, the reconstructed human epidermis (RhE) test for skin irritation testing (last updated in 2021). In 2018, the OECD TG was adapted for an International Organization for Standardization (ISO) sponsored interlaboratory validation study of medical device extracts. Results were essentially equivalent to those obtained with *in vivo* tests,[12] leading ISO to publish a new ISO 10993-23 standard on skin irritation testing that gives preference to *in vitro* methods for evaluating medical devices. Given the existing extensive validation of RhE models for skin irritation and the Food and Drug Administration's (FDA's) participation in the ISO study, the FDA Center for Devices and Radiological Health should fast-track acceptance of this method.

Policies

We urge ICCVAM member agencies to swiftly enact policies that clearly indicate their acceptance of new testing approaches. For example, robust non-animal test methods are available for anti-caries testing of over-the-counter fluoridated toothpastes, and the FDA must adopt policies that allow and encourage their use. In a 2001 Advance Notice of Proposed Rulemaking (ANPR), the FDA requested information and comments on intra-oral appliance models as replacements for the rat caries test to demonstrate the availability of fluoride in over-the-counter dentifrice formulations. In the 20 years since FDA's initial request, studies have continued to demonstrate the human relevance of the available animal-free methods, and anticaries test methods have been included as a planned proposed order in the FDA's Over the Counter monograph annual forecast for the past two years, yet there has not been a public statement on the outcome of the ANPR or a final rule issued. As another example, the EPA Office of Pesticide Programs released its guidance for waiving acute dermal toxicity tests for pesticide formulations and supporting retrospective analysis in November 2016,[13] while the similar guidance for pesticide technical chemicals was not released until December 2020.[14] While the data analysis and guidance drafting accounts for about half of that time, this means an approximately two year delay for the policy to be approved by the Office of Management and Budget.

Overall, to best protect human health and the environment, we need mechanisms that allow for the rapid uptake of new testing approaches that are as good as or better than currently used test methods. We encourage ICCVAM agencies to take advantage of opportunities to increase efficiency in accepting valid approaches, and we are happy to help in these efforts.

Thank you for considering our comments.

Sincerely,
(signature redacted)

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