AN INTERNATIONAL ORGANIZATION DEDICATED TO PROTECTING THE RIGHTS OF ALL ANIMALS

PETA

PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

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September 11, 2024

Dr. Milene Brownlow
Designated Federal Officer for SACATM
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Dear Dr. Brownlow and SACATM members,

These comments are submitted on behalf of People for the Ethical Treatment of Animals (PETA) in response to the National Institutes of Health's August 2, 2024 Federal Register Notice "Scientific Advisory Committee on Alternative Toxicological Methods; Notice of Public Meeting; Request for Public Input" (89 FR 63207).

ICCVAM biennial report

We commend the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) for their success in advancing the development and use of reliable and relevant non-animal approaches for assessing toxicity. The ICCVAM 2022-2023 Biennial Progress Report details numerous important projects with potential to reduce animal use in toxicity testing and increase protections for human health and the environment.

The recently launched Method Developers Forum highlights ICCVAM's dedication to implementing the ideas described in its 2024 report on "Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies" by creating a space for dialogue between regulators, method developers, and relevant stakeholders. In future forum discussions, we hope to see more engagement from all ICCVAM member agencies on relevant topics. Efforts such as these, that bring together multiple stakeholders and regulatory agencies, are vital to advance new methods.

Whether the Method Developers Forum, the annual ICCVAM Public Forum, the annual SACATM meeting, or other meetings, we ask that SACATM encourage ICCVAM member agencies to send subject matter experts and decision-makers who are enthusiastic to actively participate in meetings in which the advancement of reliable and human-relevant non-animal testing approaches are discussed. For example, progress in the implementation of established non-animal approaches for toxicity testing has been stalled at the Food and Drug Administration (FDA) in areas such as UV filters, fluoridated toothpastes, medical devices, and shellfish because of a lack of productive and progressive dialogue that includes relevant stakeholders alongside FDA reviewers, experts, and decision-makers.

The ICCVAM Biennial Progress Report highlights developments in computational toxicology, including the CATMoS model, the Open (Quantitative) Structure-activity/property Relationship App (OPERA), and the Integrated Chemical Environment (ICE), among others. The Environmental Protection Agency participated in a webinar on August 28th that clarified their thinking on the CATMoS model and its application to pesticide assessments within the agency. We urge SACATM to advise additional ICCVAM member agencies to clarify their pathway for consideration and regulatory acceptance of newly developed approaches in computational toxicology as the development of a model, or even the publication of a guidance document, does not necessarily translate into its adoption by industry and regulators.

Validation of non-animal methods

ICCVAM's report on "Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies" outlines a process for establishing confidence in a method. The report reiterates that many animal toxicity tests lack reproducibility and/or human-relevance and that newer, non-animal methods may have the ability to provide more reliable and biologically relevant information as well as mechanistic insights. Thus, the results from non-animal testing should not be expected to directly replicate the results of the traditional tests on animals. Instead of relying on direct comparisons between animal and non-animal data, agencies should ensure that new methods fulfill their intended purposes and provide technically reliable information that is relevant to the understanding of human biology and health protective for the endpoint of concern.

For the reasons above, SACATM should encourage ICCVAM member agencies to ensure that staff are following a thorough yet efficient process to establish confidence in new methods that keeps pace with advances in science and the most health protective testing approaches. For example, the reconstructed human epidermis (RhE) test for skin irritation testing has been assessed by numerous countries and agencies and has been an Organisation for Economic Co-operation and Development (OECD) test guideline (TG 439) since 2010. The need for such a method was supported by a publication showing substantial variability in the traditional rabbit skin irritation test and issues obtaining the same hazard classification when the test is repeated (Rooney et al., 2021). Another recent publication assessed all available *in vivo, in vitro,* and *ex vivo* methods for their relevance to mechanisms of human skin irritation and concluded that the non-animal methods were as, if not more, relevant to human biology than the currently accepted *in vivo* test (Raabe et al., 2024). In 2018, the *in vitro* RhE test was adapted for an International Organization for Standardization (ISO)-sponsored interlaboratory validation study of medical device extracts, in which 16 laboratories, including the FDA, participated. The publication on this round robin study, which included FDA coauthors, concluded that "the results demonstrate that RhE tissues are a robust model for the detection of irritant activity, and can be used for the identification of low levels of strong irritants in medical device extracts" (De Jong et al., 2018). As a result, ISO published a new ISO 10993-23 standard on skin irritation testing that gives preference to *in vitro* methods for evaluating medical devices. This ISO standard is now recognized by the European Union member states, Australia, Japan, and China. However, the method has yet to be accepted by the FDA, which continues to ask for increasingly more data. This example demonstrates how lack of coordination and a defined process for characterizing new methods slows scientific progress.

NAMs Pipeline – Future Directions

We are pleased to see ICCVAM member agencies develop innovative programs to advance the development of non-animal methods and establish confidence in their use. We look forward to seeing progress within the Complement Animal Research in Experimentation (Complement-ARIE) program in advancing the use and regulatory acceptance of non-animal methods. Complement-ARIE also provides an opportunity to facilitate a transition to the use of animal-free reagents in funded research as opposed to the use of their more variable counterparts (such as fetal bovine serum and animal-derived antibodies).

Sincerely,

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Works Cited

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