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May 14, 2024

Nicole Kleinstreuer, Ph.D.
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Dear Dr. Kleinstreuer,

On behalf of People for the Ethical Treatment of Animals (PETA), we thank the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) for the opportunity to comment on its goals and activities to advance the development, regulatory acceptance, and use of non-animal test methods that protect human health and the environment. Our comments specifically address developing guidance to facilitate the uptake of non-animal methods, updating strategies for gaining scientific confidence in the regulatory acceptance of new testing approaches, and embracing opportunities to integrate non-animal methods in specific areas.

Guidance to facilitate uptake of modern test methods

Timely formal acceptance of and guidance on the use of non-animal methods for regulatory purposes is needed for successful uptake. Importantly, the Food and Drug Administration (FDA) should enact a policy to clarify acceptance of the use of *in vitro* reconstructed human tissue models for assessing skin irritation potential of medical device extracts that have been extensively validated, are included in an International Organization for Standardization (ISO) standard, and are accepted by the European Union member states, Australia, Japan, and China. This *in vitro* skin sensitization method is one of several that have been stalled for years in the FDA's inefficient Medical Device Development Tools (MDDT) program, along with well-established methods for pyrogenicity and vaginal irritation assessment, leaving regulated industries in recognition that regulators in the United States are lagging behind other countries in continuing to require data from animal tests.

In addition to enacting policies to advance the use of non-animal test methods, ICCVAM member agencies should ensure that policies do not introduce barriers to the adoption of non-animal methods when they are updated. For example, when industry initiates an Over-the-Counter Monograph Order Request (OMOR) with the FDA to update a monograph (such as M021: Anticaries Drug Products for Over-the-Counter Human Use), it may be subject to a substantial fee, thereby hindering the replacement of outdated test methods with improved methods that better protect human health. The FDA should initiate timely monograph updates when updated safety or efficacy test methods are warranted and should institute a free process for nominating updates. Similar to the fee waiver granted to OMORs that strengthen drug safety via drug facts labeling, OMORs that modernize test methods, including updates to incorporate methods that reduce and replace the use of animals in testing while best protecting human health and safety, should warrant fee waivers.

We commend the transparency in the Environmental Protection Agency (EPA) Office of Pollution Prevention and Toxics' (OPPT's) new eye irritation decision framework, which discourages the use of the *in vivo* rabbit Draize test in favor of approaches using human cells and other non-animal methods that assess the range of severity of eye irritants from corrosive to non- or minimally irritating substances. The EPA Office of Pesticide Programs (OPP) also recently updated the webpages on its Strategic Vision

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for Adopting New Approach Methodologies.[1] To provide further clarity and uptake of these methods, the EPA OPP should also publish more formal guidance or notices on its acceptance of non-animal testing approaches. These steps in the EPA's progress towards adopting modern, non-animal methods allow it to make better informed decisions regarding the potential risks of chemical exposure to humans and the environment. To continue to progress, the EPA should ensure that any 'me-too' or similar methods added within Organisation for Economic Co-operation and Development (OECD) test guidelines are automatically included in EPA guidance and that any new OECD test guidelines are accepted with no or little re-validation.

Alongside the enactment of guidance, agencies should collect metrics on submissions using animal and non-animal test methods to help evaluate their impact. The European Union has a history of reporting animal numbers, species, and use of animals in Member States, and the European Commission notes, "To progress towards the ultimate goal of full replacement, it is crucial to understand where, how and why animals are still required to be used for scientific purposes." The EPA OPP has taken a step towards reporting,[2] and it would be useful to see further details as well as additional ICCVAM member agencies taking such steps.

Updating strategies for gaining scientific confidence

Earlier this year, ICCVAM published *Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies*, a report on establishing confidence in new toxicological test methods.[3] The document includes an emphasis on assessing biological relevance when validating new methods rather than solely relying on direct comparisons to *in vivo* animal data, and it acknowledges that new testing approaches may provide better quality and more relevant information for regulatory decision-making than traditional animal test methods. ICCVAM member agencies should update their validation strategies accordingly to meet the pressing demand for the prompt implementation of non-animal methods to fulfill regulatory data needs, and they should never prospectively request the generation of animal data to validate a new method.

A specific area where the updated ICCVAM report, *Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies*, can be applied today is to the FDA's regulation of sunscreen active ingredients. For decades, sunscreens have been safely used by millions of people around the world to prevent skin cancer—the most common type of cancer. Nevertheless, the FDA is demanding animal data to keep these products on the market and show they are safe to use. The FDA should align with the goals of its *Predictive Toxicology Roadmap*[4] and the ICCVAM validation report to answer any questions it may have about sunscreen ingredients, specifically by using modern, non-animal testing approaches and the evidence drawn from years of safe product use in humans.

Embracing opportunities

ICCVAM member agencies should embrace opportunities where non-animal approaches can be quickly implemented and tests on animals avoided. For example, for both scientific and ethical reasons, there is an urgent need to gain regulatory acceptance of methods that can be used to assess tobacco products (in particular, in the spaces of inhalation toxicity and genotoxicity). Several *in silico* and *in vitro* methods are available to conduct a robust toxicity analysis of products regulated by the FDA's Center for Tobacco Products (CTP). In cases where the results do not allow for a clear conclusion on the product's toxicity, CTP should simply not allow the product on the market or only allow it with mandated clinical post-market surveys. After all, any tobacco and tobacco-derived product poses a potential health risk of which the

[1] U.S. Environmental Protection Agency. Strategic vision for adopting new approach methodologies. Accessed May 13, 2024. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-new-approach
[2] U.S. Environmental Protection Agency. Strategic vision for adopting new approach methodologies – metrics. Accessed May 13, 2024. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-new-approach-0
[3] Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Validation Workgroup. *Validation, qualification, and regulatory acceptance of new approach methodologies*. March 2024. https://doi.org/10.22427/NICEATM-2
[4] U.S. Food and Drug Administration. *FDA's predictive toxicology roadmap*. December 2017. Accessed May 13, 2024. https://www.fda.gov/science-research/about-science-research-fda/fdas-predictive-toxicology-roadmap

consumer is aware. No animals should suffer for the assessment of these voluntary use products (or purely for marketing reasons in the case of Modified Risk Tobacco Products).

Non-animal affinity reagents also can be rapidly adopted in place of animal-derived antibodies. While antibody development is often not the primary outcome of projects, antibodies are commonly used and essential tools in research. The scientific advantages of animal-free antibodies are well established, and there is now a need for researchers to devote resources and make changes in their specific projects. Some organizations are beginning to include information about antibodies in funding guidelines. For example, in 2023, Colgate-Palmolive noted a preference for animal-free antibodies in their Society of Toxicology awards for alternative research and student research training in alternative methods, and the awards state that the type and source of antibodies must be described.[5,6] Requiring grant applicants to assess their proposed antibodies in each project is one approach to encourage the analysis of antibodies. This analysis is important to address research quality as the use of traditional, animal-derived antibodies is a driver of the reproducibility crisis in research.

Thank you for considering our comments.

Sincerely,

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[5] Colgate-Palmolive Award for Student Research Training in Alternative Methods. Accessed May 14, 2024. https://sotapply.toxicology.org/prog/colgate-palmolive_award_for_student_research_training_in_alternative_methods/
[6] Colgate-Palmolive Grant for Alternative Research. Accessed May 14, 2024. https://sotapply.toxicology.org/prog/colgate-palmolive_grant_for_alternative_research/