PhysiciansCommittee
for Responsible Medicine
PCRM.ORG
5100 Wisconsin Ave. NW, Suite 400 • Washington, DC 20016 • Tel: 202-686-2210 • Fax: 202-686-2216 • pcrm@pcrm.org

May 15, 2024

Dr. Nicole Kleinstreuer, Director
National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

RE: 2024 ICCVAM Public Forum

Dear Dr. Kleinstreuer and ICCVAM Committee Members:

Thank you for your very important work towards integrating testing strategies that protect human health and the environment while replacing and reducing animal use. Advancing new methods takes hard work, dedication, and strong leadership, which NICEATM and ICCVAM leaders consistently demonstrate. We appreciate the opportunity to provide input on NICEATM and ICCVAM activities.

Policy Updates
As we all have come to learn, integrating new methods involves so much more than developing and evaluating the science. New approaches begin at a disadvantage due to decades of inertia supporting animal use, making policies that support the use of new approaches a key part of advancement. We consistently hear from certain agencies that animal tests are not required, despite written regulations and guidance that require, recommend, and favor animal use. In some instances, there is a clear disconnect in agency view of policies and how stakeholders view the policies. Whether or not agencies agree that written policies appear inflexible, they are understood to be so. Therefore, it is incumbent upon agencies to take a leadership role to amend policies to account for the intended flexibility. Companies need regulatory certainty as part of confidence building in using new approaches. **We ask ICCVAM agency representatives to spearhead this work within their organizations.**

Training Programs
The Physicians Committee commends the EPA on its commitment to a dedicated NAMs training program. Websites such as the EPA NAMs Training page provide an important, trusted source of information. In the past year, the EPA has offered virtual training on GenRA, and httk, and in-person training that covered many NAMs. Dedicated training programs like this are essential to establishing confidence among regulators and end users. **We ask the EPA to continue offering training, and request that other agencies also offer virtual and in-person opportunities for training on methods relevant to respective agencies.**

We also appreciate that NICEATM and ICCVAM member agencies participate in external trainings and conferences. On May 23, NICEATM director Dr. Nicole Kleinstreuer is presenting

via a New Approach Methodologies Use in Regulatory Application (NURA) webinar on ICCVAM's report on Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies. We are thankful that NICEATM and ICCVAM representatives continue to present on NAMs at conferences, such as the Society of Toxicology Annual Meeting, the American Society for Cellular and Computational Toxicology (ASCCT), and the Physicians Committee's 2024 Summer Immersion on Innovative Approaches in Science. **We ask ICCVAM agencies to continue prioritizing scientific outreach.**

Metrics

After years of work to implement new methods with replacement and reduction of animal use as goals, metrics are still lacking to evaluate success. **We ask agencies to publicly report on numbers of animals submitted to and used by agencies, by species, endpoint, and assay.**

EPA

The EPA continues to be a leader in advancing NAMs, and we are grateful for the many activities the agency undertakes in order to integrate methods that reduce and replace animal use. That said, we have a few comments to help further reduce animal use.

NASEM Framework Expands NAMs' Regulatory Application

Following last year's ICCVAM public forum, the National Academies of Science, Engineering and Medicine (NASEM) published its report, "Building Confidence in New Evidence Streams for Human Health Risk Assessment." The EPA originally requested that NASEM review the variability and relevance of existing mammalian toxicity tests to inform approaches for establishing scientific confidence in using NAMs. The NASEM Committee stressed that EPA should only compare test methods after each is evaluated independently and noted that some *in vivo* methods include more categories than warranted based on their variability. Importantly, to enable the creation of new NAM-based evidence streams for both hazard identification and dose-response assessment, the Committee proposed the use of parallel PECO (Population, Exposure, Comparator, and Outcomes) statements – an intended target human PECO and a test method PECO – for both mammalian and nonanimal test methods. Further, the Committee urged EPA to work with partners to develop a harmonized registry of toxicity test methods documenting their purpose and context of use (including parallel PECO statements), validity, and variability. We strongly support these recommendations and offers continued partnership in developing such a registry. **We ask that EPA update its List of Alternative Test Methods and Strategies under the Toxic Substances Control Act (TSCA) to include new guidelines and policies, such as EPA's decision framework for evaluating eye irritation, alternatives for Tier 1 screening assays in the Endocrine Disruptor Screening Program, and integrated approaches for reviewing biofuels and mixed metal oxides.**

The NASEM Committee also recommended that EPA broaden its definition of NAMs to exclude "avoiding the use of intact animals." We continue to advocate for reducing animal use *without* conducting new animal tests. This year, EPA's ORD unveiled its Transcriptomic Assessment Product (ETAP), a 5-day exposure study to determine permissible chemical exposure limits for chemicals that lack toxicity test data. To the extent that fewer animals are exposed for less time, if adopted, the ETAP promises to reduce and refine animal use compared to traditional toxicity studies; until then, however, it is an additional study that increases animal use in the short term.

While the ETAP predicts adverse outcomes in animals, the relevance of the changes observed to human outcomes is still questionable. **We urge EPA to intensify its efforts to fully replace traditional animal toxicity studies by developing predictive methods, such as transcriptomics and metabolomics, in cells and reconstructed tissues of human origin.**

FDA

New Alternative Methods Program

We commend the FDA on establishing the New Alternative Methods Program to advance cross-cutting, agency-wide efforts to support nonanimal innovation for more predictive testing, streamlined medical product development, and reduced animal use. We continue to support this important and groundbreaking program, and urge the FDA to provide further detail about the short- and long-term goals, activities, and timelines involved within this initiative. Given that the program received taxpayer funds for the past two funding cycles, we believe greater public transparency on plans and progress of this program is warranted. **We encourage the FDA to establish a publicly available work plan for the New Alternative Methods Program to provide transparency and help guide and measure progress toward the program's crucial goals.**

Within this work plan, it will be important to include plans for: updating policies to communicate acceptance of NAMs, increasing access for NAMs to be qualified, publicly tracking which NAMs have been accepted and total numbers of animals used in tests, assessing staffing needs for program goals, providing NAMs trainings for staff, and evaluating NAMs based on human data as much as possible. We ask that there be public opportunity to provide input on planning for New Alternative Methods Program priorities, and that updates on work plan activities are regularly reported to the public.

Center for Tobacco Products

We thank CTP for addressing the many comments that CTP received in response to its Strategic Plan that express broad public support for avoiding animal use in testing tobacco products. While we appreciate CTP's support for developing innovative nonanimal test methods relevant to human exposure, these methods apply primarily to the assessment of products that present significant risks or novel scientific issues. As we noted last year and documented in our comments on the *Strategic Plan*, thousands of animals have already been used in testing to support the few PMTAs that have so far been approved, while PMTAs for similar products have been approved without new animal test data. **To avoid animal use in testing that CTP does not need to make these determinations, we ask FDA to promulgate clear regulations and guidance**. Among the priorities identified in its *Regulation and Guidance Policy Agenda*, CTP includes Investigational Tobacco Product (ITP) applications. We support comments on FDA's 2019 draft guidance on the use of ITPs calling for regulations that apply a risk-based approach to their authorization. Excluding animal test data from preclinical requirements for products with well-understood risks and attributes would facilitate conducting definitive clinical studies of ITPs with current tobacco users, providing the human-relevant data CTP needs without animal use. We welcome continued engagement with CTP to avoid animal use in testing tobacco products as it implements its *Strategic Plan*.

NIH

Advancing NAMs at the NIH

As we will hear in this meeting, the NIH is making great progress toward the broader development and use of NAMs in biomedical research. The Advisory Committee to the Director NAMs Working Group made its final set of recommendations in December, which were then accepted by the agency in February. The newly approved Complement Animal Research in Experimentation (Complement-ARIE) Common Fund Program will soon begin implementing some of the Working Group's recommendations, and ICCVAM and the National Center for Advancing Translational Sciences (NCATS) will no doubt play an important role as well. An NIH-wide investment in more ethical and effective nonanimal, human-specific methods will benefit patients, animals, and the drug development economy. **The Physicians Committee commends these efforts to advance NAMs at the NIH.**

The Common Fund has engaged in innovative and exemplary strategic planning activities for the Complement-ARIE Program. First, like NCATS's recent comprehensive public engagement in its strategic planning process, including through external stakeholder meetings and public roundtables, the Common Fund hosted a series of listening sessions to gather broad stakeholder input on the goals and structure of the forthcoming Complement-ARIE Program. In addition, the Common Fund hosted a crowdsourcing competition for innovative ideas NAMs as part of the strategic planning process to refine the Complement-ARIE program concept. This Complement-ARIE Challenge prize competition offered $1,000,000 in total prize money to diverse teams with ideas for new ways of using NAMs to conduct basic research, uncover disease mechanisms, and translate knowledge into products and practice. Finally, by offering two public opportunities for written feedback on the NCATS Strategic Plan for 2024–2029—first on the goals and themes of the plan, then more recently on the pre-decisional draft of the plan—NCATS has demonstrated what comprehensive strategic planning consultation looks like. **The Physicians Committee applauds these strategic planning efforts that comprehensively engage federal and non-federal stakeholders and encourages NCATS, Complement-ARIE, and ICCVAM to share the success of these approaches with other NIH institutes, centers, and offices, as well as the NIH-Wide Strategic Plan team to inspire similar efforts.**

Among the many great recommendations from the Advisory Committee to the Director NAMs Working Group that we look forward to seeing further explored is regarding the important role scientific review plays in the successful use and deployment of NAMs. Although the NIH Center for Scientific Review cannot train reviewers how to evaluate NAMs, funding opportunity announcements can specify review criteria to ensure that the unique value of NAMs is properly evaluated by scientific review groups. It is important that Complement-ARIE and other programs intending to invest in NAMs research implement such criteria. Other measures that can help ensure NAMs are fairly evaluated include: (1) broadening the pool of NAMs expertise available for scientific review groups, (2) creating NAMs-specific funding streams so that NAMs projects are not competing with animal-based projects, and (3) training reviewers to identify, address, and report incidences of animal methods bias. The NIH Center for Scientific Review is already working to implement this last measure by expanding its Bias Awareness and Mitigation Training for reviewers, chairs, and Scientific Review Officers to include information and vignettes about scientific bias—the preference for one's own science or approach—an umbrella concept under which animal methods bias can be considered.

As the NIH continues to implement the many great recommendations from the Advisory Committee to the Director NAMs Working Group, **we encourage the agency to parallel the aforementioned spirit of robust public engagement and accountability by making as many metrics of progress, success, and impact publicly available as possible through data dashboards, frequent reports, webinars, and other venues.**

OECD

The US is an active participant in OECD Test Guidelines programme activities. We appreciate the commitment to NAM-centered projects on the Test Guidelines Programme workplan, such as the Defined Approach to Skin Sensitization project, Respiratory Sensitization project, and the important update of Guidance document 34. **We ask that efforts such as these be prioritized by relevant ICCVAM agencies to facilitate harmonized, global use of non-animal approaches.**

Our team appreciates NICEATM and ICCVAM's continued commitment to advancing science while reducing animal testing. We look forward to continued collaborations that support new science, policy, and training.

Sincerely,

(signature redacted)

Elizabeth Baker, JD (and team)
Director of Research Policy
Physicians Committee for Responsible Medicine
ebaker@pcrm.org