PhysiciansCommittee
for Responsible Medicine
PCRM.ORG
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May 19, 2023

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

RE: 2023 ICCVAM Public Forum

Dear Dr. Kleinstreuer and ICCVAM Committee Members:

Thank you for your continued commitment to developing, evaluating, and integrating testing strategies that protect human health and the environment while replacing and reducing animal use. Both NICEATM and ICCVAM are comprised of leaders that are willing to do the hard work of advancing science. There are so many reasons to do so, including advancing human health, scientific innovation, and saving animals. But, as many of us have come to understand, developing and evaluating science is just one important factor in advancing new approaches. Policies that govern testing must also advance. And we must provide training to those that use and review these approaches. We appreciate the opportunity to share ideas that we believe complement the great progress that NICEATM and ICCVAM leaders are accomplishing.

There are a number of considerations that apply to multiple agencies.

Validation Standards
For many years, we have heard that whole animal studies were the standard by which new approaches should be validated. In recent years, criticisms arose and grew, largely because many new approaches were developed out of scientific need to do better than the traditional animal studies they seek to replace. We commend NICEATM for its efforts to retrospectively evaluate the performance of animal studies, as it is important to take a hard look at, and better understand the capabilities and limitations of existing methods, particularly when these methods are held as a so-called gold standard. **We ask ICCVAM agencies to make every effort to use human information to evaluate human-specific models, and if it is determined that animal data are needed, to work with agency partners to use existing data.**

Policy Updates
As new strategies become available, policies must keep pace. There is such inertia behind animal use, and many in industry wait for clear written policy communications from agencies regarding acceptance of NAMs. **We ask ICCVAM scientists to work alongside policymakers at agencies to ensure policies are updated to explicitly allow for NAM use.**

Training
More and more, we hear from scientists of diverse backgrounds and career stages, that they want more NAMs training. Training is crucially important because it can demonstrate the robustness of NAMs and how to interpret data from them to increase their acceptance for regulatory decision-making practices. Multiple NGOs, including the Physicians Committee, have experience planning and hosting trainings. **We ask ICCVAM agencies to leverage these partnerships and provide more training opportunities to staff.**

Metrics
Despite commitments to reduce and replace animal use, the number of animals used in research and testing in the U.S. remains unknown. This should no longer be deemed acceptable because it prevents NICEATM, ICCVAM, and interested parties from measuring the progress of these efforts and from identifying additional opportunities to reduce animal use. We understand that there are inherent challenges around collecting and reporting this information, and we urge ICCVAM to support innovative solutions to these issues, such as those being developed in the AI4Tox program of the National Center for Toxicological Research. **We ask ICCVAM agencies to track the numbers of animals submitted by species, test, and endpoint, and to make these metrics publicly available.**

We also have specific input based on the presentations listed in the meeting agenda.

EPA Office of Pesticide Programs
Environmental Justice
Through a proposed ENVJ working group in the chartered Pesticide Programs Dialogue Committee, **we encourage EPA leadership to engage with stakeholders and explore how NAMs can fulfill ENVJ objectives more effectively, efficiently, and relevantly to diverse and vulnerable communities.**

Endocrine Disruptor Screening Program
In collaboration with ORD, OPP announced the availability of NAMs as alternatives for Tier 1 screening assays in the Endocrine Disruptor Screening Program. We welcome this historic application of high-throughput *in vitro* and computational toxicology methods to overcome the limitations of animal toxicity testing in prioritizing the approximately 10,000 potential endocrine disruptors for further testing. By identifying the substances of greatest concern, these pathway models will enable EPA to better target its resources, hastening needed public health protections for vulnerable subpopulations. Further, while PCRM supports the fit-for-purpose, performance-based approach it used to establish scientific confidence in their use, we are disappointed that in the eight years since EPA proposed using these methods, several of the proprietary assays required have been discontinued and access to others remains limited. **To fully realize the benefits of this approach over expensive ring-trials, we urge EPA to consider these limitations and to accept alternatives for the remaining EDSP Tier 1 assays, which use a greater number of animals, in a timely manner.**

EPA Office of Pollution Prevention and Toxics
We continue to support OPPT's approach to determining the potential risk of new chemicals as introduced in its 2019 *Decision-Making Framework* and modified in 2021, under the current

administration**.** By affirming EPA's preference for tiered testing and non-vertebrate testing strategies, as well as by more generally describing the information to help characterize potential health and environmental effects, rather than by listing specific recommended tests, these policies eliminated a ten-fold spike in animal testing requirements documented in the first year of the Lautenberg Chemical Safety Act's implementation. Further, by publishing chemical submissions in nearly real-time, we are now able to track voluntary data submissions, enhancing our communication to notice submitters to first attempt to develop information by means of alternative test methods or strategies before conducting new vertebrate animal tests. **We welcome OPPT's redesign and update of its statistics webpage with metrics on the Agency's review process under TSCA and encourage it to also measure progress on reducing animal use by chemical manufacturers**

Late last year, EPA's Board of Scientific Counselors evaluated the New Chemicals Collaborative Research Program. We enthusiastically support this implementation of ORD's next generation blueprint for computational toxicology, which includes advancements in category identification, read-across, QSARs, predictive models, NAMs-based tiered testing, and an updated TSCA chemical information management system to support new data streams, facilitate sharing, and enable iterative refinement of the evaluation process. **We look forward to continued updates on the collaboration's progress and opportunities for participation.**

Regarding existing chemicals, we are encouraged by Assistant Administrator Freedhoff's recent description of OCSPP's new approach to existing chemical evaluations, and especially by her suggestion that the Agency would seek public comment on its draft risk conclusions; we hope that this participatory approach will extend to all TSCA section 4 testing proposals, such as those for PFAS chemicals. As NAMs efficiently make relevant information available for EPA's consideration when identifying the best available science, they are ideally suited to such a pragmatic approach, and we look forward to once again providing the Agency with our input. We fully support EPA's ongoing partnership with the National Toxicology Program to test representative PFAS in high-throughput, tiered toxicity assays evaluating toxicological endpoints including toxicokinetics and urge EPA to integrate these assays into its ongoing PFAS testing program at the first opportunity.

FDA Advancing Alternatives for Regulatory Use

New Alternative Methods Program

We are thrilled that the FDA has put forth its New Alternative Methods Program, an agency-wide effort to innovate and improve testing outcomes while reducing animal use, in its budget requests to Congress over the past two years. Important aspects of the program will include providing greater access for NAMs to be evaluated and integrated in the agency's qualification programs, and policy updates to accommodate acceptance of NAMs. **Given that the NAMP is funded by public funds, we ask that the public be given opportunity to participate in its planning, that near- medium- and long-term goals be identified in a publicly shared planning document, and that progress toward achieving NAMP's goals be regularly reported.**

National Center for Toxicological Research
Budget requests over the past two years also included funding to support FDA's Predictive Toxicology Roadmap. We are concerned that the National Center for Toxicological Research intends to use these funds to conduct new animal testing. **We urge the FDA to prioritize a strategy that avoids conducting new animal tests.**

At the recent NCTR Scientific Advisory Board meeting, we were disappointed to learn that a much-needed project to organize CDER guidance was turned away by the Division of Bioinformatics and Biostatistics due to lack of resources. Our recently published analyses of animal use summarized in reviews of New Drug Applications for approved drugs consistently revealed opportunities to significantly reduce animal use simply by clarifying guidance to industry. **We urge ICCVAM to investigate how this guidance update project can be revived, and gladly offer whatever support we can.** In addition, we were excited to learn more about the the Division's innovative projects, including AnimalGAN to develop virtual animal models to simulate animal study results using AI and SafetAI to develop AI models for toxicological endpoints to assess drug safety. We look forward to increased participation in these efforts.

OECD Activities
Within the OECD, work to support replacing animal tests with in vitro test methods ensures a meaningful reduction in animal use by global harmonization of test methods. We appreciate these efforts and support projects co-lead by ICAPO, the International Council on Animal Protection in OECD programs.

National Cancer Institute
CAR-T cell therapies are ground-breaking, life-saving technologies that demonstrate the inadequacy of animal methods to address 21st century needs. We are excited to see NCI developing and supporting in vitro methods to evaluate the safety of these therapies, that have extraordinarily high risk for fatal adverse reactions from tumor lysis syndrome, thereby making these therapies available to more patients.

NICEATM Tools Update
Computational toxicology is a hallmark of 21st century toxicology and we commend NICEATM not only for it's at development of state-of-the-art, open-access comptox tools but also for its ongoing commitment to continuing education in this area, breaching generational divides to make comptox methods as accessible as possible.

NICEATM continues to champion scientifically sound and objective evaluation of not only in vitro and in silico methods, but also of the in vivo methods that were adopted before formal validation processes were established. We appreciate NICEATM's efforts to address long-held assumptions about the value of animal testing methods used for acute toxicity and work toward establishing reasonable and objective performance standards for NAMs. In particular, we appreciate NICEATM's leadership in redefining human health as the gold standard for human health risk assessment.

US Department of Agriculture
We continue to seek easily accessible and understandable metrics regarding research animal use under the Animal Welfare Act. **We encourage the USDA to generate open-access summaries of research animal use over time so that progress in reduction and refinement can be measured and additional opportunities to reduce animal use can be identified.**

FDA Center for Tobacco
We thank FDA CTP for responding to our FOIA request for nonclinical study reports supporting Premarket Tobacco Product Applications for similar Electronic Nicotine Delivery Systems from two manufacturers. It appears that one application was granted marketing approval, appropriately, on the basis of results from an established *in vitro* test battery and from ethically conducted clinical studies, while the other application also included results from 14- and 90-day inhalation studies in rats on combustible cigarettes as well as ENDS. The FDA has repeatedly observed that nonclinical studies are insufficient to demonstrate new tobacco products are appropriate for the protection of the public health and that clinical studies will always be required. **If the FDA can approve such products for marketing without considering studies in animals, it is imperative that this be clearly communicated to applicants so that tests repeatedly exposing animals to ENDS vapor and cigarette smoke are avoided.**

National Center for Advancing Translational Sciences
We appreciate the work NCATS is doing through its Tissue Chip program to refocus testing onto human biology. We hope the progress made through this program will be reflected in recommendations made by the Advisory Committee to the Director on NAMs.

Finally, thank you for your continued commitment to advancing science while reducing animal testing. We look forward to working together towards a future where 'alternative' strategies are the norm.

Sincerely,

(signature redacted)

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