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THE ETHICAL
TREATMENT
OF ANIMALS

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Dr. Warren Casey
Director, NICEATM
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Dear Dr. Casey,

The following comments are submitted on behalf of People for the Ethical Treatment of Animals (PETA) in response to the April 6th *Federal Register* notice by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). Our comments focus on the progress that has been made on the recently published roadmap, as well as addressing animal-derived antibodies, an area relevant to ICCVAM's mission.

The Strategic Roadmap

We congratulate ICCVAM on the completion of *A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States*. We are happy to see the support for this roadmap and the motivation to accomplish its goals. Since its publication just four months ago, ICCVAM has already taken steps to begin achieving those goals, particularly to foster public-private partnerships, connect end users with *in vitro* method developers, publish on regulatory needs, collect existing data, and establish working groups charged with strategically tackling specific tasks. We look forward to seeing these and other activities continue.

To expedite the implementation of non-animal test methods, we recommend that a portion of ICCVAM working group meetings be opened up to the public. Similar to the regular public meetings of the Environmental Protection Agency (EPA) Office of Pesticide Programs Acute Toxicity Stakeholder Group, this would provide a forum for exchanging ideas, identifying remaining gaps, and giving progress updates.

One goal of the roadmap is to foster partnerships between federal agencies and stakeholders and facilitate the sharing of knowledge and data. A successful example of this was the April 2018 ICCVAM workshop on Predictive Models for Acute Oral Systemic Toxicity. This was truly a public-private partnership that started with the curation of existing rat acute oral toxicity data by the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the EPA National Center for Computational Toxicology, followed by a global call for *in silico* models using the data. Subsequently, the toxicity predictions generated by the models will be made available via the EPA's Chemistry Dashboard, and there is ongoing discussion about using the models in a regulatory context. We hope to see similar projects that quickly produce tangible results developed for other endpoints.

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The roadmap encourages the development of agency-specific mechanisms for monitoring progress and measuring success. Having such frameworks in place has become increasingly important for multiple reasons. First, the number of non-animal testing strategies accepted by agencies continues to increase; for example, just last month, the EPA released an interim draft policy to allow the use of defined *in vitro* approaches to skin sensitization testing of certain chemicals. Tracking the success of these policies is important to accurately gauge their use by industry and identify any barriers to implementation. Second, the revelation that the number of animal tests requested by the EPA Office of Pollution Prevention and Toxics under the amended Toxic Substances Control Act increased from 21 in 2015 to 331 in 2017 highlights the importance of monitoring requested and submitted tests. To assess progress, agencies could track the number of requested and submitted animal tests and non-animal tests. This would allow agencies' endpoints of concern and any obstacles to the implementation of non-animal testing strategies to be addressed.

Antibodies

Antibodies are ubiquitous in science and used across federal agencies and in studies submitted for regulatory approval. However, there is a growing consensus that commercial antibodies often show poor specificity or fail to recognize their targets. In a February 2015 *Nature* commentary, 109 academic and industry scientists joined Drs. Andrew Bradbury and Andreas Plückthun in calling for an international shift to the use of recombinant antibodies for reasons that include increased reliability and decreased lot-to-lot variability in affinity reagents.[1] Bradbury and Plückthun note that they believe that poorly characterized antibodies were in large part to blame in a study in which the scientific results of only six out of 53 landmark preclinical studies could be replicated. Furthermore, a May 2015 *Nature* news feature reports that antibodies may be the laboratory tool most commonly contributing to the "reproducibility crisis."[2] This year, a systematic analysis of 185 commercially available hybridoma monoclonal antibodies found that one-third were not reliably monospecific, and the authors recommended the transition to sequence-defined recombinant antibodies.[3]

In addition to the lack of scientific reliability, there are significant animal welfare and economic issues related to using animal-derived antibodies. Tens to hundreds of thousands of animals are used in the production of affinity reagents every year. Unlike the US, a number of countries, such as Australia, the Netherlands, the United Kingdom, Germany, Switzerland, and Canada, have restricted or banned the production of antibodies via the ascites method because of animal welfare concerns.[4] Economically, there are potential cost savings associated with the more reproducible research that would result from using higher-quality antibodies. Bradbury and Plückthun (2015) estimate that $800 million is wasted annually worldwide on unreliable antibodies, $350 million of that in the United States alone.[5]

In 1999, the National Research Council (NRC) published a National Institutes of Health-commissioned study evaluating the scientific necessity of using animals to produce monoclonal

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[1]Bradbury ARM, Plückthun A. Reproducibility: Standardize antibodies used in research. *Nature*. 2015;518(7837):27-29.

[2]Baker M. Reproducibility crisis: Blame it on the antibodies. *Nature*. 2015;521(7552):274-276.

[3]Bradbury ARM, Trinklein ND, Thie H, *et al*. When monoclonal antibodies are not monospecific: Hybridomas frequently express additional functional variable regions. *MAbs*. 2018;27:1-8.

[4]Groff K, Brown J, Clippinger AJ. Modern affinity reagents: Recombinant antibodies and aptamers. *Biotechnol Adv*. 2015;33(8):1787-1798.

[5]Bradbury ARM, Plückthun A. Reproducibility: Standardize antibodies used in research. *Nature*.

antibodies.[6] The report, titled *Monoclonal Antibody Production*, did not include information about recombinant antibodies (rAbs), aptamers, or other non-animal affinity reagents. In the nearly 20 years since, significant advances have been made in rAb and aptamer technology, highlighting the need for an updated version of this report. Considering the substantial scientific, animal welfare, and economic benefits offered by modern, non-animal affinity reagents, we recommend that an updated report be commissioned and that ICCVAM agencies develop a plan to prioritize the use of non-animal antibodies.

Thank you for considering our comments. We would particularly like to thank you as well as Drs. Nicole Kleinstreuer, Anna Lowit, Emily Reinke, and David Allen for your leadership within NICEATM and ICCVAM. The completion of the roadmap was a significant achievement, and we are happy to see that its implementation is already progressing. We look forward to continuing to collaborate with NICEATM and ICCVAM agencies to achieve the roadmap's goals, and to seeing additional ICCVAM agencies become more engaged in this effort.

Sincerely,

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[6]National Research Council. 1999. Monoclonal antibody production. A report of the Committee on Methods of Producing Monoclonal Antibodies, Institute for Laboratory Animal Research, National Research Council. Washington, D.C.: National Academy Press.